

ORIGINAL ARTICLE

# Waist-hip ratio and low HDL predict the risk of coronary artery disease in Pakistanis

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## SUMMARY

*Objective:* To establish risk factor causal associations for coronary artery disease (CAD) in the native Pakistani population.

*Methods:* We conducted a hospital-based, case-control study of 200 cases with angiographically documented CAD and 200 age- and sex-matched controls without angiographic evidence of CAD. Patients on lipid lowering therapy were excluded. Lifestyle, anthropometric and biochemical risk factors were assessed in both groups.

*Results:* The presence of CAD was associated with current, past or passive smoking, a history of diabetes and high blood pressure, a positive family history of CAD, body fat percentage, waist-hip ratio (WHR), low apolipoprotein A1 or low HDL, lipoprotein (a), glucose, insulin, insulin resistance, C-reactive protein (CRP), total cholesterol to HDL ratio (TC/HDL) and creatinine on univariate conditional logistic regression analysis. In multiple regression analysis, significant independent

associations were found with low HDL (OR 0.11; 95% CI 0.04–0.34;  $p < 0.001$ ) positive family history (OR 1.79; 95% CI 1.09–2.93;  $p = 0.02$ ), CRP (OR 1.45; 95% CI 1.19–1.75;  $p < 0.001$ ) and WHR (OR 1.04; 95% CI 1.01–1.08;  $p = 0.01$ ). Angiograms were also quantified for the extent and severity of CAD by the Gensini scoring system. Quantitative angiographic data showed associations with age ( $p = 0.01$ ), the duration of diabetes ( $p = 0.04$ ), WHR ( $p = 0.06$ ), low HDL ( $p < 0.001$ ), lipoprotein (a) ( $p = 0.001$ ), creatinine ( $p < 0.001$ ) and CRP ( $p = 0.007$ ). Results indicate that total and LDL cholesterol were not significant risk factors in this study; levels were below currently accepted thresholds for treatment.

*Conclusions:* The cardiovascular risk profile in this population is consistent with metabolic syndrome where low HDL and WHR can be used to predict the risk of CAD. Results suggest the need to redefine the currently practised approach to CAD management in this population to fit local needs.

## Introduction

Atherosclerotic disease is projected to become the leading cause of global morbidity and mortality by 2020<sup>1</sup>; this trend has grave implications for countries in South Asia<sup>2</sup>. Rates of coronary artery disease (CAD) are higher in South Asians who have migrated and some studies suggest that rates of disease in the Indian subcontinent parallel those in the industrialised world<sup>3,4</sup>. Located in South Asia, Pakistan has a population of 140 million<sup>5</sup>; surveys in Pakistan indicate very high prevalence rates of cardiovascular disease risk factors, with over 30%<sup>6</sup> of the population over 45 years of age affected. This calls for aggressive preventive strategies. However, setting goals for preventive initiatives necessitates the definition of the risk factor profile of a population but, for the Pakistani population, absence of relevant data makes this difficult. Ideally, efforts at uncovering the risk factor profile should have been undertaken in a well-designed multicentre prospective cohort design; however, issues of time, resources and time lag made this impractical. Given these constraints, a hospital-based case-control study was undertaken. The aim of this study was to determine the age- and sex-adjusted differences between individuals with and without CAD as defined by coronary angiography.

## Methods

### Subjects

#### Cases

A total of 200 consecutive patients aged 39–67 (inclusive), having undergone diagnostic coronary angiography during the previous month, and labelled as having angiographically-defined CAD, were prospectively recruited within a circumscribed period from two tertiary referral sites in Pakistan. A total of 115 cases were recruited from the Pakistan Institute of Medical Sciences (PIMS) over a 2-year period, and additionally 85 cases were recruited from the Armed Forces Institute of Cardiology (AFIC) over a 4-month period. These centres are located in the twin cities of Rawalpindi/Islamabad. Together, both these centres serve the urban and the adjoining rural population of over 3 million. There are no differences in the catchment population and characteristics of the population presenting for treatment between the two centres.

A total of 415 diagnostic coronary angiograms were performed at the Pakistan Institute of Medical Sciences during the study period (December 1998 to September 2000). Out of these, 115 were enrolled as cases and 59 as

controls. Of those that were not enrolled, 34.9% (84/241) were on lipid lowering therapy, 19.5% (47/241) did not consent to participate in the study, 15.4% (37/241) could not be categorised into cases or controls based on criteria specified in the study, 7.5% (18/241) were excluded because of deranged biochemical parameters. 12% (29/241) of participants were enrolled initially but did not complete the study protocol and for 10.7% (26/241), the attending physicians did not give their consent. At the Armed Forces Institute of Cardiology, 123 coronary angiograms were labelled as being abnormal according to the study criteria during the period of the study (January 1999 to April 1999). Of these, 85 were enrolled as cases, 73.7% (28/38) were excluded as they were on lipid lowering therapy, 23.7% (9/38) did not consent to participate, and 2.6% (1/38) were excluded because of deranged biochemical parameters.

#### Definition of CAD

CAD was defined as more than 50% luminal stenosis identified in a minimum of two views, in the case of single-vessel involvement. Angiograms were scored by two experienced observers, unaware of the diagnosis. The degree of stenosis was quantified from the moving cineangiogram by visual evaluation of the percentage of the luminal diameter reduction relative to the caliber of the adjacent normal segment of vessel. In cases of a disagreement between the two observers, the degree of stenosis in these vessels was quantified on the DX Hiline system interfaced with a digital angiography system, using the geometric method.

Angiograms were also quantified for the extent and severity of CAD using the Gensini scoring system<sup>7</sup> by observers blinded to other clinical details. This method assigns a different severity score depending on the geometrically increasing severity of lesion, the cumulative effects of multiple obstructions and the significance of their geographic locations.

#### Controls

A total of 200 controls with normal coronary angiograms were prospectively selected from within the study population in both the facilities. They were age- and sex-matched with the cases. A normal coronary angiogram was defined as one where no luminal irregularity or stenosis was identified from a minimum of two views reported by two experienced observers unaware of the diagnosis.

#### Exclusion Criteria

Among both the cases and controls, patients with hepatic disease (serum transaminases twice the normal

limit), renal disease (creatinine above 150  $\mu\text{mol/l}$  or marked hypoalbuminaemia), thyroid disease (biochemical evidence of hypo- or hyperthyroidism), malignancy and known bleeding diathesis were excluded. Patients on lipid lowering therapy were also excluded from the study, as were patients with less than 50% coronary stenosis in the case of one-vessel involvement. In addition, among the controls, those with LBBB, abnormal ST shifts on the EKG and multiform ectopics were also excluded.

### **Variables**

A trained interviewer, blinded to the diagnosis, interviewed the cases and controls in the hospital after discharge. The personal interview recorded details of demographics, clinical history, lifestyles and dietary variables, and family history. A detailed cardiovascular risk profile was obtained including smoking history, triplicate measurement of blood pressure by mercury sphygmomanometry, measurement of WHR, and body mass index using standardised protocols. Total body fat was estimated by an Omron BF300 impedance system.

### **Biochemical Investigations**

Fasting blood samples were obtained for determination of biochemical risk factors including glucose, insulin, lipids and apolipoproteins, lipoprotein (a), homocysteine, C-reactive protein, fibrinogen and baseline renal function. Samples were shipped in four consignments on dry ice from the project office in Islamabad to the Department of Chemical Pathology at St Thomas' Hospital, London where biochemical analysis was performed. Consignments were packaged in accordance with Royal Mail requirements for shipment of pathological specimens and were confirmed as being frozen on arrival by two independent observers. 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 using ABX diagnostic and Dade Behring kits. Plasma glucose was estimated by the enzymatic colorimetric test using the coupled enzyme GOD-PAP method. Serum cholesterol was estimated by the CHOD/PAP method and triglycerides by the GPO-PAP method, whereas high density lipoprotein (HDL) was estimated by selective inhibition colorimetric assay and was separated by direct anionic agents. Homocysteine was measured by liquid chromatography and tandem mass spectrometry. Insulin was measured by two-site chemiluminescent enzyme labelled immunometric assay on the Immulite automated analyzer. Apolipoprotein A and apolipoprotein B were estimated by the immunoturbidimetric methods,

whereas CRP and lipoprotein (a) (Lp(a)) were estimated utilising the principals of nephelometry.

Low density lipoprotein (LDL) was estimated by the Friedwald formula, insulin resistance was calculated by the homeostasis model (HOMA) method<sup>8</sup> and glomerular filtration rate (GFR) approximated by calculation of creatinine clearance using the Cockcroft-Gault formula<sup>9</sup>.

### **Statistical Analysis**

Statistical analysis was conducted using conditional logistic regression. Univariate analysis using simple conditional logistic regression of each variable was carried out and matched odds ratio with 95% confidence interval was obtained. In the case of binary or ordinal factors, a category with minimum risk was taken as reference category. For all continuous variables, distribution of the data was initially noted and in the case of non-normally distributed data, log of the variable was used as in the case of Lp(a) and CRP. Multivariate analysis was conducted by the best subset selection technique. Any variable whose *p*-value was found to be less than 0.2 on univariate analysis was included in the model, as were potential confounders. Angiograms were quantified for the extent and severity of coronary artery disease (CHD) by Gensini scoring using observers blinded to other clinical details. Linear regression and correlation were used by taking baseline data or log transformed data, depending on whether individual analytes showed a Gaussian distribution, to determine the relationship of Gensini scores and the exposure variables measured on the continuous scale and the nature of the relationship. Statistical analyses were conducted using SPSS 7 for Windows 98 and GB Stat 7.0 (Dynamic Microsystems, Silver Spring, Maryland, USA).

Ethical approval for this study was sought from the Ethics Committee of the Pakistan Institute of Medical Sciences, Islamabad.

## **Results**

Patient demographic and lifestyle risk factors are shown in Table 1, while biochemical risk factors are shown in Table 2. 84% of the cases were males. Cases (mean age  $51.2 \pm 9.5$ ) were on the average, 3 years older than the controls (mean age  $48.2 \pm 9.5$ ). 72.5% of the cases and 67% of the controls were currently residing in urban areas. Controls had a mean monthly income of \$310 (SE = 30.9), whereas the mean income of the cases was \$262 (SE = 34.4); the difference was not found to be significant (OR 1.00; 95% CI 1.1; *p*-value = 0.234).

**Table 1.** Anthropometric and lifestyle cardiovascular risk markers in a case-control study of Pakistani population with and without coronary heart disease. \* $p = 0.02-0.05$ ; \*\* $p = 0.01-0.001$ ; \*\*\* $p < 0.001$  (200 cases and 200 controls)

Parameter	Units	Cases	Controls	OR (95% CI)	<i>p</i> -Value
Age	Years (mean SE)	51.2 (0.67)	48.2 (0.68)	1.93 (1.64-2.27)***	0.001
Urban	%	72.5	67.0	1.28 (0.84-1.93)	0.24
Family history	%	55.3	43.7	1.65 (1.10-2.48)*	0.01
Active smoking	%	19.0	14.8	1.88 (1.02-3.49)*	0.03
Ex-smoker	%	41	34	1.88 (1.10-3.19)*	0.03
Body mass index	kg/m <sup>2</sup> (mean SE)	25.5 (0.26)	25.3 (0.26)	1.02 (0.96-1.08)	0.53
Body fat percentage	%	28 (0.59)	26 (0.62)	1.08 (1.03-1.14)***	0.001
Waist	cm (mean SE)	90.8 (0.67)	88.5 (0.80)	1.02 (1.00-1.04)*	0.02
Waist-hip ratio	Mean SE	0.94 (0.005)	0.91 (0.006)	1.06 (1.03-1.10)***	< 0.001
Diabetes	%	9.3	4.7	3.35 (1.26-8.88)***	< 0.001
Blood pressure	mmHg	130 ± 17/83 ± 9	128 ± 19/83 ± 10	1.01 (0.99-1.04)	0.54
Hypertension	%	49.5	39.4	1.57 (1.03-2.40)*	0.02

**Table 2.** Biochemical cardiovascular risk markers in a case control study of a Pakistani population with and without coronary heart disease (mean SE) \*  $p = 0.02-0.05$  \*\* $p = 0.01-0.001$  \*\*\* $p < 0.001$  (200 cases and 200 controls)

Parameter	Units	Cases	Controls	OR (95% CI)	<i>p</i> -Value
Glucose	mmol/l	6.837 (0.21)	6.057 (0.11)	1.15 (1.04-1.27)**	0.003
Insulin	pmol/l	47.417 (5.08)	26.485 (3.63)	1.01 (1.00-1.01)**	0.001
Insulin resistance		16.784 (2.12)	8.480 (1.63)	1.01 (1.00-1.02)**	0.001
Total cholesterol	mmol/l	4.28 (0.07)	4.24 (0.07)	1.03 (0.86-1.23)	0.74
Triglycerides	mmol/l	1.37 (0.04)	1.40 (0.05)	1.03 (0.78-1.22)	0.60
HDL	mmol/l	0.73 (0.01)	0.85 (0.01)	0.09 (0.03-0.25)***	< 0.001
LDL	mmol/l	2.92 (0.99)	2.71 (0.93)	1.20 (0.98-1.47)	0.07
ApoA1	g/l	1.09 (0.01)	1.19 (0.01)	0.06 (0.02-0.19)***	< 0.001
ApoB	g/l	0.93 (0.23)	0.91 (0.27)	1.03 (0.47-2.35)	0.14
Lipoprotein(a) log	g/l	-2.71 (0.07)	-2.88 (0.06)	1.24 (1.00-1.53)*	0.05
Fibrinogen	mmol/l	2.33 (0.06)	2.40 (0.13)	0.96 (0.84-1.11)	0.60
CRP log	mg/l	2.05 (0.08)	1.36 (0.09)	1.52 (1.28-1.81)***	< 0.001
Homocysteine	µmol/l	20.418 (0.66)	20.140 (0.68)	1.01 (0.98-1.02)	0.62
Creatinine	µmol/l	103 (37)	93 (19)	1.01 (1.00-1.02)**	0.002
TC/HDL	Mean SE	6.31 (0.29)	5.25 (0.13)	1.27 (1.16-1.44)***	< 0.001

There was also no difference seen in the mean duration (years) for which the cases (mean 10.98 ± 4.70) and controls (mean 10.40 ± 5.07) had been educated ( $p$ -value = 0.23).

In all, 52% of the cases had triple-vessel disease, 30% had double-vessel disease and 18% single-vessel disease. Mean Gensini scores were 57 (8-224) and 0 in the cases and controls, respectively ( $p < 0.001$ ).

A significant association of diabetes, high blood pressure and current and past status of smoking was found with CAD (Table 1). Cases smoked for a significantly higher mean number of pack years (222.755 ± 32; SE = 32.01) compared with controls (122.810 ± 231; SE = 16.39) (OR 1.001; 95% CI 1.00, 1.002;  $p = 0.001$ ). Cases also had a significantly higher odds of exposure to passive smoking compared with controls (OR 2.87, 95% CI 1.28, 6.42;  $p$ -value = 0.01) and of being exposed daily (OR 3.87; 95% CI 1.68, 8.86;  $p = 0.001$ ) when no exposure was taken as a reference category. Among the cases, spousal exposure

was the most significant source of exposure (OR 2.38; 95% CI 1.04, 5.42;  $p = 0.04$ ).

In all, 55.3% of the cases and 43.7% of the controls had a family history of one of the cardiovascular ailments, namely: hypertension, diabetes, coronary heart disease and sudden non-accidental death or a combination of these; the difference was found to be significant (OR 1.65, 95% CI 1.10, 2.48;  $p$ -value = 0.01).

Total cholesterol in the populations averaged 4.28 mmol/l in cases and 4.24 mmol/l in the control groups. Plasma HDL-cholesterol levels were 0.73 mmol/l and 0.85 mmol/l, respectively. Similarly, all showed a degree of insulin resistance, due to moderate hyperglycaemia and significant hyperinsulinaemia, which was significantly increased in cases.

Significant differences were seen between cases and controls in univariate conditional logistic regression analysis for body fat percentage, WHR, creatinine, HDL-cholesterol or apolipoprotein A1, Lp(a), CRP and homocysteine but not for LDL-cholesterol or

**Table 3.** Results of multivariate regression analysis

Factors	Adjusted OR (95% CI)	
C-reactive protein (log)	1.45 (1.19, 1.75)	<i>p</i> -value < 0.001
HDL	0.11 (0.04, 0.34)	<i>p</i> -value < 0.001
Waist-hip ratio	1.04 (1.01, 1.08)	<i>p</i> -value 0.01
Family history		
no	1	
yes	1.79 (1.09, 2.93)	<i>p</i> -value 0.02

apolipoprotein B (Table 2). Plasma homocysteine was raised in both groups (mean 20.4 and 20.14 µmol/l, respectively) but was not associated with CHD and showed a weak relationship with triglycerides (*p* = 0.10), but not creatinine or calculated GFR.

In multiple regression analysis (Table 3), significant independent associations were found with low HDL (OR: 0.11; 95% CI 0.04–0.34; *p* < 0.001) positive family history (OR 1.79; 95% CI 1.09–2.93; *p* = 0.02), CRP (OR 1.45; 95% CI 1.19–1.75; *p* < 0.001) and WHR (OR 1.04; 95% CI 1.01–1.08; *p* = 0.01).

Linear regression analysis of risk factors by the semi-quantitative Gensini scoring method for assessing severity of disease is shown in Table 4. Severity of disease was strongly associated with HDL, Lp(a), creatinine, CRP, years of diabetes and WHR. The association of CAD with creatinine occurred despite creatinine levels being in the 'normal' range and persisted after correction for usage of diuretics. However, calculation of creatinine clearance and hence correction for age, sex and body mass index showed that clearance was 81 (17–257) ml/min in cases compared with 88 (23–167) ml/min in controls with a significant number of patients (38.5 vs 26%; *p* = 0.005) showing significant renal impairment (< 70 ml/min).

## Discussion

There is increasing interest in the higher rates of CAD in both South Asian migrants to the industrialised world and in the rapid increase in the rate of CAD in the

Indian subcontinent<sup>10,11</sup>. A number of studies have investigated CAD risk factors in migrant South Asian populations and identified the higher incidence of diabetes, low HDL, moderately raised LDL, body mass index, homocysteine and CRP as risk factors<sup>12–15</sup>. The contribution of smoking, Lp(a) and fibrinogen have been variable between different studies<sup>11,14–19</sup>. However, studies conducted in South Asian populations *in situ* are less frequent and have generally assessed CAD as a categorical variable in contrast to studies in migrant populations that have included quantification of severity of CAD by angiography<sup>11</sup> or used surrogate markers such as carotid intima media thickness with similar results<sup>20</sup>. Prevalence of CHD risk factors is known to be high in Pakistan for some time now<sup>6</sup>, but no effort has previously been made to identify the risk-factor causal associations in the Pakistani population. Ideally such associations should have been determined in a prospective cohort design; however, time and resource constraints necessitated that this be looked at in a case-control design. This is therefore the first study that establishes risk factor causal associations for coronary heart disease in the indigenous Pakistani population.

There are several strengths and weaknesses of this study. Gold standard criteria were used for case definition; also, controls underwent the same investigative procedures as the cases. Efforts were made to mitigate the traditional sources of bias in conventional case-control studies. Because of the high response rate and low level of dropouts and non-participants, biases such as the non-response bias, the non-participant bias and the drop-out bias were eliminated to a very large extent. An attempt was also made to eliminate several other biases; a single interviewer was used throughout the period of the study, thus minimising inter-observer variation. There were also efforts made to ensure quality control and corrections for intra-observer variation. Blinding the interviewer to the diagnosis at the time of the interview helped in eliminating the exposure-suspicion bias; this was aided by strict standardisation of the anthropometric and laboratory protocols and the use of a single observer.

**Table 4.** Associations of cardiovascular risk factors with a semi-quantitative measure of severity of coronary atherosclerosis (Gensini score) in patients with/without occlusive coronary arterial disease

Variable	Beta coefficient	Standard error (B)	<i>t</i> -Value	<i>p</i> -Value
Age	0.693002	0.29111	2.3806	0.01
Diabetes (years)	1.253905	0.625521	2.0046	0.04
Waist-hip ratio	65.872181	34.908368	1.887	0.06
Fat mass	-0.60399	0.3688	-1.6377	0.1
HDL	-45.593604	11.588733	-3.9343	< 0.001
Creatinine	0.330471	0.088795	3.7217	< 0.001
Lp(a) log	9.46344	2.870273	3.2971	< 0.001
CRP log	5.618057	2.073161	2.7099	< 0.001

However, there are also several weaknesses in this study. Cases and controls were matched for age within 5 years; however, due to the consistent recruitment of younger controls, albeit within 5 years, there was a statistically significant difference in the age of the cases and controls. Because of matching, however, it was not possible to study the relationship of disease to age.

This study, which is similar to other studies carried out on expatriate Pakistani populations<sup>21</sup> and native populations in India<sup>22</sup>, showed an association of CAD with hypertension, diabetes and smoking. In particular, it showed the relevance of current heavy smoking, either in cases or their spouses, to CAD which is similar to data found in expatriate Bengalis<sup>23</sup>. In contrast to studies in Southern India<sup>20</sup>, a weaker relationship was found with LDL and total cholesterol (TC). Similar data have also been reported for Pakistani migrants, where mean serum total cholesterol levels are known to be lower than that of the white population<sup>24</sup>. Indeed, in this study the cases had levels of total cholesterol and LDL below currently accepted thresholds for treatment in the developed countries, although within the range that showed benefit from statin therapy in the Heart Protection Study (HPS)<sup>25</sup>. When interpreted in the context of the HPS data, there may be a case for recommending further lowering of lipid levels in the Pakistani population to what would be considered as 'normal lipid levels' for the white population in the secondary prevention setting. However, such recommendations need to be evidence-based, which suggests that clinical endpoint trials would be required in the Pakistani setting to define the best therapeutic strategy for treatment of CHD. Such recommendations also have to weigh the benefit of statin therapy against economic feasibility, since the cost of statins which is prohibitive in Pakistan<sup>26</sup>.

In contrast, in this study, the ratio of TC/HDL and HDL has shown a strong association with CAD. This appears to be part of the metabolic syndrome, other components of which have also shown a strong association with CAD in this study. In addition, WHR, CRP and low HDL emerged as the strongest predictors of CAD in the multivariate analysis. These findings are consistent with the earlier hypothesis which suggested that glucose intolerance and insulin resistance underlie the increased risk of CAD in the expatriate South Asian population and that the effect of insulin resistance is likely to be mediated through changes in lipoprotein metabolism<sup>27-29</sup>.

The metabolic syndrome is also associated with increased inflammatory markers<sup>30-32</sup>. Expatriate South Asians are known to have increased levels of inflammatory markers compared with the white population; these correlate with central obesity and insulin resistance<sup>12</sup>. Results of this study support the hypothesis that inflammation may mediate the

increased coronary risk associated with insulin resistance; CRP was seen to correlate strongly with WHR, which is one of the hallmark abnormalities of the insulin resistance syndrome (Pearson correlation coefficient 0.12,  $p$ -value = 0.01). The strong association of CAD with Lp(a) shown in this study confirms some of the published data<sup>19,33</sup>. Whether it reflects the association of Lp(a) with family history of atherosclerotic disease, very-low density lipoprotein metabolism, or the acute phase reaction is uncertain.

The consistent association of CAD with creatinine, after correction for diuretic therapy, in this cohort is novel and calculation of GFR showed that 38.5% of cases had significant renal impairment despite superficially 'normal' levels. Recent evidence has established an association of creatinine with increased vascular events in diabetics<sup>34</sup>; in addition, recent studies also support the hypothesis that renal disease and ischaemic heart disease progress in parallel<sup>35</sup>. Consistent associations of creatinine have not only been found with CHD in patients with severe renal failure<sup>36</sup>, but also in women with 'normal' renal function and angiographic CHD<sup>37</sup> which correlate with endothelial dysfunction and microalbuminuria<sup>14,38</sup>. Impaired renal function in patients with insulin resistance is associated with elevations in creatinine and increased albumin excretion<sup>39</sup>, but microalbuminuria was not measured in this study.

The cardiovascular risk profile in this population is consistent with the effects of smoking on the metabolic syndrome allied to inflammation and possibly insulin resistance associated nephropathy. There are several practical implications of this study, both from the population and clinical approach, on the prevention and control of CAD. Findings from this study support the notion that health promotion initiatives in this population should reinforce the importance of physical activity and diet among other things such as cessation of tobacco use<sup>40</sup>. In addition, primary and secondary prevention strategies could be based on measurement of WHR and HDL as these were the best predictors of CAD in this group. This information has important implications for CAD risk assessment indicating that the simple, easy-to-perform, cost-sensitive clinical measure of WHR may be the most sensitive measure of CAD risk in this group of predisposed individuals.

The study also has implications for management of patients with CAD in Pakistan. Levels of total cholesterol and LDL were below currently accepted thresholds for treatment in the developed countries<sup>40,41</sup>, although within the range that showed benefit from statin therapy in the Heart Protection Study<sup>25</sup> and in the Pravastatin Pooling Project<sup>42</sup>. Despite the recent data on the efficacy of statins at low LDL levels, the lipid profile in this study better resembles the low HDL-low LDL-cholesterol cohort recruited to the Veterans Affairs

HDL Cholesterol Intervention Trial (VA-HIT)<sup>43</sup>. There are suggestions that fibrate therapy in VA-HIT may be more efficacious than statin therapy in this group<sup>44,45</sup>. However, such recommendations need to be evidence-based, which suggests that clinical endpoint trials will be required in the Pakistani setting to define the best therapeutic strategy for treatment of CAD. Any recommendations arising from such studies will also have to weigh the benefit of drug therapies against economic feasibility in the developing world.

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