Microalbuminuria, Cardiovascular Morbidity, and Mortality in Diabetic and Non–Diabetic Subjects in Kirkuk City

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Abstract

Ischemic heart disease (IHD) which, leading cause of death in industrialized nations.
Traditional risk factors for (IHD) such as hypertension, smoking, diabetes, and hyperlipidemia may not be able to predict cardiovascular events accurately in male and female. Early detection and prevention of (IHD), especially among the elderly, remains a major public health issue. The aim of this study was estimate the frequency of microalbuminuria in patients with and without diabetes mellitus (DM), answering the question: 'How relevant for general practice are epidemiological findings that microalbuminuria is a significant risk indicator for the development of cardiovascular syndromes?' and analyze prospectively whether the urinary albumin to creatinine (A/C) ratio can indepenendently predicts ischemia heart disease (IHD) in a population suffering from diabetes mellitus (DM) in Kirkuk city.

The study group conducted on (120) patients with (IHD) and (DM) their age ranging between (20-79) years and (100) aged matched health control subjects .The males consisted (52.27%) of the total patients, while females (47.73%). They characterized by sex, age, body mass index (BMI), blood pressure (Bp), fasting blood glucose (FBG), serum albumin and creatinine.

An interaction between microalbuminuria and IHD with DM was observed, and presence of microalbuminuria more than doubled predictive effect of the conventional atherosclerotic risk factor for development of IHD. Urinary albumin/creatinine ratio is recommended for microalbuminuria assessment, because it reflects urinary albumin excretion. Muscular mass could affect albumin/creatinine ratio, because urinary creatinine reflects muscular mass. Prevalence showed significant higher in the normal male than female

individuals and this attributed to the difference in the lean muscle mass between the two sex and more fragrantly in (BMI) of (24-26) Kg/m^2 in male groups than females. The relationship of obesity on microalbuminuria and (IHD) was statistically significant the (P) values was found to be (<0.05) in the both sexes.

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The prevalence of the patient groups suffering from previous signs of (IHD) with type (I) diabetes mellitus in the nonhigh (uACR) groups were (23.3%), high (uACR) without microalbuminuria groups were (30%) and high (uACR) with microalbuminuria groups were (46.7%) while in the groups with patient suffering from previous signs of (IHD) with type (II) diabetes mellitus were (20%),(32.2%) and (47.7%) respectively. The excess of the patient groups suffering from previous signs of (IHD) with type (II) diabetes mellitus prevalence in the high (uACR) groups reflected the combination of dissimilar data between the subgroups with and without microalbuminuria .In comparison to the nonhigh (uACR), the patient groups suffering from previous signs of (IHD) with type (II) diabetes mellitus prevalence was significantly increased ($P<0.05$) in the high (uACR) subgroup with microalbuminuria but not in the high (uACR) subgroup without microalbuminuria

Introduction

Microalbuminuria, slightly elevated urinary albumin excretion, was initially demonstrated in the patient with diabetes mellitus, where it was shown to be associated with atherogenic changes in the cardiovascular risk profile[1,2] and to predict increased mortality and cardiovascular disease[3,4,5] .

Several studies have demonstrated an associated between slightly increased urinary albumin execrations and cardiovascular risk factors, even in the general population [6]. Microalbuminuria is an independent predictor of cardiovascular disease and all case mortality in both diabetic [3] and non-diabetic men and women [7] and may be stronger indicator for future cardiovascular events the systolic blood pressure (SBP) or serum cholesterol[7]. Detecting microalbuminuria is an important screening tool to identify people who are at high risk for cardiovascular events and the progression of kidney disease and who need more intensive therapy compared with the subjects with the normal albumin execration rates[8].

Diabetes mellitus (DM), the most common endocrine is a specific clinical syndrome due to absolute (type I) or relative (type II) deficiency of insulin. Its incidence is rising in

developed [9] and development countries [10] .An estimated 2.1% of the world's population as diabetes [11] but almost 50% of cases of type (II) remain undetected [10].

Microalbuminuria the most reliable indicator of diabetes, also predicates development of cardiovascular disease (CVD) which has been reported to count for almost 80% of deaths in diabetes[12] .Many explanations have been suggested for the association of microalbuminuria with

(CVD) such as endothelial dysfunction, hypertension, dyslipidemia, insulin resistance, smoking [9,13] and advanced glycated proteins[14].

In addition to that, left ventricular hypertrophy, which occurs early in the course of diabetic nephropathy, is an independent risk factor for myocardial ischemia and sudden death [15]. In diabetic pregnancies, preexisting microalbumin also predicts the development of preeclampsia, which is substantially increased in incidence and is associated with higher maternal and perinatal morbidity and mortality[12].

Screening for microalbumin is recommended for type (I) patients annually from (5) years after diagnosis and for type (II) patients annually from the time of diagnosis [16].

Now made more convenient by the adyent of a reliable urine dipstick method and the ability to concomitantly measure creatinine in a random urine sample, and thus yields an albumin: creatinine ratio[17] this methods when compared with albumin concentration , it had a better performance in screening for microalbumin[10]. The aim of this study was to estimate the frequency of microalbuminuria in patients with and without diabetes mellitus, answering the question: 'How relevant for general practice are epidemiological findings that microalbuminuria is a significant risk indicator for the development of (IHD).

Materials and Methods

The study group conducted on (120) patients with (IHD) and (DM) their age ranging between (20-79) years and (100) aged matched health control subjects who showed no protein urea by dipstick and sulfosaliculic acid test.

The males consisted (52.27%) of the total patients, while females (47.73%). The (IHD) groups comprised of patients with myocardial infarction (MI), and angina pectoris admitted to the cardiac care unit (CCU). The healthy control group subjects were voluntaries. They had normal resting electrocardiogram (ECG), had no history of (IHD), hypertension (HT) or diabetes mellitus (DM).

Blood and urine sample were obtained from patients with (IHD and DM) and volunteers after an overnight fasting (10-16 hours). Blood samples were drowning from the antecubital vein and then serum was separated by centrifugation at (3000 rpm) for (10 minutes). Then divided into two tubes. One of these tubes was used immediately and the other were stored at (– 30oC) prior to analysis. Each sample was measured three times and means results was calculated.

DM has been classified as type (I) based on insulin decency to overcome proneness to ketoacidosis at any stage of the disease, age of onset below (30) years, and if insulin therapy has

been started with in (2) years of diagnosis, otherwise it was classified as type (II) [18] . We obtained data on blood pressure, weight, height, fasting blood glucose (FBG)[19], serum creatinine by using Jaffe methods [20] serum albumin by using Bromocresol green methods [21].

Hypertension was defined as diastolic pressure ≥95 mmHg and systolic pressure ≥ 160mmHg and or use of antihypertensive drugs [22].

Information about smoking habits and dietary intake was obtained with standardized questionnaires [23].Subjects were classified as having normal albuminuria, when the mean albumin to creatinine ratio was ≤ 2.0 mg /mmol and as having (micro) albuminuria when the albumin /creatinine ratio was > 2.0 mg/mmol as high sensitivity to detect an albumin excretion rate > 30µg/min[24].

A fasting serum and urine sample from each patient was tested for albumin by using the Bromocresol green (BCG) methods [21]. Although this methods is constructed for serum albumin, but it has shown good results for measuring urinary albumin after some sort of interference study has been performed and recovery test proved the result[25].Serum and urine creatinine was also determined by the using the same methods except that the urine was diluted (50) times with the distilled water[22]. The concomitant measurement of urinary albumin and creatinine yields and albumin, creatinine ratio (ACR) the normal range is < 2.5 mg albumin/ mmol creatinine in males and4.5mg/ mmol in females because of their lower creatinine execration; borderline range is up to 10 mg / mmol; while the microalbuminuria range (positive test) is > 10 mg/ mmol up to 30 mg/ mmol[16].

Albumin / creatinine ratio and urinary albumin excretion rate (ACR) are used to detected microalbuminuria execration (excessive albumin execration) in-patient with DM, which is of predictive value to identify. Data were examined for statistical differences using Chi-square test (χ-2).Student t-test, statistical significance levels were ($P<0.05$). The Duncan multiple range test was carried out in order to test the differences between the mean of each groups and their risk factors included in the study within the sex and age [26].

Results and Discussions

The distributions of sex and age among all groups of subjects studied were given in Table (1).
It showed that highest frequency (52.27%) were recorded among males while (47.73%) females. It was seen in both sexes the patient that suffers from previous signs of (IHD) with type (II) diabetes mellitus more obvious which was (51.52%) in the male while in female were (41.94%).It has been found that estrogen produced by the premenopausal females protect them from hypertension

[27,28] because estrogens and progestrogens both possess mineralocorticoid and glucocorticoid properties that predispose to hypertension and (DM). The table also showed that the correlation between (IHD) with history of (DM) and sex were statistically significant the P values found to be (<0.005).

Table (1): The proportion of ischemic heart disease (IHD)cases compared to control groups according to history of diabetes mellitus (DM) and sex

Type of DM	Male *No.* (%)*		Female *No.* (%)*		Total
	Control	IHD	Control	IHD	
Type I	6(12.24)	21(31.82)	4(9.30)	17(27.42)	48
Type II	5(10.20)	34(51.52)	7(16.28)	26(41.94)	72
Not patient	38(77.55)	11(16.67)	32(74.42)	19(30.65)	100
Total	49	66	43	62	220
	115(52.27)		105 (47.73)		

- *No*: Number of case, % :Percentage, *: (P< 0.005)

The our results showed that the (mean ± SD) of serum Albumin, creatinine and Albumin/Creatinine ratio (ACR) in the control subject were (3.9 ± 0.59g/dL), (1.1 ± 0.092mg/dL) and (3.59± 4.41g/mg) respectively as shown in Table (2) and Figure (1).

Table (2):- Details of serum Albumin, Creatinine and Albumin, Creatinine ratio (ACR) according to sex in control and patient suffering from previous signs of (IHD) with type (I) and type (II) diabetes mellitus (DM)

	Sex	*No.*	Mean± SD S. Albumin (g/dL)*	Mean± SD S. Creatinine (mg/dL)**	Ratio S. Albumin /S. creatinine (g/ mg)
Control	Male	49	4.1±0.32	1.0 ± 0.06	4.1 ± 0.37
	Female	51	3.7± 1.3	1.2 ± 0.092	3.08± 2.2

	Both	100	3.9 ±0.59 a	1.1 ± 0.092 a	3.59 ±4.41 a
IHD with type (I) DM	Male Female	17 13	5.0±0.92 4.8±1.91	1.37 ± 0.21 1.39 ±0.11	3.65 ±1.18 3.45 ± 0.09
	Both	30	4.9±2.41 b	1.38 ±0.183 b	3.55 ±2.3 ab
IHD with type (II) DM.	Male Female	43 47	5.5±5.3 5.2±4.1	1.48 ±0.04 1.47 ± 2.3	3.7± 1.52 3.54 ± 0.11
	Both	90	5.4 ±1.3 bc	1.48 ±0.74 c	3.61 ± 0.62 ab

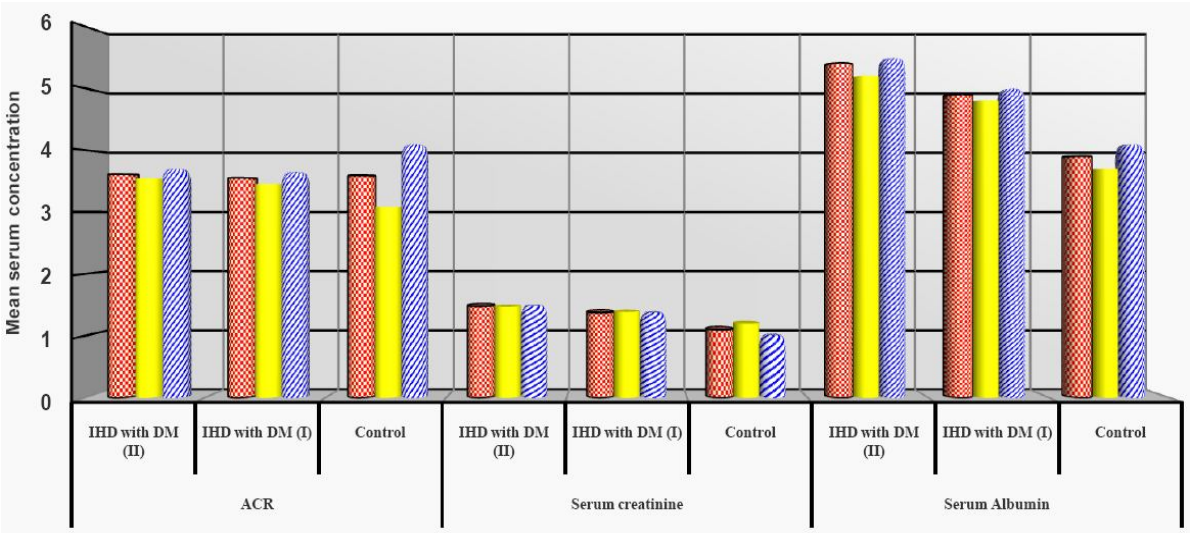
*To conversation Albumin from g/dL multiply to 10 g/L.

** To conversation creatinine from mg/dL to µ mol/L multiply it to 88.4.

-In vertical columns, similar letters means, not significant.

It has been recorded that the levels of serum albumin in the patient suffering from previous signs of (IHD) with type (I) diabetes mellitus were statistically significant (P< 0.025) in comparison with control groups but insignificant in these value when comparison with the patient suffering from previous signs of (IHD) with type (II) diabetes mellitus . Mahmoud TJ et al.[29] obtained in his study the same results and this is attributed to pre-renal; renal and post- renal causes.

The most important of the pre-renal causes, are the cases in which there is dehydration with reduced volume of body fluids and so of plasma volume which leads to reduced gloumer filtration rate (GFR) and similar values for serum creatinine were obtained by Robert et al.[30] and Mohan et al.[31] in diabetics. It has been also found in the same table the statistically significant (P<0.005) in the level of serum albumin when comparison control groups with the groups of the patient suffering from previous signs of (IHD) with type (II) diabetes mellitus. While, El-Hazmi, et al.[32] in a study carried out on Saudi Arabian's population found that the range of serum creatinine level was (0.5-1.3) mg/dL. The results of these workers are similar to our results. In the same table the level of serum creatinine showed statistically significant (P<0.005) in the all groups, while the values of serum (ACR) in the same groups in correlation to control groups was statistically insignificant.



	ACR			Serum creatinine			Serum Albumin		
	IHD with DM (II)	IHD with DM (I)	Control	IHD with DM (II)	IHD with DM (I)	Control	IHD with DM (II)	IHD with DM (I)	Control
Male	3.7	3.65	4.1	1.48	1.37	1	5.5	5	4.1
Female	3.54	3.45	3.08	1.47	1.39	1.2	5.2	4.8	3.7
Both	3.61	3.55	3.59	1.48	1.38	1.1	5.4	4.9	3.9

Figure (1):- (A)-mean S.albumin (g/dL),(B) mean S.creatinine(mg/dL),(C) mean S.Albumin/Creatinine Ratio (ACR)(g/mg) conceration in control and ischemic heart disease (IHD) patient suffering from type (I) and (II) diabetic according to sex

Table (3):- Association of Microalbuminuria with body mass index (BMI) of patients suffering from (IHD) with type (I) & (II) diabetes mellitus

BMI (Kg/m^2)	Males *No.* (%)*			Females *No.* (%)*			Total
	control	IHD & type (I) DM	IHD & type (II) DM	control	IHD & type (I) DM	IHD &Type (II)DM	
<21	3(6.1)	0(0)	1(2.2)	4(9.3)	0(0)	2(4.1)	10
21-23	5(10.2)	2(9.5)	4(19)	8(18.6)	1(7.7)	5(10.2)	25
24-26	21(42.9)	3(14.3)	5(11.1)	9(20.9)	2(15.4)	7(14.3)	49
27-29	10(20.4)	4(19)	9(20)	12(27.9)	4(30.8)	10(20.4)	51
30-32	8(16.3)	10(47.6)	22(48.9)	6 (14)	6(46.2)	19(38.8)	67
>32	2(4.1)	2(9.5)	4(8.9)	4(9.3)	0(0)	6(12.2)	18
Total	49	21	45	43	13	49	220

- *No.*: Number of case, % :Percentage , *: (P<0.05)

Regarding the distribution of microalbuminuria with body mass index (BMI) in control and the patient suffering from previous signs of (IHD) with type (I) and (II) diabetes mellitus were shown in the Table (3) and Figure (2).

They showed that the control groups in males were more frequently in (BMI) of (24-26) Kg/m2 than females and this is similar to results obtain by El.Hazumi, et.al.[32],Wilding. et al.[33],and Al.Kubasiy[34]which showed significant higher in the normal male than female individuals and this attributed to the difference in the lean muscle mass between the two sex.

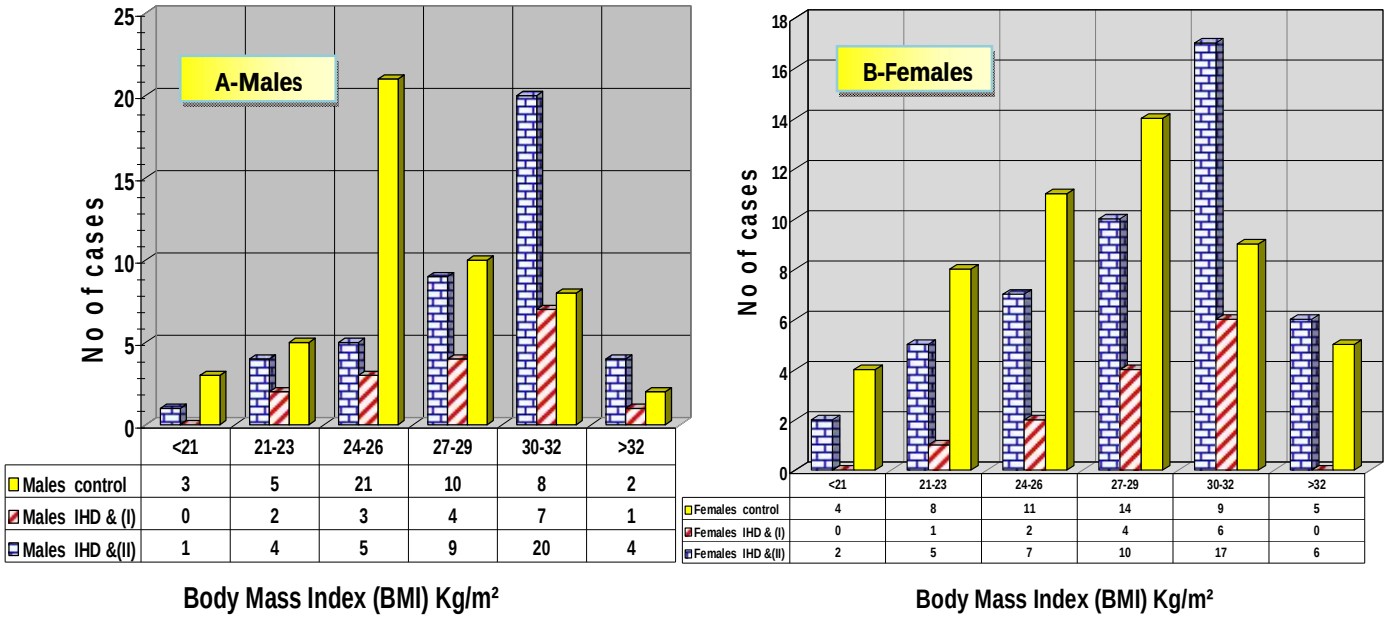


Figure (2):-The proportion of Microalbuminuria according to sex(A-Males, B-Females)

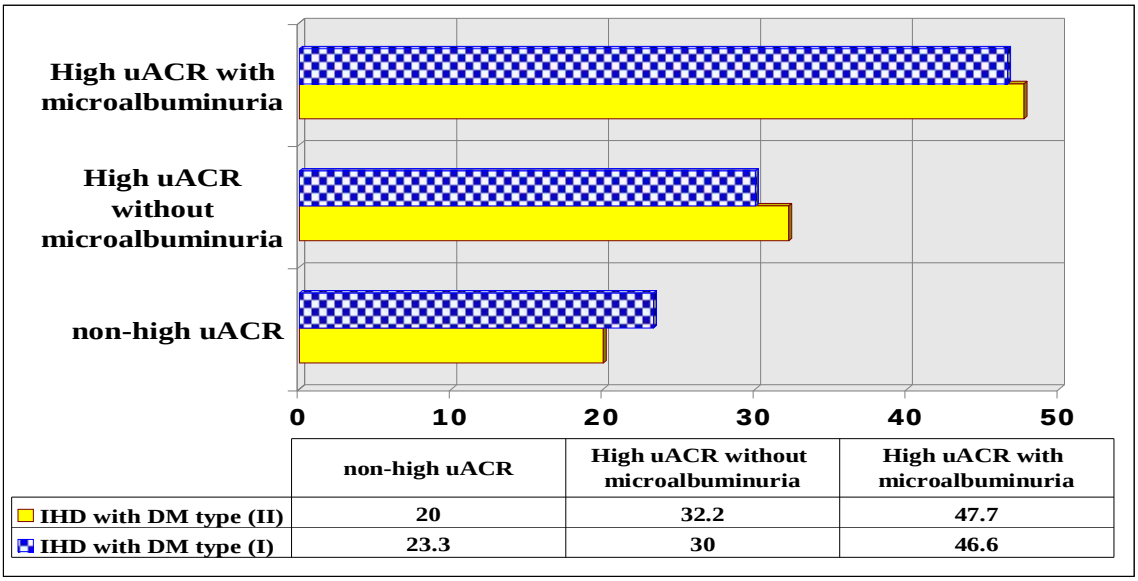
In the same figure also showed the patient groups suffering from previous signs of (IHD) with type (II) diabetes mellitus were high frequency in the males than females in (BMI) of (30-32)Kg /m^2 ,the same results was detected in patient suffering from previous signs of (IHD) with type (I) diabetes mellitus in female groups. The relationship of obesity on microalbumin and (IHD) was statistically significant the (P) values was found to be (<0.05) in the both sexes.

The females groups in control subjects was significant higher (P<0.05) when comprise with the males groups this similar to the results obtained by Warwood[35] which found similar results and concluded that to insulin resistance in patients with the type (II) DM which is associated with obesity.

Figure (3) shows data for male and female combined on the patient suffering from previous signs of (IHD) with type (I) and (II) diabetes mellitus prevalence in the group of persons with nonhigh

urinary albumin creatinine ratio (uACR). Persons with high (uACR) were also analyzed as two subgroups: the subgroups without microalbuminuria and the subgroup with microalbuminuria.

The patient suffering from previous signs of (IHD) with type (II) diabetes mellitus prevalence was significantly higher in the patients group with high (uACR) than the patient groups with nonhigh (uACR). Findings were similar for the patients groups suffering from previous signs of (IHD) with type (I) diabetes mellitus,(prevalence of the patient groups suffering from previous signs of (IHD) with type (I) diabetes mellitus in the nonhigh (uACR) groups were (23.3%), high (uACR) without microalbuminuria groups were (30%) and high (uACR) with microalbuminuria groups were (46.7%) while in the groups with patient suffering from previous signs of (IHD) with type (II) diabetes mellitus were (20%),(32.2%) and (47.7%) respectively).



	non-high uACR	High uACR without microalbuminuria	High uACR with microalbuminuria
IHD with DM type (II)	20	32.2	47.7
IHD with DM type (I)	23.3	30	46.6

Figure (3) :- Comparison of IHD with type (I&II)DM prevalence between person with nonhigh (uACR) group , high (uACR) without microalbuminuria groups and high (uACR) with microalbuminuria. P values are by $\chi 2$ analyses in comparison with persons with nonhigh (uACR).

The excess of the patient groups suffering from previous signs of (IHD) with type (II) diabetes mellitus prevalence in the high (uACR) groups reflected the combination of dissimilar data between the subgroups with and without microalbuminuria .In comparison to the nonhigh (uACR), the patient groups suffering from previous signs of (IHD) with type (II) diabetes mellitus prevalence was significantly increased ($P<0.05$) in the high (uACR) subgroup with microalbuminuria but not in the high (uACR) subgroup without microalbuminuria. In the present study, we found that microalbuminuria is predictor of the development of (IHD), independent of other established atherosclerotic risk factor such as sex, arterial, hypertension, dyslipidemia, smoking, old age, and

obesity. The general effect of microalbuminuria in this study was that the risk associated with conventional risk factors was more than doubled when the individual had microalbuminuria as well. The specific pathogenic mechanisms behind this association are still poorly understood. We have previously shown that healthy individuals with microalbuminuria have a generalized increase in transvascular escape of albumin [36]. In animals, increased transvascular albumin transport is associated with an increased transport of lipoproteins into the arterial wall,[37,38] and therefore we speculated that microalbuminuria might be a marker of increased susceptibility to the atherogenic effect of other established risk factors rather than a classic risk factor per se (ie , directly involved in the pathogenic mechanism). However, no significant interaction was observed between microalbuminuria and dyslipidemia for the development of (IHD) in this study. It is concluded that microalbuminuria is not only an independent predictor of IHD but also substantially increases the associated with other established risk factors.

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