Can urine protein to creatinine ratio predict the severity of coronary artery disease?

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Abstract

BACKGROUND: Albuminuria is one of the abnormalities in diabetics. Although different studies have shown its relationship with cardiovascular diseases, few studies have been performed to show the relationship between albuminuria level and coronary artery disease (CAD) severity. This study was thus designed in order to assess the relationship between the albuminuria and the severity of CAD.

METHODS: In this cross-sectional study, 164 (80 male and 84 female) non-insulin dependent diabetes mellitus patients with angina pectoris were included. All patients were hospitalized for diagnostic or therapeutic angiography in Chamran Hospital, Isfahan, Iran. First morning urine samples were taken from all participants to calculate protein to creatinine (Pr/Cr) ratio. The standard angiography video was assessed by three cardiologists through Seldinger method. CAD was scores from zero to 21 based on the Extent method. The relationship between CAD severity and urine Pr/Cr ratio was assessed by bivariate correlational methods and multivariate analysis. $SPSS_{15}$ was used for all data analyses.

RESULTS: Among the 164 studied patients, mean levels of morning urine protein was and creatinine were 22.77 ± 30.99 and 0.07 ± 0.04, respectively. Urine Pr/Cr ratio was 760.94 ± 401.56 mg/g (median: 181.02). Mean CAD score was equal to 13.34 ± 6.24. There was no correlation between urine Pr/Cr ratio and CAD severity (P = 0.778; r = 0.022). In multivariate analysis model controlled for age, gender, fasting blood sugar, captopril consumption, and history of hypertension and hyperlipidemia, increased urine Pr/Cr ratio led to increased CAD severity (P = 0.021).

CONCLUSION: Albuminuria level measured based on morning urine Pr/Cr ratio might be an independent risk factor for the severity of CAD. It can thus predict the severity of Cad. These findings signify the importance of albuminuria diagnosis and treatment.

Keywords: Severity, Coronary Artery Disease, Albuminuria, Angiography.

ARYA Atherosclerosis Journal 2012, 7(Suppl): S88-S93

Date of submission: 23 Dec 2011, ***Date of acceptance:*** 29 Jan 2012

Introduction

Diabetes mellitus is one of the important risk factors for premature mortality, disability, and cardiovascular disease.[1] On the other hand, cardiovascular diseases are the main cause of mortality in patients with type 2 diabetes.[2,3] Therefore, reducing the risk of cardiovascular disease in diabetics is the main priority to treat these patients. Microalbuminuria has the early signs of microvascular disease. It is also strongly connected with the severity of renal disease in diabetic patients.[4] The disorder is diagnosed by the daily urinary albumin excretion of 30-300 mg/dl or a protein to creatinine ratio (Pr/Cr) of between 30-300 mg/g in spot urine sample. Microalbuminuria can predict the incidence of proteinuria and the development of renal failure.[5-7] It has also been identified as a predictor of coronary artery disease (CAD) and all cause mortality in either diabetic or non-diabetic patients.[3,7-10] In addition, there was a significant relationship between microalbuminuria and the traditional and nontraditional CAD risk factors. Researchers have shown that in type 2 diabetes, increased albumin

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excretion, endothelial dysfunction, and chronic inflammation in the endothelium simultaneously and independently affect the increased mortality risk.[11] Although the main mechanism of the relationship between microalbuminuria and CAD is not well-known yet, it seems that the widespread endothelial functional impairment, microvascular damage, and the related inflammation cause CAD following albuminuria.[12,13] The prevalence of microalbuminuria is high due to the high prevalence of diabetes and hypertension in the world. In an Asian study on the prevalence of albuminuria in patients with diabetes and hypertension, about 40% of the subjects had microalbuminuria while 19% suffered from macroalbuminuria.[14] In another study in 33 countries worldwide, the prevalence of microalbuminuria and macroalbuminuria was relatively high (39% and 10%, respectively).[15] Most previous studies on albuminuria and CAD investigated disease incidence while few have evaluated the relationship between albuminuria and vascular involvement and lesions. The prevalence of diabetes among the 25-26 year-old Iranian population (2 million) has been reported as 7.7%.[16,17] On the other hand, Pr/Cr ratio can be used not only for prevention, prognosis, and treatment of albuminuria associated with kidney failure, but also to predict the severity of coronary artery disease. This study was designed to determine the severity of coronary artery lesions and its relationship with albuminuria in diabetic patients.

Materials and Methods

In a cross-sectional study, all patients with non-insulin dependent diabetes who were hospitalized for angiography (diagnostic or therapeutic) in Chamran Hospital (Isfahan, Iran) due to pectoral angina from October 2007 to February 2008 were evaluated. The inclusion criteria were aging 40-70 years old, absence of simultaneous chronic renal disease or any other pharmacological or non-pharmacological renal disease (Cr > 1.5 mg/dl), absence of a concurrent febrile disease or uncontrolled blood pressure, not having a history of valve surgery or percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) surgery, and not using corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), rifampin, ampicillin, penicillin, sulfonamides, amoxicillin, warfarin, lithium, probenecid, carbimazole, penicillamine, gold, paramethadione, allopurinol, hydralazine, ciprofloxacin, recombinant alpha interferon, intravenous (IV) amphetamines, diltiazem, verapamil, amlodipine, enalapril, losartan, and lisinopril.

In order to obtain minimum correlation of 0.25, with the first type error of $\alpha = 0.05$ and power of $\beta = 10\%$, the minimum required sample size was calculated as 164. After collecting demographic information, history of patients, and types of received diabetes medications, a 1.5-cc sample of the first morning urine was taken from each qualified patient. A blood sample was also taken to measure Cr and fasting blood sugar (FBS) levels. Within 2 hours of sampling, urine samples were tested manually by Chem enzyme kit to determine protein level. In addition, Jaffe method was used to evaluate Cr levels. Pyrogallol red reagent was used in the Chem enzyme method since it creates a colored complex in acidic conditions with proteins, which is measurable at a wavelength of 600 nm. On the other hand, in Jaffe method, Cr forms a colored complex with alkaline bicarbonate. The intensity of generated color is proportional to the amount of Cr in the sample.

Blood samples were analyzed with the RA-1000 autoanalyzer which had a computer for recording, transmitting and receiving the information, and a place for pouring patients' serum and the reagent. The device had movable arms for transferring samples and reagents to special sections for performing the reactions and creating colored complexes. After the formation of the complex, the colorimeter measured the optical absorption and transferred the information to the computer. Finally, the results were delivered.

All patients underwent standard angiography in Chamran Hospital using the Seldinger method.[18] Angiographic films were evaluated by three cardiologists. Involvement scores (between 0-21) were then calculated based on the Extent method. In order to calculate score, number of major coronary vessels with atherosclerotic involvement was scored 0 to 3. Involved segments (proximal, medial, and distal) of the main coronary stenosis were then scored from zero to 3, resulting in a total score of 0-9. Finally, the extent of atherosclerotic stenosis in each coronary artery was categorized as less than 50%, 50-75%, and more than 75% and scored 0-3. Therefore, the overall score ranged between zero and 21.[19] The collected data was entered into data entry forms using EPI software. $SPSS_{15}$ was used to perform all data analyses. The correlation between morning urine Pr/Cr ratio and the severity score of coronary artery disease was assessed by calculating Spearman's correlation coefficient according to the non-normal distribution of the two variables. Moreover, the quantitative variable of morning urine Pr/Cr ratio was classified into 3 groups of less than 300, 300-3500, and more than 3500. T-test analysis was used in the bivariate analysis in order to compare the quantitative variables of age, FBS, etc. between the consumers and non-consumers of captopril, or between patients with Pr/Cr ratios of less and more

than 300. Non-parametric Mann-Whitney test was used in the case of poor distributed data. In addition, chi-square test was used to compare qualitative variables such as gender and Pr/Cr ratios less or more than 300. In multivariate general linear model (GLM), severity of coronary artery disease was considered as the dependent variable while gender, history of hypertension, history of hyperlipidemia, smoking (current status of smoking and the number of cigarettes per day), and captopril use were regarded as fixed factors, and FBS level, Pr/Cr ratio, and age were considered as covariates. The effects of these variables on the severity of coronary artery disease were evaluated. The significance level in all analyses was considered as 0.05.

Results

Among the 175 eligible individuals during the sampling period, morning urine samples were obtained from 164 (93%) subjects including 84 females (51.2%) and 80 males (48.8%). Mean age of participants was 55.92 ± 9.87 years (range: 30-79 years). Time elapsed from diagnosis of diabetes was 6.99 ± 6.56 years with the median of 5 years. Insulin and oral drugs were used to treat diabetes in 30 (19.6%) and oral 123 (80.4%) patients, respectively. Mean FBS of the samples was 179.76 ± 70.93. Hypertension and hyperlipidemia were observed in 83 (56.6%) and 104 (63.8%) subjects, respectively. In addition, 28 patients (17.2%) were smokers. Mean blood Cr level in these patients was 0.98 ± 0.97.

Mean values of morning urine protein and Cr were 22.17 ± 30.99 (median: 12) and 0.07 ± 0.04 (median: 0.06), respectively. Urine Pr/Cr ratio was equal to 97.760 ± 56.401 mg/g with the median of 181.02. In 2 participants (1.2%), Pr/Cr ratio was more than 3500 mg/g, in 47 patients (28.7%) between 300-3500 mg/g, and in 115 patients (70.1%), between 30-300 mg/g. By merging the first two groups, number of patients with urinary Pr/Cr ratios over 300 mg/g was equal to 49 (29.9%). The severity of coronary artery disease was calculated as 13.34 ± 6.24 with a median score of 14. The Spearman's correlation coefficient for two variables of Pr/Cr ratio and coronary artery disease severity score was equal to 0.022, which was not statistically significant (P = 0.778). Severity scores of coronary artery disease in the two groups with Pr/Cr urine levels less than or equal to 300 mg/g and more than 300 mg/g were 13.25 ± 6.36 and 13.57 ± 6.01, respectively. The observed difference was not statistically significant (P = 0.765). Non-significant differences between the two groups was also confirmed by non-parametric Mann-Whitney test (P = 0.877). The two groups were not significantly different in terms of FBS levels (194.42 ± 75.19 vs. 173.51 ± 68.42; P = 0.840).

Captopril was consumed by 64 patients (39%) at a mean dose of 50.5 ± 27.5 (median: 50; range: 12.5-150 mg) (Table 1).

The multivariate GLM to investigate the relationship between the severity of coronary artery disease and urine Pr/Cr ratio in the presence of gender, captopril consumption, FBS, and age, was significant (P = 0.008; f = 3.00; df = 6) (Table 2). By adding smoking and previous history of hyperlipidemia and hypertension, only hyperlipidemia was found to have a significant correlation with disease severity. After replacing the quantitative variable of Pr/Cr ratio with a dichotomous qualitative variable based on Pr/Cr ratio (greater or less than 300 mg/g), the obtained model from the GLM test was not significant (P = 0.085; f = 1.9; df = 5). Among the dual interactions, only the history of hyperlipidemia and hypertension were significant (P = 0.020; f = 5.585; df = 1).

Table 1. Comparison of protein to creatinine (Pr/Cr) ratio, severity of coronary artery disease, and other related variables between captopril consumers and others

	Captopril consumers (n = 64)	**Captopril non-consumers (n = 100)**	**P**
Age (years)	57.45 ± 9.67	54.92 ± 9.92	0.110
Duration of diabetes (years)	7.14 ± 6.49	6.90 ± 6.63	0.824
Fasting blood sugar (mg/dl)	185.46 ± 77.06	176.11 ± 66.86	0.412
Pr/Cr ratio (mg/g)	273.73 ± 416.81	483.46 ± 908.56	0.047*
Pr/Cr > 300	20.3% ± 13%	36% ± 36%	0.032
Coronary artery disease severity	14.31± 5.67	12.73 ± 6.53	0.114**

All values are expressed as mean ± SD.
* P of the non-parametric Mann-Whitney test was equal to 0.050.
** P of the non-parametric Mann-Whitney test was equal to 0.150.

Table 2. The relationship between the severity score of coronary artery disease and protein to creatinine (Pr/Cr) ratio in the presence of age, gender, fasting blood sugar (FBS), and captopril consumption in general linear model (GLM)

	P	f	B (95%CI)
Age	0.018	5.730	0.122 (0.021-0.223)
FBS	0.151	2.084	0.010 (-0.004-0.024)
Pr/Cr ratio	0.021	5.436	0.001 (0.000-0.003)
Male gender	0.821	2.641	-1.473 (-14.321-11.375)
Captopril consumption	0.031	1.765	14.061 (1.314-26.807)
Hypertension history	0.785	0.064	8.264 (-4.251-20.780)
Hyperlipidemia history	0.016	5.908	26.696 (43.142-10.250)
Cigarette smoking	0.425	0.166	-5.982 (-20.764-8.800)

Discussion

According to the results of this study, no significant difference between microalbuminuria based on morning urine Pr/Cr ratio and the severity of coronary artery disease was revealed by the bivariate analysis among patients with type 2 diabetes. However, Pr/Cr ratio was significantly and positively associated with the severity of coronary artery disease in multivariate model and in the presence of other proven risk factors of CAD. Therefore, albuminuria based on urine Pr/Cr ratio can be an independent prognostic factor for the severity of coronary artery disease.

Albuminuria is a common disorder in diabetic patients. Marshall evaluated the prevalence of microalbuminuria in type 2 diabetic patients. They showed the prevalence of the disorder to be about 25% in patients with a 10-year history of diabetes. In general, every 6.5 years of having diabetes increased the prevalence of microalbuminuria by 26%.[20] Many studies have shown microalbuminuria to increase morbidity and mortality due to cardiovascular diseases and all-cause death rates. The risk remains the same even adjustments for traditional risk factors of cardiovascular diseases.[21-24]

It is noteworthy that microalbuminuria is significantly associated with the incidence of myocardial ischemia and ST-T changes. Derhaschnig et al. suggested microalbuminuria levels after myocardial infarction to be related with myocardial infarct size and the in-hospital mortality rate. They also indicated that the one-year mortality rate can be predicted by measuring microalbuminuria within one week following myocardial infarction.[25]

Unlike previous studies, we evaluated the relationship between albuminuria levels based on urine Pr/Cr ratio and the severity of coronary artery disease rather than its existence. Most performed studies have assessed the association between albuminuria with cardiovascular diseases or their related mortality and morbidity. However, in this study, the Extent method was used to quantitatively determine the extent of coronary artery disease. In addition, the level of albuminuria was measured based on albumin to Cr ratio which is a highly sensitive screening method.[26] Although urine Pr/Cr ratio is slightly less sensitive and less specific than 24-hour urine protein measurement, it is favorable in daily practice due to its simplicity and availability.[26,27] According to the results of this study, urine Pr/Cr ratio was an independent significant prognostic factor. Age, history of hyperlipidemia, and captopril consumption have also been identified as predictors of the severity of coronary artery disease. Considering the coefficients of age and urine Pr/Cr ratio on the severity of coronary involvement and the range of their changes, it can be said that in addition to the high impact of confirmed risk factors on the severity of coronary artery disease, the impact of albuminuria would remain significant due to the wide range of urine Pr/Cr ratio (30-3,000 units). In fact, based on table 2, an increase of 100 units in quantitative form of urine Pr/Cr ratio was as effective on the severity of coronary artery disease as a one-year increase in patients' age. In other words, the severity of coronary artery disease can be predicted by evaluating urine Pr/Cr ratio.

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are currently recommended for controlling albuminuria in diabetic or hypertensive patients. Consuming such drugs, including captopril, would control albuminuria and thus renal and cardiovascular diseases.[18] Based on the results of this study, urine Pr/Cr ratio in captopril consumers was significantly less than others. However, there was no difference between the severity of coronary involvement between patients taking or not taking captopril. However, the positive coefficient of captopril consumption in table 2 indicates the increased severity of coronary artery disease in the regression model. Such finding might

have resulted from the cross-sectional design of the study with unknown time sequence in causality analysis which had possibly reversed the causal relationship. In other words, captopril might have been prescribed for patients with more severe cardiovascular disorders.

Finally, according to the results of this study, albuminuria is effective on the severity of CADs and can thus be used as an independent risk factor in the assessment of the disease. Therefore, controlling and modification of albuminuria through ACEI and ARB medications are a priority in the treatment of diabetic patients. Moreover, this relationship makes urine Pr/Cr ratio a screening test for investigating the severity of CAD in diabetic and even hypertensive patients.

Acknowledgment

The authors sincerely thank and appreciate the Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

The Persian version of this article has been previously published in Journal of Isfahan Medical School: 2009, No: 93; 75-84.

Conflict of Interests

Authors have no conflict of interests.

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