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ORIGINAL ARTICLE

Association of microalbuminuria with ischemic heart disease in non-diabetic Asian-Indians: A case control study

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ABSTRACT

Context: Microalbuminuria is a known indicator of atherosclerosis and its association with ischemic heart disease (IHD) has been extensively studied in the diabetic population. The significance of urine microalbumin in non-diabetics, however, is yet to be elucidated. **Aim:** To determine whether an independent association exists between microalbuminuria and IHD in non-diabetic Asian-Indians, and the level of microalbuminuria predictive of concomitant IHD. **Materials and Methods:** A cross-sectional case-control study was conducted between July 2009 and June 2011. Non-diabetic patients undergoing evaluation for IHD were divided into cases and controls, based on the presence or absence of IHD, respectively. Fifty cases and 50 controls were included, and matched by age, sex, smoking habit, hypertension and body-mass index (BMI). Fasting blood glucose (FBG), fasting lipid profile, and urine microalbumin were recorded for all patients. **Results:** Mean fasting glucose, mean low density lipoprotein (LDL)-cholesterol and mean urine microalbumin were all significantly higher in cases compared to controls. Urine microalbumin was independently associated with IHD, and microalbumin greater than 12.6 mg/g was predictive of IHD (OR: 13.5; 95% CI, 4.6–39.9; $P < 0.001$). **Conclusion:** Urine microalbumin is independently associated with IHD in non-diabetics and levels greater than 12.6 mg/g are predictive of IHD.

Key words: Asian-Indian, ischemic heart disease, microalbuminuria, non-diabetic

INTRODUCTION

Ischemic heart disease (IHD) has now become one of the leading causes of death worldwide, accounting for more than 7.3 million deaths in 2008 alone.[1] Moreover, over 80% of cardiovascular deaths now occur from low- and middle-income countries.[2] Of these deaths, again over 25% occur in the South Asian region, so that cardiovascular disease is now responsible for 24% of all deaths in India.[3] The situation is further grim by the fact that an estimated 31.8 million Indians currently live with IHD; the death rate from cardiovascular disease in India is projected to rise by an astounding 111 percent over rates in 1990 by 2020,[4] with IHD contributing the bulk.[5] These alarming figures, as well as the massive economic burden imposed by the morbidity and mortality associated with IHD underscore the need for early diagnosis and risk stratification for IHD in the general population. To this end, numerous biomarkers have been proposed and evaluated including markers of systemic inflammation such as C-reactive protein and lipoprotein associated phospholipase A2 and indicators of subclinical atherosclerotic disease such as intima-media thickness and ankle-brachial index.[6]

Urine microalbumin has been extensively studied in diabetes mellitus (DM) and is now recognized as a marker for systemic atherosclerosis.[7] Microalbuminuria has been traditionally defined as a urinary albumin excretion rate greater than 30 mg/24 hours or a urine albumin creatinine ratio greater than 30 mg/g in an early morning sample.[8,9] It is pertinent to note that these cut-off values have been primarily defined for proteinuria in diabetic individuals, and are yet to be rigorously validated in non-diabetic individuals. In terms of a temporal model of association of biomarkers with evolving IHD,[10]

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urinary microalbumin occupies the early end of the spectrum, as an indicator of subclinical disease. The close association between microalbuminuria and coronary artery disease is readily explained by the shared pathogenetic mechanisms of endothelial dysfunction, systemic inflammation and vascular injury;[11] it is reasonable to assume that such a relationship should exist regardless of the concomitant presence or absence of diabetes. The relative paucity of data on the link between urine microalbumin and IHD in non-diabetics as compared to diabetics is therefore unexpected.

This study was designed to determine whether an association exists between urine microalbumin and IHD in non-diabetic Asian-Indians and the level of urine microalbumin predictive of increased risk of IHD in this population.

MATERIALS AND METHODS

Study settings

The study was conducted in the departments of Medicine and Cardiology at a tertiary care centre in coastal south India.

Study design

This study was designed as a cross-sectional case-control study. Non-diabetic individuals undergoing evaluation for IHD were divided into cases and controls, based on the presence or absence of IHD, respectively. Fifty cases and 50 controls were included in the study. Cases and controls were matched by age, sex, smoking habit, hypertension and body-mass index (BMI). Exclusion criteria included age below 18 years, presence of DM, congestive cardiac failure, presence of vaginal discharge in female patients, dipstick-positive proteinuria, greater than 10 leucocytes or red blood cells (RBC) per high power field on urine microscopy, prior therapy with angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) and acute or chronic renal failure.

Institutional ethical committee approval was obtained before starting the study. Informed consent was obtained from all subjects prior to inclusion in the study.

Absence of diabetes was defined as failure to satisfy American Diabetes Association (ADA) criteria for DM.[12] Presence of IHD was defined by occurrence of documented ST-elevation myocardial infarction or non-ST-elevation myocardial infarction, and/or a positive treadmill test, and/or demonstration of a regional wall motion abnormality on trans-thoracic echocardiography conforming to a vascular territory, and/or demonstration of complete or partial atherosclerotic occlusion of an epicardial artery by coronary angiography. Absence of IHD was defined by a normal resting electrocardiogram, normal echocardiography and a negative treadmill test and/or normal epicardial arteries by coronary angiography. Presence of congestive cardiac failure was assessed by clinical findings of pitting pedal edema and raised jugular venous pressure and echocardiographic evidence of ventricular systolic or diastolic dysfunction. Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured for all subjects in the fasting state in their undergarments. BMI was calculated by dividing body weight (in kilograms) by the height squared (in meters). Past history of systemic hypertension, and details of anti-hypertensive therapy where relevant, were obtained for all patients. Subjects were also questioned regarding current or past history of smoking.

Fasting blood glucose (FBG), fasting serum lipid profile (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol), and urine microalbumin were recorded for all patients.

Fasting blood glucose was estimated by hexokinase method. Serum total cholesterol, triglycerides and HDL-cholesterol levels were estimated by enzymatic method. LDL-cholesterol was calculated by Friedwald's formula. Urine microalbumin estimation was performed on an early morning spot urine sample by immunoturbidimetric method. Urinary creatinine was estimated in the same sample by alkaline picrate method, and the ratio of microalbumin to creatinine was calculated to yield the albumin-creatinine ratio.

Statistical analysis

Data analysis was performed using SPSS Statistics version 17.0 (Chicago IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed and as median with interquartile range if not. Independent samples *t*-test or Mann-Whitney U-test were employed to compare means or medians of variables with (former) or without (latter) a normal distribution. Binomial logistic regression was performed to determine the independent association of variables with the presence of IHD. Receiver-operating curve (ROC) was used to calculate sensitivity and specificity of urinary microalbumin for associated IHD. *P* values less than 0.05 were considered to indicate statistical significance. Confidence intervals were set to 95%.

RESULTS

The fifty cases and 50 controls were matched for baseline characteristics including age, sex, ethnicity, BMI, prior history of hypertension, smoking habit and mean blood pressure [Table 1].

Comparison of biochemical parameters [Table 2], showed a statistically significant difference in serum total cholesterol and LDL cholesterol and urine microalbumin between cases and controls [Figure 1]. A trend towards higher fasting blood glucose was also observed in the cases as compared to the controls, and the number of individuals with impaired fasting glucose was significantly higher among the cases (OR: 4.70; 95% CI, 1.93–11.42; $P < 0.001$). Binary logistic regression confirmed urine microalbumin to be associated with IHD independent of fasting blood sugar, total and LDL-cholesterol ($P = 0.015$) [Table 3].

Analysis by receiver-operating curve (ROC) [Figure 2] demonstrated 100% specificity but only 32% sensitivity of urine microalbumin for the presence of concomitant IHD when using the conventional cut-off of 30 mg/g. Utilising a lower cut-off of 16.15 mg/g improved sensitivity to 50% without affecting specificity. Lowering of the cut-off to 12.6 mg/g further increased the sensitivity to 60% while maintaining a specificity of 90%. Furthermore, the conventional cut-off of 30 mg/g yielded a prevalence rate of 17/50 that is, 34% in the cases and 0/50 that is 0% in the controls. Conversely the reduced cut-off of 12.6 mg/g yielded a prevalence rate of 60% in those with IHD and 10% in those without IHD.

DISCUSSION

There is limited data available on the usefulness of urine microalbumin as a biomarker for IHD in a non-diabetic population. This is particularly surprising when the current trend for identifying and validating newer biomarkers of IHD is considered. Urine microalbumin possesses several characteristics that lend an obvious advantage over other putative biomarkers. Being an older biomarker and a well-validated indicator of early diabetic nephropathy, microalbumin is both affordable and widely available.[9] This advantage gains further significance in light of the shifting global burden of cardiovascular mortality from high-income

Table 1: Baseline characteristics-cases and controls

Characteristics	Cases (*N*=50)	Controls (*N*=50)	*P* value
Age (years)	54.98±11.2	54.86±11.5	0.958
Sex (M: F)	27:23	26:24	0.841
H/o smoking	7	7	1.000
Hypertension	24	24	1.000
BMI (kg/m^2)	24.01±2.7	24.96±4.5	0.366
Mean blood pressure (mmHg)	94.5±13.3	97.9±9.8	0.156

BMI: Body mass index

Table 2: Biochemical parameters-cases and controls

Parameter	Cases (*N*=50)	Controls (*N*=50)	*P* value (95% CI)
Mean fasting blood glucose (mg/dL)	107.31±13.8	99.27±17.3	0.057 (−16.30-0.23)
Mean total cholesterol (mg/dL)	176.53±40.5	151.80±32.1	0.024 (−46.01-−3.45)
Mean triglycerides (mg/dL)	107.21±46.7	100.16±39.0	0.579 (−32.4-18.31)
Mean HDL-cholesterol (mg/dL)	38.26±12.3	38.68±10.8	0.902 (−6.37–7.21)
Mean LDL-cholesterol (mg/dL)	116.73±36.8	92.13±28.7	0.015 (−44.24-−4.97)
Median urine micro-albumin	15.95 (3.9-36.05)	2.95 (1.18-6.68)	< 0.001(<0.001)

CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table 3: Binary logistic regression demonstrating independent association of urine microalbumin with IHD

Variable	95% CI	*P* value
Fasting blood glucose	0.95-1.04	0.933
Total cholesterol	0.94-1.10	0.738
LDL cholesterol	0.94-1.10	0.702
Urine microalbumin	1.03-1.36	0.015

CI: Confidence interval, IHD: Ischemic heart disease, LDL: Low density lipoprotein

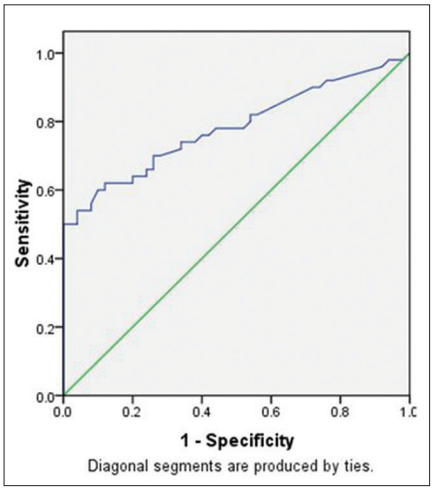

Figure 1: Receiver-operating curve (ROC) demonstrating 100% specificity but only 32% sensitivity of microalbuminuria for presence of concomitant IHD utilizing the conventional cut-off of 30 mg/g

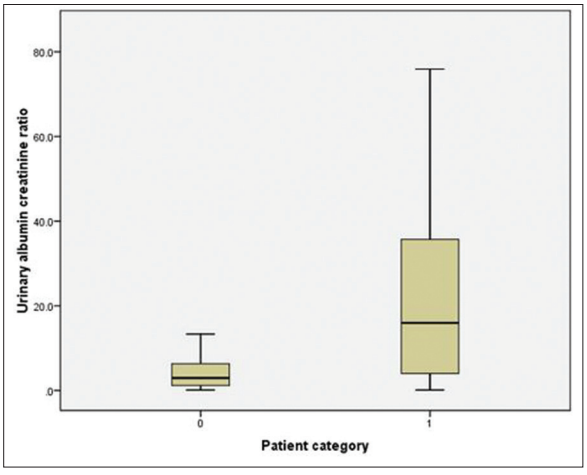

Figure 2: Box-plot demonstrating significant difference in urine microalbumin between cases and controls (0: controls, 1: cases)

countries towards low- and middle-income countries.[2] Moreover being a urinary test, it is non-invasive and can be repeatedly assayed with no discomfort to the patient. Finally, analyses have confirmed the cost-effectiveness of therapy with ACE-I in patients with microalbuminuria for the prevention of future cardiovascular events.[13]

In our study, urine microalbumin was found to bear a strong association with IHD, even within the non-diabetic population. A brief comparison of our results with those of other available studies lends further support to this contention. For instance, a cross-sectional study conducted in Pakistan involving 100 non-diabetic individuals with IHD found a prevalence of 37% for microalbuminuria utilizing the conventional cut-off value of 30 mg/g.[14] Yet another study from Pakistan in non-diabetic individuals with angiographically proven coronary artery disease found significantly higher values of urine microalbumin in patients with IHD as compared to age- and sex-matched controls.[15] Interestingly, this study yielded a mean urine microalbumin value of 36.58 mg/g in cases with IHD, extremely close to the conventional cut-off value of 30 mg/g. This finding is congruent our own that a lower cut-off value might be more appropriate for non-diabetic patients relative to diabetics, possibly due to the contributory impact of diabetic nephropathy on microalbuminuria. Arnlov *et al.*, also questioned the validity of the conventional cut-off value, and also demonstrated the robustness of urine microalbumin as a biomarker for cardiovascular risk regardless of pretest probability.[16]

The strong association between cardiovascular disease and microalbuminuria is also borne out by several large population-based studies, all of which demonstrated significantly elevated risk for cardiovascular morbidity and mortality amongst persons with microalbuminuria [Table 4].[17-21] These studies do have notable drawbacks, however, such as the inclusion of diabetics in some instances, and an understandable inability to conclusively rule out asymptomatic or minor IHD in all individuals by means of treadmill testing and/or coronary angiography. Nevertheless, these studies provide strong support for the need to conduct larger prospective studies to validate the role of urinary microalbumin as a biomarker of IHD in the non-diabetic population.

Table 4: Selected population-based studies reporting cardiovascular risk associated with microalbuminuria

Study	Whether diabetics excluded	Conventional criteria used for microalbuminuria	Risk associated with microalbuminuria
PREVEND[17]	No	Yes	CV death: RR 1.29
Hoorn study[18]	No	Yes	CV death: RR 3.22
EPIC-Norfolk[19]	No	Yes	IHD death: HR 2.01
Danish MONICA[20]	Yes	Yes	IHD: RR 2.3
PREVEND[21]	Yes	Yes	Major ischemia: OR 1.43

CV: Cardiovascular, IHD: Ischemic heart disease, PREVEND: Prevention of renal and vascular endstage disease, EPIC-Norfolk: European Prospective Investigation into Cancer in Norfolk, OR: Odds ratio, MONICA: MONItoring of Trends and Determinants in CArdiovascular Disease, RR: Relative risk

CONCLUSIONS

In conclusion, urinary microalbumin appears to be a viable candidate for determining the risk of IHD in non-diabetic individuals. The strong and independent association of elevated urine microalbumin with IHD demonstrated in our study, despite the limitation of a small sample size, contributes further evidence in favor of microalbuminuria as a biomarker of IHD in non-diabetics albeit at levels below those encountered in their diabetic counterparts.

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