Serum creatinine is independently associated with angiographic extent of coronary artery disease in patients with stable angina pectoris

Kararlı anjina pektorisli hastalarda serum kreatinini bağımsız olarak koroner arter hastalığının anjiyografik yaygınlığı ile ilişkilidir

Şule Korkmaz, Burcu Demirkan, Hakan Altay[1], Meltem Refiker Ege[2], Vedat Çaldır, Mehmet Birhan Yılmaz[3], Yeşim Güray, Ümit Güray, Hatice Şaşmaz

Clinic of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara
[1]Department of Cardiology, Başkent University, Adana Teaching and Research Hospital, Adana,
[2]Clinic of Cardiology, Yalova State Hospital, Yalova
[3]Department of Cardiology, Faculty of Medicine, Cumhuriyet University, Sivas-*Turkey*

ABSTRACT

Objective: Renal dysfunction has been shown to be linked to high risk for cardiovascular events. Even milder forms of creatinine elevation are associated with poor cardiovascular outcomes. We designed a retrospective study and searched the association of angiographic extent of coronary artery disease and creatinine levels in patients without overt renal dysfunction.

Methods: We retrospectively reviewed 892 consecutive patients with typical stable angina pectoris (311 female with mean age of 62±10 years, 581 male with mean age of 56±11 years) at Türkiye Yüksek İhtisas Hospital and creatinine level ≤3 mg/dl without history of hemodialysis. Patients without overt renal disease were divided into 3 groups according to level of creatinine (Group A: Cr level <1.2 mg/dl, Group B: Cr level ≥1.2 and <1.5 mg/dl and Group C: Cr level ≥1.5 -≤3 mg/dl). Additionally after evaluation of coronary angiograms, patients were also classified according to those with high stenosis (stenosis score ≥16) and high extension scores (extension score >50%) versus low stenosis and low extension scores. Logistic regression analysis was performed to establish the clinical predictors of high total stenosis and high extension scores.

Results: Each group of patients according to level of creatinine showed marked difference in terms of angiographic extent of coronary artery disease (p<0.001). Those in the highest creatinine group (≥1.5 mg/dl, but not above 3 mg/dl) had the highest total stenosis (17±6, p<0.001) and extension (78±25, p<0.001) scores irrespective of age and gender. Creatinine was shown to be significantly correlated with both stenosis and extension scores. Age (OR:1.035, 95% CI:1.016-1.054, p<0.0001), being male (OR:1.746, 95% CI: 1.135-2.685, p=0.011), presence of hypertension (OR:1.507, 95%CI: 1.005-2.25 p=0.047), presence of diabetes mellitus (OR: 1.865, 95%: 1.250-2.783, p=0.002), previous history of myocardial infarction (OR: 1.624, 95%CI: 1.094-2.413, p=0.016), wall motion score index (OR:1.203, 95%CI: 1.108-1.305, p<0.0001) and creatinine (OR:4.037, 95%CI: 2.530-6.443, p<0.0001) level were found to be independent predictors of high total stenosis score. Furthermore, age (OR:1.042, 95%CI: 1.026-1.059, p<0.0001), being male (OR:2.587, 95%CI: 1.794-3.731, p<0.0001), presence of hypertension (OR:1.536, 95% CI:1.100-2.147, p=0.012), previous myocardial infarction (OR:6.183, 95%CI: 4.340-8.807, p<0.0001), total cholesterol/HDL ratio (OR:1.215, 95%CI: 1.114-1.327, p<0.0001) and creatinine (OR:3.814, 95%CI: 2.149-6.768, p<0.0001) were found to be independent predictors of high extension score.

Conclusion: Serum creatinine seems to denote severity of angiographic extent of coronary artery disease in patients with typical chest pain.
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Key words: Creatinine, coronary artery disease, extension, mild renal dysfunction, logistic regression analysis

ÖZET

Amaç: Renal bozukluğun kardiyovasküler olaylar için yüksek riskle bağlantılı olduğu gösterilmiştir. Kreatinin yüksekliğinin hafif formları bile kötü kardiyovasküler sonuçlarla ilişkilidir. Aşikar renal bozukluğun olmadığı hastalarda kreatinin düzeyleri ile koroner arter hastalığının anjiyografik yaygınlığının ilişkisini araştırmak için retrospektif bir çalışma tasarlandı.

Yöntemler: Tipik kararlı anjina pektoris ile Türkiye Yüksek İhtisas hastanesine başvuran ve diyaliz öyküsü olmadan kreatinin düzeyi ≤3 mg/dl olan 892 ardışık hasta (ortalama yaşı 62±10 yıl olan 311'i kadın ve ortalama yaşı 56±11 yıl olan 581 erkek) retrospektif olarak tarandı. Aşikar renal hastalığı

Address for Correspondence/Yazışma Adresi: Dr. Burcu Demirkan, Department of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara-*Turkey*
Phone: +90 312 306 18 28 Fax: +90 312 324 39 83 E-mail: burcume@gmail.com
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olmayan hastalar kreatinin düzeyine göre 3 gruba ayrıldı (Grup A: Kr<1.2 mg/dl, Grup B: ≥1.2-<1.5 mg/dl ve Grup C: ≥1.5 -≤3 mg/dl). Çalışma hastaları ayrıca angiyografik değerlendirme ile elde edilen darlık ve yaygınlık skorlarına göre yüksek (darlık için skoru ≥16 olan, yaygınlık için skoru >50%) ve düşük skor gruplarına ayrıldılar. Yüksek darlık ve yaygınlık skorlarının klinik öngördürücülerini belirlemek amacı ile lojistik regresyon analiz yapıldı.
Bulgular: Kreatinin düzeyine göre ayrılan her bir grubun koroner arter hastalığının anjiyografik yaygınlığı farklıydı (p<0.001). En yüksek kreatinin düzeyi grubunda olanlar (≥1.5 mg/dl olan ama 3 mg/dl'yi aşmayan) yaş ve cinsiyete bağlı olmaksızın en yüksek toplam darlık (17±6, p<0.001) ve yaygınlık skoruna (78±25, p<0.001) sahipti. Kreatininin hem darlık, hem de yaygınlık skoru ile anlamlı korele olduğu gösterildi. Yaş (OR:1.035, %95 GA:1.016-1.054, p<0.0001), erkek cinsiyet (OR:1.746, %95 GA:1.135-2.685, p=0.011), hipertansiyon varlığı (OR:1.506, %95 GA:1.005-2.256 p=0.047), diyabet varlığı (OR:1.865, %95 GA: 1.250-2.783, p=0.002), önceki miyokardiyal enfarktüs öyküsü (OR:1.624, %95 GA:1.094-2.413, p=0.16), duvar hareket skor indeksi (OR:1.203, %95 GA:1.108-1.305, p<0.0001), total kolesterol/HDL oranı (OR:1.255, %95 GA: 1.144-1.377, p<0.0001) ve kreatinin (OR:4.037, %95 GA: 2.530-6.443, p<0.0001) yüksek toplam darlık skorunun bağımsız göstergeleri olduğu bulundu. Yaş (OR:1.042, %95 GA :1.026-1.059, p<0.0001), erkek cinsiyet (OR:2.587, %95 CI:1.794-3731, p<0.0001), hipertansiyon varlığı (OR:1.536, %95 GA:1.100-2.147, p=0.012), geçirilmiş miyokart enfarktüsü öyküsü (OR:6.183, %95 GA:4.340-8.807, p<0.0001), total kolesterol/HDL oranı (OR:1.215, %95 GA:1.114-1.327, p<0.0001) ve yüksek kreatinin (OR:3.814, %95 GA:2.149-6.768, p<0.0001) düzeyi toplam yaygınlık skorunun bağımsız göstergeleriydi. Tüm diğer faktörler değerlendirildikten sonra, kreatinin yüksek toplam darlık ve yaygınlık skoru için bağımsız bir göstergesi olduğu bulundu.
Sonuç: Tipik göğüs ağrısı olan hastalarda serum kreatinin düzeyi koroner arter hastalığının anjiyografik yaygınlığının ciddiyetini göstermektedir.
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Anahtar kelimeler: Kreatinin, koroner arter hastalığı, yaygınlık, hafif renal bozukluk, lojistik regresyon analizi

Introduction

It has been shown in population studies that there is inverse relationship between renal function and prevalence of cardiovascular disease (CVD) (1-3). It is well known that more than 50% of deaths among patients with end-stage renal disease are due to cardiovascular events (4). Furthermore, the risk for subsequent cardiovascular events is higher among patients with chronic renal dysfunction (RD) than those with normal renal function (5). This might be due to several reasons including clustering of coronary risk factors, less frequent use of evidence-based therapy, which improve cardiovascular risk and end points, and probably more extensive involvement of vascular territory (6). Even milder forms of RD might be associated with angiographically documented severity of coronary artery disease (CAD), though, demonstrated only in women (7).

Creatinine (Cr) as a measure of glomerular filtration rate is subject to error, as it is influenced by age, sex, race and lean body mass. Nevertheless, it is a common and readily available parameter for assessing renal function, and, has been frequently used as a preferred marker of renal function in real life practice (5, 8, 9). Novel risk factors associated with renal dysfunction may play a role in adverse cardiovascular outcomes in these patients, and are being currently investigated. Inflammation, altered calcium-phosphate homeostasis, increased oxidative stress, elevated homocysteine and uric acid levels collaborate in concert, hence, accelerate atherosclerosis and endothelial dysfunction (1, 2, 6). We aimed to show whether creatinine has any influence on angiographically shown stenosis and extension of coronary atherosclerosis in patients with stable CAD.

Hence, we designed a retrospective study and searched the extent of CAD with Sullivan's method (10) in patients with typical stable angina pectoris and without overt RD.

Methods

Study design and patients

We retrospectively evaluated the records of 892 consecutive patients with typical stable angina pectoris and with Cr level ≤3 mg/dl without history of hemodialysis (311 female with mean age of 62±10 years, 581 male with mean age of 56±11 years), who were referred for diagnostic coronary angiography to our Türkiye Yüksek İhtisas Hospital. "Typical" angina pectoris was accepted if a patient had two out of three of the following criteria: chest pain following emotional or physical stress (exercise), stress induced chest pain which is located substernally with or without referring to other sites, chest pain which subsides via rest or nitrates. Patients with acute coronary syndromes (within last 2 months) considering the fact that acute thrombosis and/or endothelial denudation might have overestimated the exact atherosclerotic burden, acute renal failure, and those taking nephrotoxic drugs for any reason (cyclosporin, high dose nonsteroidal antiinflammatory drugs) were not included into study.

After getting institutional ethics committee approval, included patients were classified according to Cr levels such that those with Cr level of less than 1.2 mg/dl (n=768, Group A, control group), those with Cr level ≥1.2 and <1.5 mg/dl (n=63, Group B, mild RD) and those with Cr level ≥1.5 mg/dl (n=61, Group C, moderate RD) irrespective of gender (11). Clinical and laboratory variables were compared among three subgroups. After evaluation of coronary angiograms, the stenosis and extension scores were calculated. Then, patients were also further classified according to those with high (involvement of more than half, HSS) stenosis (stenosis score ≥16) and high (involvement of more than half, HES) extension scores (extension score >50%) versus low stenosis and low extension scores. The correlation between both scores (stenosis and extension) and Cr was searched and the factors affecting the development of high stenosis and extension scores for CAD were evaluated.

Clinical and laboratory variables

Laboratory and clinical data were obtained from patients' files. Hypertension (HT) was defined as blood pressure ≥140/90 mmHg or being on treatment, diabetes mellitus (DM) was defined as fasting blood glucose≥126 mg/dl on two occasions or being on treatment (12, 13).

Plasma glucose, urea and Cr levels and lipid profile which were measured in the morning fasting blood sample before the

angiogram were taken into consideration. After centrifugation of blood samples, creatinine level was measured by using Jaffe method and analyzed with Cobas Integra 800 analyzer (Roche Diagnostics Ltd, UK). Glomerular filtration rate was calculated from the determined creatinine level according to Cockcroft-Gault equation (14). Levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in serum were measured using an Abbott Aeroset autoanalyzer-with original kits (Abbott Laboratories. Abbott Park, Illinois, U.S.A). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation (15). Complete blood counts were analyzed by standard methods.

Evaluation of coronary angiography

Coronary angiograms were evaluated by experienced authors, who were blinded to study plan, via Sullivan's method (10) to assess the atherosclerotic involvement. Vessel score was used to assess the number of vessels with significant stenosis (70% diameter stenosis) with a score ranging from 0 to 3 indicating the number of vessels involved. Stenosis score was used as defined previously (10) such that the most severe score of each vessel was graded as 1 for 1%-49% diameter stenosis, 2 for 50%-74% diameter stenosis, 3 for 75%-99% diameter stenosis, and 4 for 100% diameter stenosis. Total coronary arterial tree was divided into 8 segments as left main artery, left anterior descending artery, main diagonal branch, first septal perforator, left circumflex artery, obtuse marginal and posterolateral vessels, right coronary artery, and main descending branch (10). The scores for each of the 8 segments yielded to give the sum out of a theoretical total of 32. A score of greater than and equal to 16 was considered high stenosis score (i.e, involvement of more than half of coronary arterial territory). Extension score was used as defined previously (10) to assess the atherosclerotic involvement of the entire coronary arterial endothelium. The extension score of 8 segments consecutively were given 5, 20, 10, 5, 20, 10, 20, 10 as percentages totally adding up 100%, if any involvement of intimal surface by atherosclerosis was observed. When a vessel was occluded and thus not seen, the proportion of the vessel that was not visualized was given the mean extent score of the remaining vessels. The score of each vessel yielded to give a total out of 100% of the intimal surface affected by atherosclerosis. A score of greater than and equal to 50% was considered high extension score. Wall motion score index (WMSI), evaluated by ventriculography, were calculated sum of motion scores (normokinesia=1, hypokinesia=2, akinesia=3, dyskinesia&aneurysm=4) of 5 segments obtained during right anterior oblique projection.

Statistical analysis

SPSS 10.0 version (SPSS Inc, Chicago, USA) was used to perform statistical procedures. Continuous variables were expressed as mean±standard deviation, and categorical data as percentages. Continuous variables with normal distribution were compared by Student t-test, those without normal distribution were compared by Mann-Whitney U test, and categorical data via Chi- square test. Cr groups were compared according to ANOVA test, and between groups comparisons were performed according to Tukey's HSD test. Correlations were searched by Pearson's correlation. Variables, found to have significant differences in univariate analysis ($p<0.1$) were evaluated for multicolinearity and then enrolled into multivariable logistic regression analysis (stepwise forward LR). Then, in order to search independent impact of Cr, adjustments were done for variables, which had significant association with Cr, and multivariate logistic regression was repeated. A p value ≤ 0.05 was accepted significant.

Results

Patients subgroups

Seventeen patients had completely normal appearing coronary arteries during coronary angiogram in our study group. Those with angiographically normal appearing coronary arteries had significantly lower Cr levels than those without (0.7±0.1 vs. 0.9±0.3, $p<0.001$).

Angiographic extent of CAD according to creatinine levels

In terms of stenosis score and extension score, three groups (A, B, C) were significantly different from each other ($p<0.001$) irrespective of age and sex. In terms of individual comparisons, mean stenosis score and extension score of Group A (creatinine <1.2 mg/dl) were significantly lower than Group B (creatinine ≥1.2 and <1.5 mg/dl, mild RD) (10±5 vs. 12±5, p=0.004, and 50±28 v.s. 62±21, p=0.003 respectively). Mean stenosis score and extension score of Group A were significantly lower than Group C (creatinine ≥ 1.5 mg/dl and ≤3 mg/dl, moderate RD) (10±5 v.s. 17±6, $p<0.001$, and 51±28 vs. 78±25, $p<0.001$ respectively). Mean stenosis score and extension score of Group B were significantly lower than Group C as well (12±5 vs. 17±6, $p<0.001$, and 62±21 vs. 78±25, $p<0.001$ respectively). Patients in Group C and B were significantly older than those in Group A ($p<0.001$ and p=0.006 respectively). Distribution of males was different among Group A, B and C (63.4% vs. 88.9% vs. 62.3%, $p<0.001$). In terms of correlation between Cr and stenosis and extension scores, Cr, as a whole, was significantly and modestly correlated with both stenosis and extension scores (r=0.377 and r=0.325 respectively, $p<0.001$ for both, Fig. 1). The degree of correlation was more apparent in female patients (r=0.433, $p<0.001$, and r=0.396, $p<0.001$, respectively) than in male patients (r=0.300, $p<0.001$, and r=0.222, $p<0.001$, respectively).

Clinical and laboratory characteristics of patients with high and low total stenosis scores (Table 1)

When patients were compared, according to groups of high total stenosis versus low total stenosis score, it was noticed that there were 183 patients with high total stenosis score (HSS) and 709 patients with low stenosis score (LSS).

Patients with HSS were significantly older ($p<0.001$), more frequently male (p=0.01), had more frequently HT (p=0.002), DM

(p<0.001), had poorer functional capacity (in terms of Canadian Cardiovascular Society angina classification) (p=0.002) (16), significantly higher ratio of total cholesterol/HDL cholesterol (6±2.3 vs. 5.3±1.8, p<0.001), and higher WMSI (p<0.001), had more frequent previous history of myocardial infarction (MI) (those before 2 months) (p<0.001), and had significantly higher triglyceride (p=0.006), total cholesterol (p=0.001), LDL cholesterol (p=0.028), glucose (p<0.001), Cr levels (p<0.001) than those with LSS (Table 1).

Clinical and laboratory characteristics of patients with high and low total extension scores (Table 2)

There were 494 patients with high total extension score (HES) versus 398 patients with low extension score (LES). Patients with HES were significantly older (p<0.001), more frequently male (p<0.001), had more frequently HT (p=0.02), DM (p=0.004), had poorer functional capacity (in terms of Canadian Cardiovascular Society angina classification) (p<0.001) (16), significantly higher ratio of total cholesterol/HDL cholesterol (5p<0.001), and higher WMSI (p<0.001), had more frequent previous history of MI (p<0.001), and had significantly higher glucose (p<0.001) and Cr levels (p<0.001) than with LES (Table 2).

Calculated glomerular filtration rate, according to Cockcroft-Gault equation (14) was significantly lower in high total stenosis (p<0.001) and extension scores (p<0.001) than in low scores consecutively (Tables 1, 2).

Multivariable analyses of predictors of high total stenosis and extension scores

Variables, presented in Table 3 and 4, were enrolled into multivariate stepwise logistic regression analysis in order to evaluate their predictive value for presence of HSS and HES.

Multivariable stepwise logistic regression analysis yielded that age, being male, presence of hypertension, presence of diabetes mellitus, previous MI, WMSI, total cholesterol/HDL ratio and creatinine were independent predictors of high stenosis score (p<0.05 for all) (Table 3).

Furthermore, age, being male, presence of HT, previous MI, total cholesterol/HDL ratio and creatinine were found to be independent predictors of high extension score (p<0.05 for all) (Table 4).

Discussion

According to our study results presence of coronary artery disease and both its extension and severity were associated with serum Cr level in patients without overt renal dysfunction.

It is thought that Cr and Cr clearance are integrated markers of metabolic abnormalities, neuroendocrine activation, and end-organ damage due to constellation of several cardiac risk factors, including HT, atherogenic dyslipidemia, DM, and vascular disease (17). As renal function declines, a series of interrelated abnormalities, which include changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors that have been related to CVD, develops beyond elevation of Cr levels (18, 19). End stage RD has been shown to be associated with highly increased mortality due to increased risk for ischemic heart disease (2). Even milder forms of RD have been demonstrated to indicate poor cardiovascular prognosis, independent from traditional cardiovascular risk factors including those seen after acute MI (20, 21). Such increased risk for cardiovascular outcomes might be driven by both lack of evidence-based therapy, which improves outcomes, and constellation of traditional and nontraditional risk factors, which were designated by end-organ damage, namely RD (20).

In a study by Reis et al. (7) it was shown that mild RD was indicative of significant CAD in women. However, although, it was previously indicated (1, 2, 22), association of degree of renal function and angiographic extent of CAD in both sexes was not

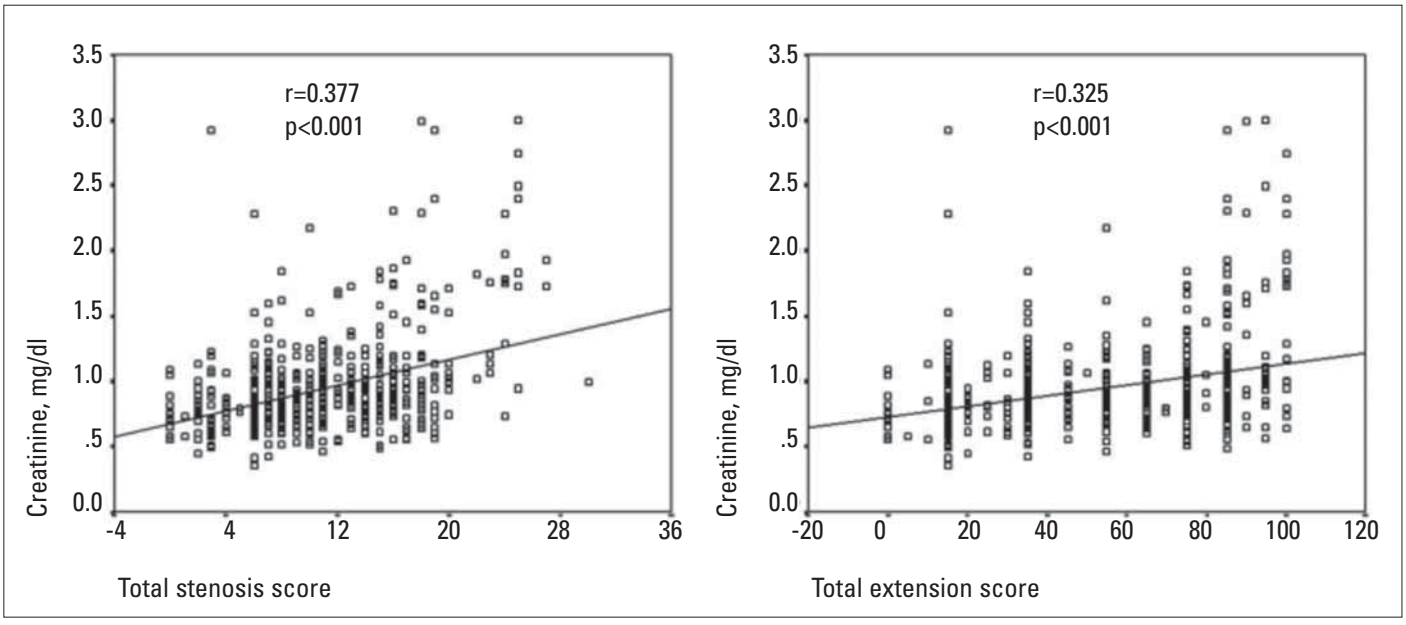

Figure 1. Correlation graph of creatinine with total stenosis and total extension scores

Table 1. Patients classified according to stenosis score as high stenosis score (stenosis score ≥16) and low stenosis score (stenosis score <16)

Variables	High stenosis score (n=183)	Low stenosis score (n=709)	p*
Age, years	62±9	58±12	<0.001
Male gender, n (%)	134 (73.2)	447 (63)	0.010
Hypertension, n (%)	117/183 (63.9)	361/709 (50.9)	0.002
Diabetes mellitus, n (%)	70/183 (38.3)	144/709(20.3)	<0.001
Smoking, n (%) **	55/183 (30.1)	241/709 (34)	0.313
Family history, n (%)	65 (35.5)	225 (31.7)	0.330
Hemoglobin, gr/dl	13.4±1.6	13.6±1.7	0.288
Total cholesterol, mg/dl	227±64	210±53	0.001
LDL cholesterol, mg/dl	146±56	135±46	0.028
HDL cholesterol, mg/dl	43±27	43±17	0.781
Triglyceride, mg/dl	179±116 141 (66-607)	154±87 134 (49-760)	0.006
Creatinine, mg/dl	1.1±0.5	0.9±0.2	<0.001
Glucose, mg/dl	120±41	103±30	<0.001
WMSI	8±2	6±2	<0.001
Total cholesterol/HDL ratio	6±2.3	5.3±1.8	<0.001
Functional class (CCS), n (%)	13/134/36 (7.1 /73.2 /19.7)	114/503/92 (16.1 /70.9 /13)	0.002
Previous history of MI, n (%)	93 (50.8)	225 (31.7)	<0.001
Glomerular filtration rate, ml/min***	69±29	90±55	<0.001

Data are presented as mean±SD, median (min-max) values or numbers (percentages).
*Student t-test, Mann-Whitney U test, and Chi-square test
CCS - Canadian Cardiovascular society angina classification, HDL - high-density lipoprotein, LDL - low-density lipoprotein, MI - myocardial infarction, WMSI - wall motion score index,
**current smokers, ***calculated according to Cockcroft-Gault equation (14)

Table 2. Patients classified according to extension score as high extension score (extension score >50%) and low extension score (extension score ≤50%)

Variables	High extension score (n=494)	Low extension score (n=398)	p*
Age, years	60±11	57±12	<0.001
Male gender, n (%)	369 (74.7)	212 (53.3)	<0.001
Hypertension, n (%)	282/494 (57.1)	196/398 (49.2)	0.020
Diabetes mellitus, n (%)	137/494 (27.7)	77/398 (19.3)	0.004
Smoking, n (%) **	170/494 (34.4)	126/398 (34)	0.385
Family history, n (%)	160 (32.4)	130 (32.7)	0.931
Hemoglobin, gr/dl	13.5±1.7	13.6±1.7	0.188
Total cholesterol, mg/dl	217±61	210±49	0.070
LDL cholesterol, mg/dl	140±54	135±42	0.100
HDL cholesterol, mg/dl	42±23	44±16	0.109
Triglyceride, mg/dl	161±91 139 (50-607)	157±99 131.5 (49-760)	0.590
Creatinine, mg/dl	1±0.4	0.8±0.3	<0.001
Glucose, mg/dl	120±61	108±45	<0.001
WMSI	7±2	6±2	<0.001
Total cholesterol/HDL ratio	5.7±2	5.1±1.7	<0.001
Functional class (CCS), n (%)	35/392/67 (7.1/79.4/13.6)	92/245/61 (23.1/61.6/15.3)	<0.001
Previous history of MI, n (%)	257 (52)	61 (15.3)	<0.001
Glomerular filtration rate, ml/min***	76±27	97±69	<0.001

Data are presented as mean±SD, median (min-max) values or numbers (percentages).
*Student t-test, Mann-Whitney U test, and Chi-square test
CCS - Canadian Cardiovascular society angina classification, HDL - high-density lipoprotein, LDL - low-density lipoprotein, MI - myocardial infarction, WMSI - wall motion score index,
**current smokers, ***calculated according to Cockcroft-Gault equation (14)

evaluated before. In our study, we have shown that patients without overt renal disease, stratified according to level of Cr, differ from each other in terms of angiographic extent of CAD, defined according to definition and previously validated (10). Those in the highest Cr group (≥1.5 mg/dl, but not above 3 mg/dl) had the highest total stenosis and extension scores irrespective of age and sex. Besides, Cr was shown to be significantly, but modestly, correlated with both stenosis and extension scores. Interestingly, correlation appeared more striking in females compared to male patients. When, patients were subclassified according to extent of involvement of coronary artery territory as high (involvement of more than half of coronary tree) versus low stenosis and extension scores; it was shown that older age, male sex, higher fasting glucose, presence of HT, DM, poor functional status, poor lipid profile, poor WMSI and previous history of MI were associated with high total stenosis and extension scores along with significantly higher Cr levels.

In the multivariable analysis, age, male gender, presence of HT, presence of DM, previous history of MI, total cholesterol/HDL ratio, WMSI and Cr level were found to be independent predictors of high total stenosis score. In a recent study including diabetic patients, it was shown that renal function was one of the most important factors associated with extent and severity of coronary artery disease whereas classical coronary risk factors or metabolic control were not (23). On the other hand, age, male gender, presence of hypertension, previous history of MI, total cholesterol/HDL ratio and Cr were found to be independent predictors of high total extension score. Herein, neither DM nor glucose (replaced DM in the model) was independent predictor. Presence of DM, de novo, predicted stenosis of coronary arteries rather than extension of coronary atherosclerotic involvement among patients with stable angina pectoris. However, it is important to keep in mind that coronary angiography is not ideal test to designate extension of atherosclerosis.

Table 3. Factors to predict high stenosis score in multivariable regression analysis

Variables	Odds ratio	95% C.I.		p
		Lower	Upper	
Gender (M)	1.746	1.135	2.685	0.011
HT	1.506	1.005	2.256	0.047
Previous MI	1.624	1.094	2.413	0.016
Total cholesterol/HDL	1.255	1.144	1.377	<0.0001
WMSI	1.203	1.108	1.305	<0.0001
DM	1.865	1.250	2.783	0.002
Age	1.035	1.016	1.054	<0.0001
Creatinine	4.037	2.530	6.443	<0.0001

DM - diabetes mellitus, HDL - high-density lipoprotein, HT - hypertension, LDL - low-density lipoprotein, M - male, MI - myocardial infarction, WMSI - wall motion score index

Table 4. Factors to predict high extension score in multivariable regression analysis

Variables	Odds ratio	95% C.I.		p
		Lower	Upper	
Gender (M)	2.587	1.794	3.731	<0.0001
HT	1.536	1.100	2.147	0.012
Previous MI	6.183	4.340	8.807	<0.0001
Total cholesterol/ HDL ratio	1.215	1.114	1.327	<0.0001
Age	1.042	1.026	1.059	<0.0001
Creatinine	3.814	2.149	6.768	<0.0001

HDL- high-density lipoprotein, HT- hypertension, M-male, MI- myocardial infarction, WMSI- wall motion score index

In our study, we have shown that Cr, in patients with typical stable angina pectoris, predicted angiographic extent and narrowing of CAD in a range of Cr from normal to moderate range of RD. We think that even mild elevation of Cr, which probably indicates starting or ongoing end-organ damage at renal site, might be indicative of remote end-organ damage at the site of coronary arteries through more extensive atherosclerotic involvement in patients with angina complaints. Besides, more extensive atherosclerotic involvement, irrespective of specific etiology, might account for poor outcomes in patients with normal renal function towards the range of moderate RD. However, these issues require further study to support initial findings.

Study limitations

Our study was a non-randomized, retrospective analysis, and as such, it is possible that both identified and unidentified confounders may have influenced the outcomes. Besides, our subjects had clinically indicated coronary angiography to evaluate chest pain, which results in referral bias. Decrease in the level of kidney function has been associated with increased levels of nontraditional CVD risk factors, such as elevated homocysteine levels, protrombotic factors (increased fibrinogen, tissue plasminogen activator and decreased plasminogen activator inhibitor), oxidative stress, cholesterol subparticles and proinflammatory factors (C-reactive protein), which may be possible mechanisms of the complex and severe coronary lesions in patients with impaired renal function (24, 25). However these factors were not measured in our study and, therefore, not adjusted for in the analysis. Some may speculate the value of angiographic findings, and intravascular ultrasonographic findings might underline the impact better, though, it is costly. Besides, angiographic nature of the evaluation, particularly in those with total occlusion might have caused overestimation of atherosclerotic burden, and hence, overestimation of the correlation of Cr and both scores. Furthermore, selection of cut off point of 1.2 and 1.5 mg/dl might be criticized without considering sex based differences of cut off points for creatinine. However, we corrected for age while searching for correlations, and it may be considered for a larger group enrolling equally each sex. Besides, many other studies used arbitrary classifications, and actually, exact cut off point of serum Cr has not yet been established accurately (decreasing as the new data arrive), at least for cardiovascular evaluations. It is also possible to speculate that cardiologists might avoid catheterizing known diabetic patients and those with chronic renal disease due to the increased risk of contrast nephropathy. Thus, it is likely that such patients, presenting with not-so-convincing clinical findings (and likely less severe CAD) might not be catheterized, whereas those with severe symptoms (and likely more severe CAD) would require angiography as a first step toward intervention. This bias could partially explain the greater stenosis and extension scores seen in diabetics and those with creatinine in the higher range. Creatinine, on the other hand, is unlikely to be proatherogenic, but, seems rather as a marker, as in our study, for other factors that promote atherosclerosis. Therefore, the pathophysiologic mechanism for the association between Cr and angiographic extent of CAD remains established, though, it is thought to be multifactorial. Since, it is affected by age, sex, race and lean body mass, some may criticize the accuracy of Cr, though calculated glomerular filtration rate shown similar tendency. However, it should be remembered that Cr persisted its independent predictive role after correction for confounding age and sex, and there was no difference concerning body mass (27.7±4.6 vs. 27.4±4.4, p=0.388).

Conclusion

Finally, although we used serum Cr and calculated glomerular filtration rate, both of which might not be accurate enough to classify renal function, serum Cr is preferred in clinical practice for ease of use, and, along with our study, we think that even mild elevations of serum Cr might be considered as an independent sign of more extensive atherosclerotic involvement of remote site, i.e., coronary arteries, at least, in a group of patients

with typical chest pain undergoing diagnostic coronary angiogram, even though the cut off point of Cr indicating such involvement remains to be established in this group.

Conflict of interest: None declared.

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