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Association of Albumin to Creatinine Ratio with Severity of Coronary Artery Disease

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ABSTRACT

Background: Coronary artery disease (CAD) is a major cause of mortality and morbidity in many countries. Atherosclerosis of coronary arteries is responsible for almost all cases of CAD. Pathology of endothelium is the main cause of atherosclerosis of coronary arteries. Coronary artery disease is affected by many factors and several different risk factors. **Objective:** To investigate the association between the level of microalbuminuria and the severity of coronary artery disease angiographically. **Patients and Methods:** The study was conducted on 100 patients who underwent coronary angiography in Cardiology department of Al-Azhar faculty and 6 October Cardiology Hospital on selective basis. The population study was divided into 2 groups according to microalbuminuria. Group (I): included 66 patients with angiographic evidence of coronary heart disease and without microalbuminuria. Group (II): included 34 patients with angiographic evidence of coronary heart disease and having microalbuminuria. **Results:** In the present study it was found that increased severity of coronary artery disease was more prevalent among patients with microalbuminuria compared to those with normo-albuminuria and the difference was statistically significant. **Conclusion:** Microalbuminuria is predictive for CAD independently with other risk factors. Microalbuminuria increase severity and number of CAD lesions and aggressive treatment of microalbuminuria may be beneficial in CAD patients.

Keywords: Coronary artery disease, Microalbuminuria, B-type natriuretic peptide

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and disability in many countries. Atherosclerosis of coronary artery due to endothelial pathology is the main factor for the majority of all cases of CAD. Coronary artery disease has many factors and several different risk factors; old age, male sex, hypertension, diabetes mellitus, cigarette smoking and dyslipidemia are the major and independent well known risk factors or CAD [(1)].

CAD risk factors do not entirely explain the variation in cardiovascular disease incidence and mortality between individuals and among populations. Other risk factors have been proposed to better identify patients who are potentially at risk of CAD. Many individual biomarkers have been related to cardiovascular risk, including levels of high sensitivity CRP (C-reactive protein), B-type natriuretic peptide (BNP) fibrinogen, D-dimer and homocysteine [(2)].

Among these new biomarkers is microalbuminuria (MA), which is gaining recognition as a good marker of an atherogenesis of coronary artery, owing to its association with several atherosclerotic risk factors and early systemic vascular endothelial damage [(3)].

An increasing number of studies in different patient populations have reported that MA is associated, independently of traditional risk factors, with all causes of cardiovascular morbidity and mortality in patients with diabetes, hypertension and in the general population [(4)].

Although a 24-hours urine collection is the gold standard for the detection of microalbuminuria, several studies have found that a urinary albumin to creatinine ratio is equally sensitive and specific [(5)].

Urinary albumin to creatinine ratio does not require early morning or timed collections, it gives a quantitative result that correlates with the 24-hour urine values over a wide range of protein excretion, it is cheap to perform, and repeat values can be easily obtained to ascertain that microalbuminuria, if present, is persistent [(6)].

AIMS OF THE WORK

Aims of this work are to observe the relationship between the albumin/creatinine ratio and the presence and extent of coronary artery disease, and to add microaluminuria as a simple marker to coronary artery atherosclerosis and compare it with other risk factors.

PATIENTS AND METHODS

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Study design:
This study included 100 patients with documented CAD as evident by elective coronary angiography. They were selected from patients' attending the Cardiology department of Al-Azhar Faculty of Medicine and 6 October Cardiology Hospital in the period between October 2017 and October 2018. **The study was approved by the Ethics Board of Al-Azhar University.**

Inclusion criteria:
Age: 30-80 years, either sex was included.

Exclusion criteria:
Liver insufficiency, renal insufficiency, recent urinary tract infection in the last 3 months, clinical heart failure, patients referred to G A G or C A D (disease of heart valves, congenital heart disease), patients of CABGA and PCI, patients who make weight reduction, patients who has co morbid condition.

Methods

Patients included in this study are subjected to the following: History taking with stress on history of risk factors for CAD (smoking, age, sex, hypertention ischemic heart disease, diabetic family history disease of coronary artery disease), clinical examination (pulse, blood pressure chest examination, cardiac examination, lower limb examination, jugular venous pressure, abdominal examination), laboratory investigations including: CBC, blood glucose level, blood urea, serum creatinine, lipid profile (cholesterol, triglycride HDL, LDL) and Urine sample for measurement of urinary albumin to creatinine ratio, Echocardiography, and coronary angiography.

Conventional Echo Doppler study: Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric-Vingmed). Images were obtained, with a simultaneous ECG signal. 2D images were acquired during breath hold and saved in cine-loop format from three consecutive beats. The biplane Simpson's technique was used to calculate LV end-systolic volume, LV end-diastolic volume, and LVEF [(7)].

Measurement of urinary albumin to creatinine ratio (ACR):

A- Measurement of urinary albumin:

Principle: Urinary albumin measured by ***Stanbio Total Protein LiquiColor*** based on the procedure developed by **Watanabe *et al.*** [(8)], which is a dye-binding colorimetric method utilizing pyrogallol red-molybdate complex and modified to equalize the reactivities of albumin and gamma globulin and provide good precision and linearity. The pyrogallol red is combined with molybdenum acid, forming a red complex with maximum absorbance at 470 nm. When this complex is combined with protein in acidic conditions, a blue-purple color develops with an increase in absorption to 610 nm.

Reagents: Total Protein Reagent, Cat. No. 0346: Buffered solution of pyrogallol red (2.6 mg/dL), sodium molybdate (19.4 mg/dL) and surfactants, pH 2.3.

Total Protein Standard, Cat. No. 0347 (100 mg/dL) Aqueous solution of serum albumin with sodium azide added as a preservative.

Specimen Collection and Preparation: Urine samples collected randomly. Store at 2-8°C or freeze the specimen until assayed. No special additives or preservatives are required.

B- Measurement of creatinine:

Principle Creatinine measured by ***creatinine jaffe`reaction.*** Creatinine reacts with picric acid under alkaline condition to form a yellow-red complex. The absorbance of the color produced, measured at wavelength. 492 nm, is directly proportional to creatinine concentration in the sample [(9)].

Reagent Preparation, Storage and Stability: Spectrum Creatinine reagent is supplied ready-to-use and stable up to expiry date labeled on the bottles when properly stored at 2-8 "C Thymol used for urine preservation. To determine creatinine concentration in urine, dilute 1 part sample with 49 parts isotonic saline prior to assay. Multiply result by 50 to compensate for dilution. Mix, and after 30 seconds read the absorbance A1 of the standard or specimen. After exactly 2 minutes later, read absorbance A2 of standard or specimen.

Calculation: Creatinine (mg/dl) = (A specimen /A standard) x 2 x 50. ***The ratio of urine albumin to creatinine (ACR) is used to defined microalbiminuria (normal ACR< 30mg/g & abnormal > 30 mg/g).***

Coronary angiography: The diagnostic procedure was performed by using Seldinger's technique via right femoral artery after performing local anesthesia with xylocaine. For better displaying the lesions, in order to make grading assessment possible, angiographies were performed in several views. The severity of CAD was scored on the basis of SYNTAX score. The SYNTAX score has been developed based on the following: The

AHA classification of the coronary tree segments modified for the ARTS study [10].

The ACC/AHA lesions classification system [11], the total occlusion classification system [12], the Duke and ICPS classification systems for bifurcation lesions, consultation of experts were used. Each of these classifications has been focusing on specific functional and anatomical parameters of the lesions. The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. The algorithm consists of **twelve** main questions. The first three determine the dominance, the total number of lesions and the vessel segments involved per lesion and their appear once. The maximum number of lesions allowed is twelve and each lesion is characterized by a number, 1 to 12. The lesions will be scored in the numerical order inserted in question 3. Each lesion can involve one or more segments. In this case each vessel segment involved contributes to the lesion scoring. There is no limit in the number of segments involved per lesion. The last nine questions refer to adverse lesion characteristics and are repeated for each lesion. The question referring to a total occlusion is the first one. If a total occlusion is scored, answers must be given to detailed sub-questions. The last of these sub-questions refers to the presence or absence of side branches and their size. If there are no side branches or if their diameter is <1.5 mm then the questions related to the trifurcation and bifurcation lesions will be automatically skipped since vessels <1.5 mm are not considered large enough for treatment either with PCI or CABG. If side branches with diameter 1.5 mm are involved then the lesion is considered as both total occlusion and bifurcation lesion and the algorithm will continue with all the questions. The same is the case for non-occlusive lesions. With the exception of the selection of the type in case of a bifurcation or a trifurcation lesion all the other questions of the algorithm can be answered by selecting "yes" or "no" [13].

Statistical analysis

Statistical analysis was performed using SPSS software version 17) SPSS, Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as numbers and percentages. Comparison of continuous variables among groups was made using the student's t-test. Associations between two categorical variables were tested using the Likelihood ratio χ^2 test, as appropriate. All tests of significance were two tailed and a p-value < 0.05 was considered statistically significant.

RESULTS

Table (1): Baseline characteristics of studied populations.

Group **Variable**	**Group I** (ACR ≤30) N 66 (66%)	**Group II** (ACR >30) N=34 (34%)	**Total**	**P**
Age(mean±SD)	54.06±14.17	52.47±15.08		0.604
Range	31-81	37-76		
Sex				
Male	47 (71.2%)	23 (67.7%)	70 (70.0%)	0.713
Female	19 (28.8%)	11 (32.3%)	30 (30.0%)	
DM Yes No	 31 (62%) 35 (70%)	 19 (38%) 15 (30%)	 50 (50.0%) 50 (50.0%)	0.35
HTN Yes No	 39 (59.1%) 27 (40.9%)	 24 (70.6%) 10 (29.4%)	 63 (63.0%) 37 (37.0%)	0.26
Smoking Non Smoker Current Smoker	 29 (43.9%) 17 (25.8%)	 19 (55.9%) 6(17.6%)	 48 (48.0%) 23 (23.0%)	0.49
Ex smoker	20 (30.3%)	9 (26.5%)	29 (29.0%)	
Dyslipidemia Yes No	 24 (36.4%) 42 (63.6%)	 12 (35.3%) 22 (64.7%)	 36 (36.0%) 64 (64.0%)	0.916
+ Ve family				
history of CAD Yes No	 14 (21.2%) 52 (78.8%)	 3 (8.8%) 31 (91.2%)	 17 (17.0%) 83 (83.0%)	0.20

HTN: Hypertension *ACR*:Albumin to creatinin ratio
DM: Diabetes mellitus
CAD: Coronary artery disease

The mean age was (54 ± 14) years V.S (52 ± 15) years in group I & group II respectively (P 0.6), (70%) were males, 50% were diabetics, 63% had hypertension,36% had dyslipidemia, smokers either current or prior represented 52% of patients and positive family history of coronary artery disease respresented 17% of

the study population. There was no statistically significant different between either group in demographie data

Table (2): Comparison between numbers of vessels affected per patients and diabetes mellitus:

In diabetic group:28 patients (56%) had one vessel disease while 22 patients (44%) had two or more vessels disease

In non diabetic group: 33 patients (66%) had one vessel disease while 17 patients (34%) had two or more vessels disease

So, the relation was not statiscally significant (p value = 0.31)

Pt Vessels no.	Non diabetic group	Diabetic Group	Total	P Value
One vessel	33 (66%)	28 (56%)	61 (61%)	0.31
Two or more Vessels	17 (34%)	22 (44%)	39 (39%)	
Total	50(100%)	50(100%)	100 (100%)	

Table (3): Comparison between numbers of vessels affected per patients and hypertension.

Hypertensive group:37 patients (58.7%) had one vessel disease while 26 patients (41.3 %) had two or more vessels disease

Normotensive group: 24 patients (64.9%) had one vessel disease while 13 patients (35.1%) had two or more vessels disease

So, the relation was not statiscally significant (p value = 0.54)

Pt Vessels no.	Normotensive	Hypertensive	Total	P Value
One vessel	24(64.9%)	37(58.7%)	61 (61%)	0.54
Two or more Vessels	13(35.1%)	26(41.3%)	39 (39%)	
Total	37(100%)	63(100%)	100 (100%)	

Table (4): Comparison between numbers of vessels affected per patients and dyslipidemia.

Dyslipidemic group**:** 25 patients (69.4%) had one vessel disease while 11 patients (30.6 %) had two or more vessels disease

Non dyslipidemic group**:** 36 patients (56.3%) had one vessel disease while 28 patients (43.7%) had two or more vessels disease

So, the relation was not statiscally significant (p value =0.19)

Pt Vessels no.	Non dyslipidemic group	Dyslipidemic group	Total N= 100	P Value
One vessel	36(56.3%)	25(69.4%)	61 (61%)	0.19
Two or more Vessels	28(43.7%)	11(30.6%)	39 (39%)	
Total	64(100%)	36(100%)	100 (100%)	

Table (5): Comparison between numbers of vessels affected per patients and family history of CAD.

+ve family history group**:** 13 patients (76.5%) had one vessel disease while 4 patients (23.5%) had two or more vessels disease

-ve family history group**:** 48 patients (57.8%) had one vessel disease while 35 patients (42.2 %) had two or more vessels disease

So, the relation was not statiscally significant (p value =0.25)

Pt Vessels no.	-ve FH group	+ve FH group	Total	P Value
One vessel	48(57.8%)	13(76.5%)	61 (61%)	0.25
Two or more Vessels	35(42.2%)	4(23.5%)	39 (39%)	
Total	83(100%)	17(100%)	100 (100%)	

Table (6): Comparison between numbers of vessels affected per patients and sex.

Male patients**:** 43 patients (61.4%) had one vessel disease while 27 patients (38.6%) had two or more vessels disease

Female patients: 18 patients (60%) had one vessel disease while 12 patients (40 %) had two or more vessels disease

So, the relation was not statiscally significant (p value =0.89)

Pt Vessels no.	Male	Female	Total	P Value
One vessel	43(61.4%)	18(60%)	61 (61%)	0.89
Two or more Vessels	27(38.6%)	12(40%)	39 (39%)	
Total	70(100%)	30(100%)	100 (100%)	

Table (7): Comparison between numbers of vessels affected per patients and smoking.

***Current smoker group*:** 15 patients (65.2%) had one vessel disease while 8 patients (34.8%) had two or more vessels disease

***Ex smoker group*:** 19 patients (65.5%) had one vessel disease while 10 patients (34.5 %) had two or more vessels disease

Non smoker group: 27 patients (56.3%) had one vessel disease while 21 patients (43.7 %) had two or more vessels disease

So, the relation was not statistically significant (p value =0.65)

Pt Vessels no.	Non smoker	Ex-smoker	Current smoker	Total	P Value
One vessel	27(56.3%)	19(65.5%)	15(65.2%)	61 (61%)	0.89
Two or more Vessels	21(43.7%)	10(34.5%)	8(34.8%)	39 (39%)	
Total	48(100%)	29(100%)	23(100%)	100 (100%)	

Table (8): Linear regression analysis to show the independent effect of ACR on risk of CAD:

There are direct relationship between ACR, number of vessels affected and syntax score (P value 0.001)

ACR	R	P value
No of vessels	0.919	0.001 HS
Syn score	0.888	0.001 HS

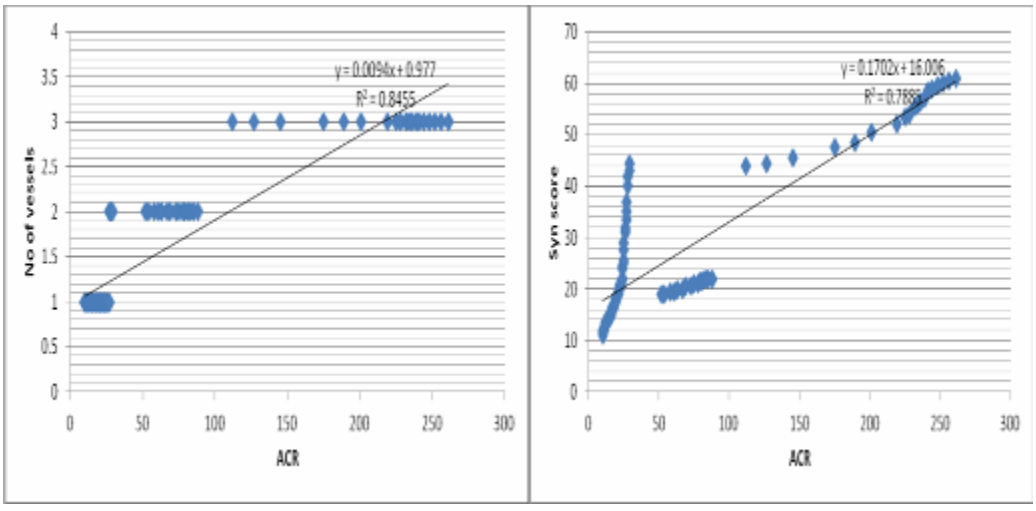

Figure (1): Relation between ACR vs numbers of vessels affected and Syntax score.

DISCUSSION

The risk factor of coronary artery diseases (CAD) is predicted by traditional risk factors including age, sex, smoking, diabetes mellitus, hypertension and dyslipidemia. However, these factors don't

entirely explain the variation of CAD incidence and mortality in individuals and populations in all around the world [1].

Non-traditional cardiovascular risk factors and reside concentration of urinary albumin is one of these factors. Microalbuminuria is predictive, and simple factor independent of classical risk factors of cardiovascular diseases and is associated with all–cause mortality and cardiovascular morbidity and mortality in patients with Diabetes, hypertension and in the general population [2].

Although the association between microalbuminuria and cardiovascular events is well described, few studies had examined the correlation of angiographic severity of CAD with microalbuminuria. So, the purpose of this study was to observe relationship between microalbuminuria and presence and extent of coronary artery disease. Urinary albumin to creatinine ratio does not require early morning or timed collections, it gives a quantitative result that correlates with the 24- hour urine values over a wide range of protein excretion, it is cheap to perform, and repeat values can be easily obtained to ascertain that microalbuminuria, if present, is persistent [6].

In the present study the albumin/ creatinine ratio (ACR) was estimated in 100 patients with angiographically- evident CAD to show if there is any correlation between microalbuminuria and severity of CAD.

Urinary albumin was measured by ***Stanbio Total Protein Liqui Color*** based on the procedure developed by **Watanabe *et al.*** [8]. Creatinine was measured by ***creatinine jaffe` reaction*** [9]. The ratio of urine albumin to creatinine (ACR) was used to define microalbiminuria. The upper normal limit is 30 mg/g.

In the present study, about one third of studied patients had abnormal ACR (group II), while the other two-third had their ratio normal (group I). ***Group I*** included 66 patients (66%) and ***group II*** 34 patients (34%).

This was concordant with that reported by **Parsa *et al.*** [14] who enrolled 77 patients,16 patients (21 %) had microalbuminuria and 61 (79%) of patients were normal regarding microalbuminuria.

Also, concordant with the results of the present study, **Hashim *et al.*** [15] found that 37% of their ischemic heart patients, had microalbuminuria and 63% had normoalbuminuria.

On the other hand **Parvizi *et al.*** [16] studied 228 ischemic heart patients and found that the level of albumin in all the studied patients was > 300mg/24h. The cause of the discrepancy between the results of the present study and later study may attributed to different no. of patients studied, different methods of evaluation or the different types of population studies.

The present study showed that 52 patients (78.8%) in group I had only one vessel affected and 14 patients (21.2%) had two or more vessels affected while in Group II 9 patients (26.5%) had one vessel affected and 25 patients (73.5%) had two or more vessels affected (p=0.001). So, patients with ACR >30 had more atherosclerotic burden in the form of multi-vessel disease than those with ACR < 30.

These results were concordant with **Hoseini *et al.*** [17] who found that patients with microalbuminuria (MA) compared with the controls had increased prevalence two (50% vs. 22.2%, $p \leq 0.001$), and three vessel disease (29.2% vs. 19.8%, $p \leq 0.001$).

Also, similar results were exhibited by **Sukhija *et al.*** [18] who found that the prevalence of two and three vessels disease increased in patients with microalbuminuria compared with the controls independent of other risk factors (p value <0.001).

Finally, **Parvizi *et al.*** [16] who studied 228 patients, all of them had albumin level > 300mg/24h, found that 114 patients with two diseased vessels and 114 patients with three diseased vessels.

In our study, 50 patients (75.8%) in ***group I*** had a low syntax score < 22 and 16 patients (24.2%) had an intermediate or high score >22, while in ***group II,*** 15 patients (44.1%) had a low syntax score <22 and 19 patients (55.9%) had an intermediate or high score >22,so there is a strong relationship between the presence of microalbuminuria and the extent and complexity of CAD (p= 0.001).

This was in concordance with ***Parsa et al.*** [14] who found that microalbuminuria was accompanied with higher Gensini score,which was statistically significant (p value < 0.001). Also **Bildirici *et al.*** [19] found a positive correlation between Gensini score and ACR (p value =0.01). Another study performed by **Ahmed** [20] found that patients with microalbuminuria had higher Gensini scores compared to those with no microalbuminuria, (73.1 ± 40 versus 43.6 ± 30.6 respectively, P value <0.001).

In our study the relation between number of vessels affected per patients and sex was not statiscally significant, 43 patients (61.4%) of ***males*** had one vessel disease while 27 patients (38.6%) had two or more vessels disease, and 18 patients (60%) of

female had one vessel disease while 12 patients (40 %) had two or more vessels disease, (p value =0.89). The same result was doucemented by **Parsa *et al.*** [14] (p value =0.31).

On the other hand **Bildirici *et al.*** [19] exhibited slightly male predominance in patients with multi-vessel CAD, Also **Hoseini *et al.*** [17] found that coronary artery disease occurred more frequently in males than in females (p value =0.053). This diversity could be due to differences in sample size, survey period, race, medications and geographic or nutritional factors.

Additionally, our study exhibited that no significant relation between number of vessels affected per patients and diabetes mellitus, 28 patients (56%) ***in diabetic group*** had one vessel disease while 22 patients (44%) had two or more vessels disease, ***in non diabetic group:*** 33 patients (66%) had one vessel disease while 17 patients (34%) had two or more vessels disease (p value = 0.31).

This result was concordant with **Sukhija *et al.*** [18] who found that the prevalence of two and three vessels disease was more in (DM+ MA+, n =101) group than (DM+ MA-, n =101), without dependent on DM as a risk factor.

Also **Hoseini *et al.*** [17] investigated the relation between microalbuminuria and the prevalence and severity of angiographically confirmed CAD in *nondiabetic* patients, found that microalbuminuria is associated with the increase prevalence of two and three vessels disease, not dependent on DM as a risk factor.

In addition, the present study found no significant relation between number of vessels affected per patients and smoking. ***Current smoker group*** had 15 patients (65.2%) with one vessel disease while 8 patients (34.8%) had two or more vessels disease, ***smoker group*****:** 19 patients (65.5%) had one vessel disease while 10 patients (34.5 %) had two or more vessels disease and ***non smoker group:*** 27 patients (56.3%) had one vessel disease while 21 patients (43.7 %) had two or more vessels disease (p value =0.89).

Parsa *et al.* [14] also found the same result (p value =0.43), but **Hoseini *et al.*** [17] found that the number of vessels affected and severity of CAD are higher in smokers than in non- smokers. (p value 0.008,0.01 respectively).The cause of the discrepancy may attributed to small no. of patients studied, different methods of evaluation or the different types of population studies.

Also, our study found no significant relation between numbers of vessels affected per patients and hypertension and family history (p value = 0.54, 0.25 respectively). This result was concordant with **Bildirici *et al.*** [19] (p value = 0.35, 0.46 respectively).

Finally, the presenting study found no significant relation between ACR and ejection fraction. ***In group I,*** the mean EF % is 55 % while in ***group II,*** the mean EF % is 54 %, which is statistically insignificant (P value = 0.591), this finding is not previously discussed in other studies.

The linear regression analysis in *Scatter diagram (1)* revealed urinary albumin to creatinine ratio (ACR) is an ***independent*** predictor for risk of CAD (number of vessels affected and SYNTAX score) (P value 0.001).

There is possible pathophysiologic mechanism that relating ACR to risk and extent of CAD. Microalbuminuria reflects vascular endothelial permeability and has been associated with many inflammatory processes [21]. Microabuminuria is closely linked to vascular endothelial function by mechanisms which might represent common pathway for the development of both large and small vessel disease [19].

This makes MA a possible marker of vascular disease activity rather than simply a marker of cardiovascular risk [22].

Pedrinelli *et al.* [23] found that patients with MA had higher plasma level of Von Willebrand factor (vWF) antigen than patients with normal albumin excretion. VWF has been associated with occlusive thrombi, thus the increased plasma vWF levels might directly contribute to the enhanced cardiovascular risk. In addition, **Clausen *et al.*** [24] suggested that the degree of vasodilatation in response to certain stimuli is relatively reduced in individuals with MA compared to those without MA.

Indeed, MA is now gaining recognition as a marker of atherogenesis, owing to its association with several coronary risk factors (especially diabetes and hypertension) and early systemic vascular endothelial damage [24]. It seems that microalbuminuria increase severity and number of CAD lesions and aggressive treatment of microalbuminuria may be beneficial in CAD patients [24].

CONCLUSION

About one-third of patients with angiographically evident CAD, have microalbuminuria. This group of patients was found to have more severe coronary artery disease compared to those with normal albumin excretion.

The albumin/creatinine ratio is an independent risk factor for presence and severity of CAD in this study. A larger studies involving multicenters and a large number of patients are need to confirm these results and to consider this ratio among coronary risk factors.

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