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ORIGINAL ARTICLE

Impaired renal function and atherosclerosis in a Pakistani cohort

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Key words: **Asian – Cardiovascular risk factor – Coronary heart disease – Glomerular filtration rate – Renal disease**

ABSTRACT

Objective: To investigate the relationship of creatinine and calculated glomerular filtration rate (GFR) with coronary arterial disease (CAD) in Pakistani patients.

Subjects: Four hundred individuals with chest pain; 200 with angiographic disease matched with 200 without occlusive disease.

Design: A prospective case-control study.

Setting: A tertiary referral cardiology unit in Pakistan.

Results: Impaired renal function as estimated by calculated GFR was common in this population. Creatinine and glomerular filtration rate, as calculated by the Cockcroft–Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulae, were associated with CAD and atherosclerotic burden in Pakistani patients. Calculation of creatinine clearance, correcting for age, sex and body mass index, showed that clearance was 81 (17–257) mL/min/1.73 m^2 in patients with CAD compared with 88 (23–167) mL/min/1.73 m^2 in controls with a significant number of patients (18.5 vs. 6.5%; RR = 2.85; $p < 0.001$) showing significant renal impairment (< 60 mL/min/1.73 m^2) by CG and more by the MDRD equation (26 vs. 9%; RR = 2.88; $p < 0.001$). The unadjusted odds ratios for CAD for a GFR < 60 mL/min/1.73 m^2 were 3.66 (1.87–7.16) and 3.29 (1.81–6.01), respectively and, after adjustment for diabetes, smoking, insulin resistance, inflammation and apolipoprotein A1, 1.04 (1.02–1.09) and 1.04 (1.02–1.09), respectively.

Conclusions: Impaired renal function is common in Pakistani patients with coronary arterial disease and is strongly associated with a risk of atherosclerosis independent of insulin resistance.

Introduction

Renal disease is associated with increased cardiovascular risk[1]. Similarly, microalbuminuria and raised creatinine are recognized as markers of target organ damage in hypertension. Impaired renal function measured by decreased glomerular filtration rate and/or microalbuminuria is often considered part of the metabolic syndrome[2,3]. Many recent studies have noted that creatinine is an independent risk factor for cardiovascular disease[4,5]. Despite the high prevalence of metabolic syndrome and insulin resistance in Asian populations, there are few studies examining

the role of creatinine, as opposed to microalbuminuria, as a risk factor for coronary artery disease (CAD) in this population. This study investigated whether elevated creatinine or decreased calculated glomerular filtration rate correlated with the presence of significant CAD and burden of atherosclerosis in a cross-sectional cohort study of patients with chest pain from Pakistan.

Methods

The study cohort consisted of 400 patients recruited, with ethical consent, who underwent coronary angiography from 1998–2001 for presenting symptoms of chest pain[6]. Two groups were selected based on the presence of significant CAD as defined by a 50% stenosis in one or more coronary arteries and an age and sex-matched control group presenting with similar symptoms but with no angiographic evidence of disease. Approximately 1000 patients were screened. Patients with established coronary heart disease (CHD) were recruited and approximately age and gender matched with a cohort of patients without significant CAD from the same centre. After discharge from hospital, patients were recruited to the study and baseline anthropometric, dietary and lifestyle variables assessed. A detailed cardiovascular risk profile was obtained including smoking history, triplicate measurement of blood pressure by mercury sphygmomanometry, measurement of waist-hip ratio and total body fat by an Omron BF300 impedance system. Doses and types of medications were recorded. Fasting blood samples were obtained for determination of biochemical risk factors including baseline renal function, liver function, glucose, insulin, lipids and apolipoproteins, lipoprotein (a) [Lp(a)], homocysteine (Hcy), C-reactive protein (CRP) and sialic acid. Biochemical analytes were measured by automated methods on Cobas Mira and Fara 2 analysers, a Behring BN2 nephelometer and the Corning ACS 180 immunoassay system, except for homocysteine, which was measured by liquid chromatography and tandem mass spectrometry. Insulin resistance was calculated by the homeostasis model (HOMA) method[7] and glomerular filtration rate (GFR) approximated by calculation of creatinine clearance using the Cockcroft–Gault (CG)[8] and Modification of Diet in Renal Disease (MDRD) formulae[9].

Statistical analysis was conducted by paired sample logistic regression analysis between CAD(+) and (–) groups. Categorical data were quantified and compared by Fisher's exact test. Analyses for the cohort were conducted using baseline data or log-transformed data depending on whether individual analytes showed a Gaussian distribution. Angiograms were quantified for the extent and severity of CAD by Gensini scoring by observers blinded to other clinical details[10]. Multiple regression analysis was conducted using both backward and forward stepwise models to ascertain co-variance and principal determinants of risk. Statistical analyses were conduced using GBStat 10.0 (Dynamic Microsystems, Silver Spring, Maryland, USA).

Results

Patient demographic, lifestyle, biochemical risk factors for CAD and drug therapy are shown in Tables 1 and 2. The distribution of angiographic disease in the CAD(+) group was 52% with three vessel disease, 30% with two vessel disease and 18% with single vessel disease. Only 2% of patients in the CAD(–) group had any evidence of disease on angiography and hence Gensini scores were 57 (8–224) (median [range]) and 0 (0–3) in CAD(+) and CAD(–) groups, respectively ($p < 0.001$). Groups with and without CAD differed most significantly in age, percentage of body fat, waist-hip ratio, prevalence of diabetes and high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 concentrations. Severity of disease, as measured by Gensini scores of the coronary angiograms, was strongly associated with HDL-C, Lp(a), creatinine, CRP, years of diabetes and waist-hip ratio.

Metabolic syndrome was present in 31.5% of the group by Nation Cholesterol Education Program Adult Treatment Panel 3 (NCEP–ATP3) criteria and 44% using adjusted waist criteria for Indian Asians. A significant excess of patients with CAD had the metabolic syndrome by both US and Asian waist circumference cut-offs (Table 1).

Calculation of creatinine clearance by CG, hence correcting for age, sex and body mass index, showed that clearance was 81 (17–257) mL/min/1.73 m^2 in cases compared with 88 (23–167) mL/min/1.73 m^2 in controls with more patients with CAD showing significant renal impairment (< 60 mL/min/1.73 m^2) compared to controls (18.5 vs. 6.5%; RR = 2.85; $p < 0.001$). Calculated using MDRD, creatinine clearance in patients with CAD was 74 (11–156) mL/min/1.73 m^2 as opposed to 78 (36–150) mL/min/1.73 m^2 and a greater proportion of patients with CAD showed renal impairment (26 vs. 9%; RR = 2.88; $p < 0.001$). A steep rise in the hazard ratio for CAD was seen with decreasing GFR (Table 2). Despite different equations, both GFR calculation methods correlated closely ($r^2 = 0.71$; $p < 0.001$).

As impaired GFR correlates with cardiovascular risk factors, adjusted relative risks for CAD were calculated (Table 3).

Further analysis by subgroups with and without CAD showed similar relationships but with higher creatinine and lower GFR values in the patients with CAD (Table 2). In an analysis with burden of atherosclerosis, the univariate regression of CG-GFR showed a weak

Table 1. *Anthropometric, lifestyle, cardiovascular risk markers and medication usage in a cohort study of a Pakistani population with /without coronary heart disease. Metabolic syndrome was assessed by standard NCEP–ATP3 waist criteria and also using values for waist circumference modified for Asians (NCEP*)*

Parameter	CHD(+)	CHD(–)	*P*
Age (years)	51.2 ± 9.5	48.2 ± 9.5	< 0.001
Family history IHD (%)	55.3	43.7	0.01
Active smoking (%)	19.0	14.8	0.03
Body mass index (kg/m^2)	25.5 ± 2.6	25.3 ± 2.6	0.53
Waist (cm)	90.8 ± 6.7	88.5 ± 8.0	0.02
Waist–hip ratio	0.94 ± 0.05	0.91 ± 0.06	< 0.001
Fat mass (kg)	20.6 ± 7.0	19.4 ± 7.5	0.14
Blood pressure (mmHg)	130 ± 17/83 ± 9	128 ± 19/83 ± 10	0.54
Metabolic syndrome (NCEP) (%)	37	27	< 0.001
Metabolic syndrome (NCEP*) (%)	47	42	< 0.001
Diabetes (%)	9.3	4.7	< 0.001
Aspirin (%)	85	54	< 0.001
Nitrates (%)	83	22	< 0.001
Calcium channel blockers (%)	52	18	< 0.001

Table 2. *Biochemical cardiovascular risk markers in a cohort study of a Pakistani population with/without coronary heart disease (values are shown as mean and standard deviation or median range based on the data distribution plots)*

Parameter	CHD(+)	CHD(–)	*P*
Glucose (mmol/L)	6.84 ± 2.05	6.06 ± 1.16	0.003
Insulin (mmol/L)	23 (2–449)	2 (2–424)	0.001
HOMA	1.40 (0.07–33.0)	0.12 (0.07–41.0)	0.001
Total cholesterol (mmol/L)	4.28 ± 0.79	4.25 ± 0.74	0.74
Triglycerides (mmol/L)	1.24 (0.37–3.62)	1.18 (0.08–3.98)	0.60
HDL-C (mmol/L)	0.73 ± 0.14	0.86 ± 0.17	< 0.001
LDL-C (mmol/L)	2.92 ± 0.99	2.71 ± 0.93	0.07
ApoA1 (g/L)	1.09 ± 0.12	1.19 ± 0.15	< 0.001
ApoB (g/L)	0.93 ± 0.23	0.91 ± 0.27	0.14
Lipoprotein(a) (g/L)	0.06 (0.02–0.65)	0.05 (0.02–0.45)	0.05
Fibrinogen (g/L)	2.20 (0.10–10.6)	2.00 (0.10–20.3)	0.60
C-reactive protein (mg/L)	8.0 (0.2–175)	3.4 (0.2–61)	< 0.001
Sialic acid (mg/L)	82.1 ± 15.8	77.6 ± 12.7	< 0.001
Homocysteine (μmol/L)	18 (6–92)	19 (7–69)	0.62
Creatinine (μmol/L)	103 ± 37	93 ± 19	0.002
Cockcroft–Gault GFR (mL/min/1.73 m^2)	81 (17–257)	88 (23–167)	< 0.001
MDRD GFR (mL/min/1.73 m^2)	74 (11–156)	78 (36–150)	< 0.001

Table 3. *Distribution of calculated glomerular filtration rate and hazard ratios for coronary artery disease at intervals of calculated glomerular filtration rate in Pakistani patients. Odds ratios are presented as raw data and adjusted for pack-years of smoking, years of diabetes, family history of cardiovascular disease, HOMA insulin resistance, apolipoproteins A1 and B, lipoprotein (a), C-reactive protein and sialic acid (values are shown as mean and standard deviation or median range based on the data distribution plots)*

Estimated GFR (mL/min/1.73 m^2)	CAD patients		Control patients		Unadjusted odds ratio		Adjusted odds ratio	
	CG	MDRD	CG	MDRD	CG	MDRD	CG	MDRD
> 60	153	146	187	182	1	1	1	1
46–60	23	25	12	17	3.66 (1.87–7.16)	3.29 (1.81–6.01)	1.04 (1.02–1.09)	1.04 (1.02–1.09)
31–45	10	12	1	1	6.30 (0.83–48.0)	12.8 (1.70–96.4)	1.09 (1.05–1.15)	1.06 (1.01–1.10)
< 30	4	5	0	0	∞	∞	–	–

positive relationship with Gensini score in the whole cohort (Figure 1a) while a significant negative correlation was seen in patients with established CAD even after censoring the whole data set for artefactually raised GFR values (> 200 mL/min/1.73 m^2) (Figure 1b). In contrast MDRD-GFR correlated inversely with CAD burden for both the whole cohort and patients with significant CAD (Figure 2) and only 1% of values had to be censored in contrast to the CG-GFR where 4% were removed. Linear regression analysis of risk factors by the

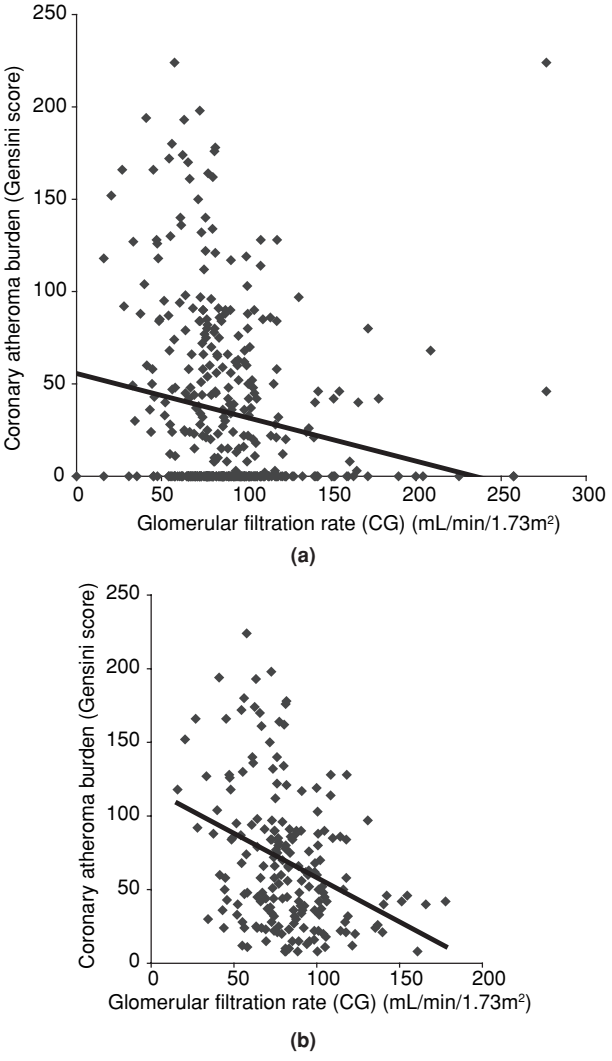

Figure 1. *(a) Relationship between coronary atherosclerotic burden and Cockcroft–Gault equation calculated glomerular filtration rate in Pakistani patients. (b) Relationship between coronary atherosclerotic burden and Cockcroft–Gault equation calculated glomerular filtration rate in Pakistani patients with significant coronary artery disease*

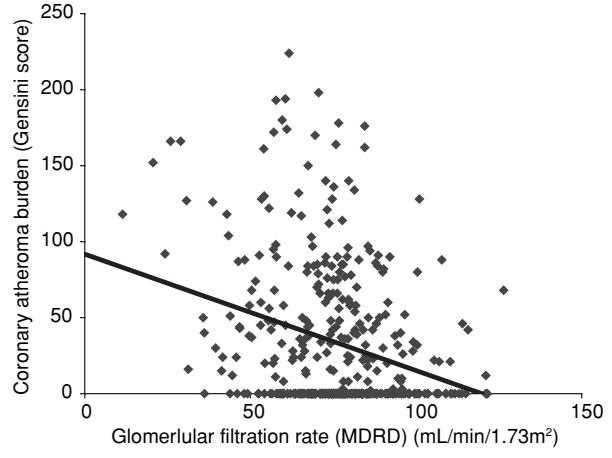

Figure 2. *Relationship between coronary atherosclerotic burden and Modification by Diet in Renal Disease (MDRD) equation calculated glomerular filtration rate in Pakistani patients*

semi-quantitative Gensini scoring method for assessing severity of disease is shown in Table 4. The significant associations persisted and the associations remained little changed when age, sex and weight (for CG equation) were removed from the model (Table 4). Calculated CG GFR (Table 3) showed a similar relationship with burden of CAD, after excluding factors involved in its calculation (age, gender) but, in contrast to creatinine, was not confounded by sialic acid levels. Renal function as calculated by the MDRD equation (Table 3) also showed relationships with similar risk factors to CG-GFR, though in this case associations with C-reactive protein or sialic acid remained associated with CAD after correction for variables involved in calculation of MDRD-GFR.

As creatinine and renal dysfunction are often considered to be related to other risk factors or the presence of the metabolic syndrome, further analyses investigated the relationships of creatinine to metabolic syndrome in this cohort. Creatinine levels correlated with age, gender, sialic acid and triglycerides but, even after adjustment for these factors, remained correlated with burden of atherosclerotic disease (data not shown). Separate analysis in patients without CAD revealed the same relationships for creatinine except that triglycerides were no longer a significant factor and occlusive CAD was absent. In patients with CAD, creatinine was related to atherosclerotic burden, age, gender and sialic acid. No correlation was found of creatinine or GFR calculated by either algorithm with calculated insulin resistance, presence of the metabolic syndrome or number of positive parameters for diagnosis of the metabolic syndrome (Figure 3).

A further analysis was performed to assess the cross-correlation of renal function with underlying risk factors. Creatinine levels correlated with risk factors associated with the calculation of the CG equation. If GFR was assessed by this equation, then residual associations persisted with smoking (expressed as log pack-years) ($\beta = -4.02$; $p < 0.001$), while the MDRD calculated GFR showed associations with pulse ($\beta = -0.16$; $p < 0.001$) and diastolic blood pressures ($\beta = 0.26$; $p < 0.001$) and a weak association with apoB levels ($\beta = 5.08$; $p = 0.02$). Again there was no association with the presence of the metabolic syndrome or number of positive diagnostic parameters for the metabolic syndrome in multiple regression analysis (Figure 3).

Discussion

It has previously been demonstrated in this Pakistani cohort that atherosclerotic disease correlates with low HDL, waist–hip ratio, markers of inflammation and insulin resistance[6] and a relationship with creatinine was

Table 4. *Multivariate linear regression analysis of calculated glomerular filtration rates with cardiovascular disease burden in a Pakistani population*

Dependent variable	Atheroma burden			
	CG-GFR		MDRD-GFR	
Independent variable	β	*P*	β	*P*
Age (years)	0.46	0.10	0.57	0.03
Smoking (pack-years)	0.017	0.05	0.19	0.02
Diabetes (years)	1.68	0.004	1.61	0.005
ApoA1 (g/L)	–38.6	0.002	–40.6	0.001
Ln Lp(a)	7.82	0.003	8.38	0.001
Ln CRP	6.03	0.002	5.60	0.004
GFR (mL/min/1.73 m^2)	–0.23	0.005	–0.31	0.008

Abbreviations: ApoA1 = apolipoprotein A1; Ln Lp(a) = log of lipoprotein(a); Ln CRP = log of C-reactive protein; GFR = glomerular filtration rate; CG = Cockcroft–Gault formula; MDRD = modification of diet in renal disease formula

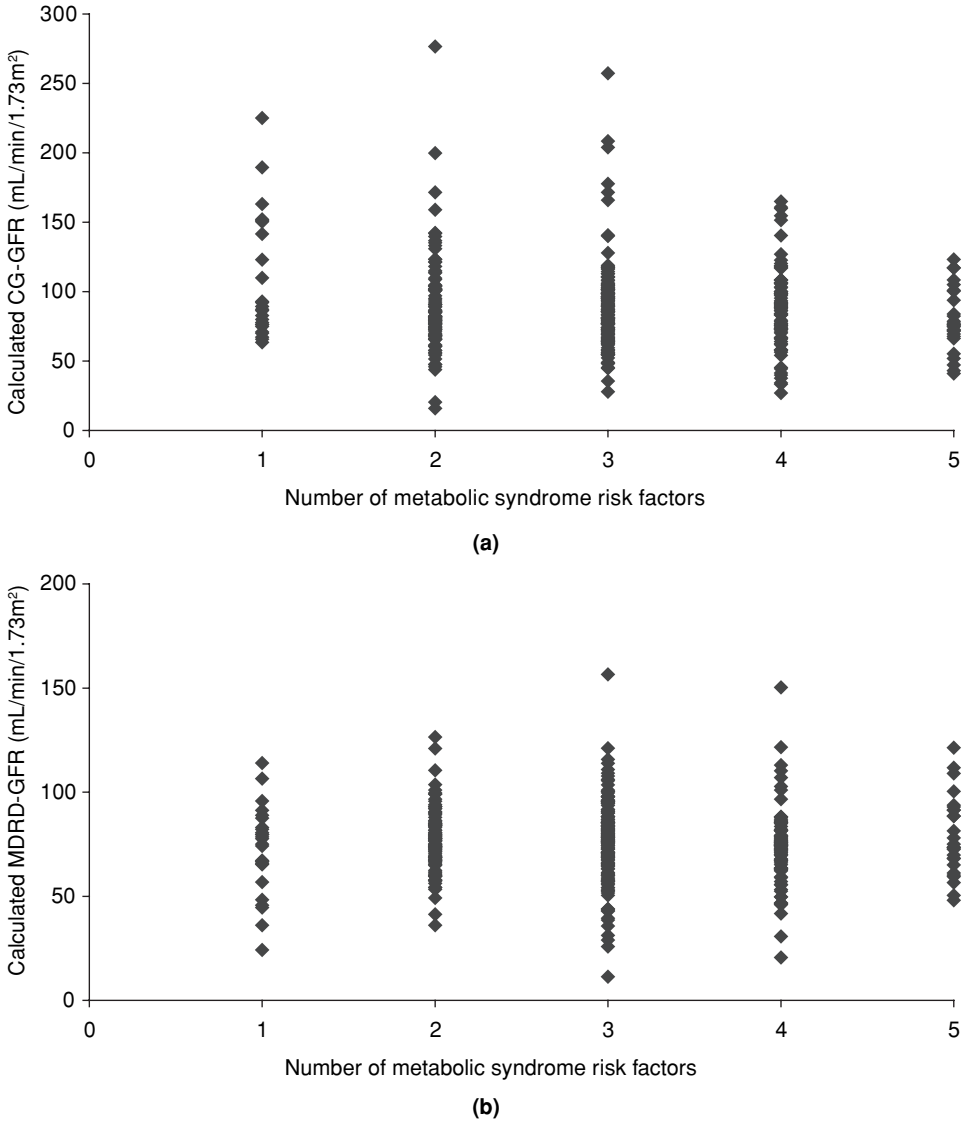

Figure 3. *(a) Relationship glomerular filtration rate (GFR) calculated by the Cockcroft–Gault formula with number of risk factors for metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel 3 modified for Asians. (b) Relationship glomerular filtration rate calculated by the Modification of diet in renal disease (MDRD) formula with number of risk factors for metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel 3 modified for Asians*

noted incidentally. The higher incidence of diabetes, low HDL, hypertriglyceridaemia, increased body mass index, insulin resistance and hence the likely presence of the metabolic syndrome are consistent risk factors for CHD in migrant Indian Asians and are confirmed in this study[11–14]. Creatinine has been recognized as a cardiovascular risk factor[15] and to be related to cardiovascular outcomes after acute myocardial infarction[16]. However, the relationship of creatinine expressed as calculated GFR to CHD in patients with chronic atherosclerosis has been less studied though many studies have found an association with the coincident proteinuria[17,18]. A relationship of creatinine with cardiovascular risk was seen in the Framingham and other cohort studies[19] although renal function was not a strong enough risk factor to be included in the Framingham cardiovascular risk calculation algorithm. It has usually been assumed that creatinine and renal dysfunction would reflect insulin resistance, hypertension and diabetic nephropathy and thus would correlate with these components of the metabolic syndrome and its consequences[20,21].

Few studies have addressed renal function as a risk factor in Indian Asian populations although some have found a strong relationship between CAD risk and proteinuria in this type of population[22]. In this Pakistani population creatinine and impaired renal function remained strong risk factors after adjustment for other cardiovascular risk factors including insulin resistance. A significant number of patients with CAD (18.5 vs. 6.5%; RR = 2.85; $p < 0.001$) showed significant renal impairment ($< 60\,mL/min/1.73\,m^2$) by CG-GFR. The effect was greater when calculated by the MDRD-GFR equation (26 vs. 9%; RR = 2.88; $p < 0.001$). The unadjusted relative risk for GFR $< 60\,mL/min/1.73\,m^2$ using either calculator (2.84–2.88) was approximately double that seen in patients in western country cohort studies[23] and was still significant in a logistic regression analysis after adjustment for other risk factors, even given the limitation of a small study cohort. It was notable that the relationship of CG-GFR was confounded by patients without significant CAD in a whole cohort analysis while a strong negative relationship was seen in patients with established CAD, in contrast to the MDRD-GFR which showed a consistent relationship in the cohort and in patients with established CAD. This confounded relationship, and the high prevalence of grossly elevated GFR ($> 200\,mL/min/1.73\,m^2$) in 4% of patients when calculated by the CG equation, suggests significant confounding by the inclusion of body mass index in the GFR calculation compared with the MDRD equation. This suggests that the simpler MDRD algorithm may be a better equation for use in this population.

Although urine albumin:creatinine ratios (ACR) were not assessed in this study, a doubling in this factor is seen in Indian Asians resident in the UK[24]. This study suggests that a high proportion of Pakistani patients presenting with cardiovascular symptoms have chronic kidney disease and the strong association of cardiovascular disease may reflect renal disease-associated risk and thus are likely to have microalbuminuria[25]. Measurement of ACR is routine in diabetic practice but even in developed societies is limited by expense and the necessity for extra samples. Creatinine, on the other hand, is routinely measured as part of any risk assessment protocol for hypertension and cardiovascular risk and is also an accepted marker of target-organ damage. Its use has been limited by its dependence on lean body mass but the increasing emphasis on reporting calculated GFR as a more accurate index of renal function allows this risk factor to be easily assessed. The predictive capacity of the MDRD equation in this, and other studies, means that GFR can be calculated based on standard demographic data alone rather than requiring extra information on weight, and only being valid up to moderate degrees of obesity, as is the case with the CG equation. Thus assessment of this powerful risk marker is easily possible in countries with limited resources to devote to laboratory investigations.

This study has a number of limitations. It is a prospective case-control study of CAD in Pakistanis rather than a prospective cohort study. The control group is provided by patients with chest pain with normal coronary lumens on angiography and thus possibly some degree of intra-mural atherosclerosis rather than healthy individuals. Calculated GFR was inferred mathematically rather than measured using direct biochemical markers of renal function e.g. cystatin C and was not correlated with evidence of nephropathy measured by extent of microalbuminuria.

As renal disease can be treated and ameliorated with standard cardiovascular drug therapies, including angiotensin-II converting enzyme inhibitors or angiotensin-II type 1 receptor antagonists, which also have shown benefits in patients with CAD, this study suggests that patients with renal dysfunction can be identified by simple biochemical tests and subsequent GFR calculations, and that these patients would be likely to show prognostic benefits from aggressive renin-angiotensin system inhibition both for cardiovascular and renal disease.

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