Soluble inter-cellular adhesion molecule-1 in urban Asian north Indians: Relationships with anthropometric and metabolic covariates

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Abstract. *Background:* High prevalence of diabetes, obesity, and dyslipidemias in people belonging to poor socio-economic strata in urban slums of northern India has been recorded recently. To assess whether this population has high levels of soluble intercellular adhesion molecule-1 (sICAM-1), a cytokine involved in the pathogenesis of atherosclerosis, we investigated subjects belonging to poor socio-economic strata in urban slums and compared them to healthy control subjects from non-slum urban areas of New Delhi.

Design: Cross-sectional study.

Methods: Subjects from a previously carried out cross-sectional study, Delhi Urban Slum Project (DUSP) were divided into two groups: Group-1 ($n = 56$) included subjects dwelling in slum area, having at least one risk factor (hypertension, hyperglycemia, hypertriglyceridemia and hypercholesterolemia), while group-2 ($n = 60$) consisted of subjects without any risk factor dwelling in the slum area. A third group ($n = 29$) of non-obese subjects without any risk factor living in non-slum urban area was included for comparison. Measurements included; body mass index (BMI), waist-hip ratio (W-HR), four skinfolds, percentage body fat, fasting plasma glucose (FPG), serum lipids, and serum levels of sICAM-1.

Results: Though statistically not significant, mean level of sICAM-1 was higher in group-1 (718.5 ± 232.8 ng/ml) as compared to the other groups. Of note, 35% of subjects in group-1 ($p < 0.05$ as compared to other two groups), and 25.3% of all subjects had levels of sICAM-1 in uppermost quartile (> 850 ng/ml). Partial correlation coefficients (R) of sICAM-1 levels with various parameters adjusted for age were statistically significant for BMI ($R = 0.27$, $p < 0.05$) in group-1; W-HR ($R = 0.26$, $p < 0.05$) and BMI ($R = 0.19$, $p < 0.05$) for group-2; and FPG ($R = 0.17$, $p < 0.05$) for all the subjects considered together. For females, the levels of sICAM-1 were significantly higher in the following: BMI ≥ 25 kg/m² ($p = 0.04$) and FPG > 7 mmol/l ($p < 0.05$). Multiple linear regression analysis suggests that an increment in BMI by one kg/m² would correspond to an increase in the levels of sICAM-1 by 8.5 units controlling for the influence of age and W-HR in the pooled data of all subjects.

Conclusions: High percentage of subjects had levels of sICAM-1 in the upper quartile in the study, particularly those dwelling in the slum area and having coronary risk factor (s). The levels of sICAM-1 strongly correlated to the anthropometric and metabolic parameters, particularly in females. These observations are of potential importance for the pathogenesis of atherosclerosis in this population, though further studies are needed to predict those prone to the complications of atherosclerosis, based on sICAM-1 levels, as has been observed in other ethnic groups.

Keywords: Soluble intercellular adhesion molecule-1, body mass index, obesity, type 2 diabetes mellitus, hyperlipidemia

1. Introduction

Recent evidence suggests that the inflammatory pathways are important for the pathogenesis of atherosclerosis. There is a growing body of evidence supporting the role of cell adhesion molecules (CAMs) in the

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initiation of atherosclerosis. CAMs are expressed on the endothelial membrane in response to inflammatory cytokines [17] and promote leucocyte adhesion to vascular endothelium and subsequent transmigration [12, 27], thus initiating the formation of 'foam cells'. Immunohistochemical assays in the hyperlipidemic experimental models show increased expression of adhesion molecules in atherosclerotic plaques [25]. Recent studies using chromatin image analysis provide further important evidence regarding sICAM and inflammatory nature of atherosclerosis [9].

High serum levels of CAMs may indicate endothelial dysfunction [14], an important feature of insulin resistance syndrome (IRS) and associated metabolic diseases [7]. Recent studies show upregulation of CAMs in obese hypertensive men [10] and in the patients with type 2 diabetes mellitus and coronary artery disease (CAD) [29]. Among various types of CAMs, soluble intercellular cell adhesion molecule-1 (sICAM-1) appears to be more specific to the atherosclerotic vascular lesions [5]. High serum levels of sICAM-1 have been reported in communicable and other non-communicable diseases, e.g. bacterial and viral infections [1,15] and respiratory disorders [23].

Asian Indians are particularly vulnerable to develop IRS and accelerated atherosclerosis. High prevalences of obesity, type 2 diabetes mellitus, and dyslipidemia have been reported in urban subjects and also in economically poor people residing in urban slums [4]. Such people undergo marked socio-economic transition, having migrated from villages to cities in the search of better livelihood. During this process they relinquish their simple penurious and physically active lifestyle, and acquire several risk factors of atherosclerosis e.g. adverse dietary profile, sedentary habits, smoking, and alcohol intake. In addition, they undergo severe psychological stress. Recently, high prevalence of risk factors for atherosclerosis and pro-atherogenic dietary profile of the urban slum population have been reported by us [3,4]. Similarly, studies in other ethnic groups also suggest that obesity and malnutrition co-exist in urban slums [8].

We studied two groups of subjects, with and without coronary risk factors (type 2 diabetes mellitus, hypertension, and dyslipidemia) from the previously carried out Delhi Urban Slum Project (DUSP), and compared them to a control group consisting of healthy subjects from urban non-slum area of New Delhi. We also examined relationships of serum levels of sICAM-1, anthropometric and metabolic parameters.

2. Methods

Three groups of subjects ($n = 145$) from two different residential areas in Southern New Delhi, based on the presence of any of the following risk factors for CAD namely hypertension, hyperglycemia, hypertriglyceridemia and hypercholesterolemia were included in the study. Group-1 ($n = 56$) consisted of subjects from urban slum area having at least one of the previously mentioned risk factors. Group-2 ($n = 60$) comprised of subjects from urban slum area having none of the risk factors mentioned above. The sanitary and hygienic conditions in the slum area were extremely poor, and the population frequently suffered from common infectious diseases (respiratory and gastrointestinal infections and enteric fever etc.) and malaria. Subjects in group-3 ($n = 29$) were non-obese, non-diabetic medical students living in urban non-slum area, having none of the risk factors and had no history any acute infections (within previous six months) or chronic infections (respiratory, gastrointestinal and others).

Group-1 and group-2 subjects were selected from the sample of population recruited for Delhi Urban Slum Project (DUSP) [4]. Out of 532 subjects initially recruited in DUSP, 116 subjects were included in groups 1 and 2 in the present study based on their risk factor profile and adequacy of frozen serum sample for analysis of sICAM-1 levels. The slum area, (Gautam Nagar colony), consisted of sixteen square kilometer area, having a population of approximately 30,000 people. People had migrated from the adjoining states, and were residing in the slum colony for a mean period of 14 months (range 45 days–5 years). Their monthly incomes in rupees were as follows; no earning –25%, < 1000 (approximately US \$25) –13%, 1000–2000 (approximately US \$20–40) –32%, 2000–4000 (approximately US \$40–80) –20%, > 4000 (approximately US \$85) –10%.

The detailed epidemiological procedures have been described elsewhere [4]. Briefly, the area was divided into four equal sectors using electoral list providing the name, age and addresses of those eligible for voting (> 18 years of age) available from the Slum Development Wing, Government of India. The data were collected within a period of 20 months, starting from January 1998. Two medical teams administered detailed questionnaires incorporating demographic profile, socio-economic data, migration pattern, relevant symptoms, tobacco and alcohol consumption, physical activity pattern, and food frequency profile to the recruited subjects. Subjects in group-3 were recruited

by advertisements in the medical school, whereupon, healthy medical students were selected for the study. Subjects with manifest CAD, history of cerebrovascular accident, peripheral vascular disease, severe end-organ dysfunction, acute illnesses, acquired immunodeficiency syndrome, pregnant females, and patients of substance abuse etc. were excluded. The institutional ethics review board approved the study. An informed consent in the local language was taken from all the subjects.

Complete physical examination was performed in all the subjects. The subjects from the slum area were examined at the site, and medical students were admitted for a short period in the General Clinical Research Center. Blood pressure was recorded in sitting position after 5 minutes rest with a mercury sphygmomanometer according to the standard guidelines. If one blood pressure reading $\geq 140/90$ mmHg was observed, a second reading was taken after 10 minutes of rest. The blood samples were collected after 12-hour overnight fast for the estimation of the metabolic parameters.

2.1. Anthropometric measurements

Weight and height were measured to the nearest kilograms and to the nearest centimeter, respectively. The body mass index (BMI) was calculated as weight (kg)/height²(m). Waist circumference was measured midway between iliac crest and lowermost margin of the ribs. The hip circumference was measured with the subject wearing minimum clothes possible at the maximum circumference of buttocks. Mean of three readings of each parameter was taken for the calculation of waist-hip ratio (W-HR). Lange skinfold calipers (Beta Technology Inc, Santa Cruz, CA, USA) were used to measure all skinfolds (biceps, triceps, subscapular, and suprailiac). With right arm pendant, fat pad was measured at the level of the nipple line for biceps skinfold. Triceps skinfold was measured midway between acromion process of scapula and olecranon process. Subcutaneous fat pads at the inferior angle of scapula and superiorly on iliac crest directly in the mid-axillary line were measured for sub-scapular and supra-iliac skinfolds, respectively. The skinfolds were measured to the nearest 1-mm and a mean of three readings at each site was recorded. By adding all skinfolds, sum of four skinfolds (sigma 4 SF) was calculated. Percentage body fat (% BF) was calculated using the equation of Durnin and Womersely [19]. For the calculation of body fat, the equation been validated in Asian Indians [31].

2.2. Biochemical tests

Blood samples were collected and transported to laboratory within 30 minutes. The samples were allowed to clot at room temperature for 45 minutes and serum was separated by centrifuging the tubes at 2000 rpm. for 15 minutes. Serum was stored frozen at -20°C until further use. Estimations for total cholesterol (TC), serum triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) were performed on the sample drawn after a 12-hour overnight fast. TC, TG, and HDL-c were estimated by the ELISA kits (Randox Laboratory, San Francisco, CA, USA) on a semi-automated analyzer (Micro Semi-Autoanalyser 2000, C.L. Micromed, Italy). Value of low-density lipoprotein cholesterol (LDL-c) was calculated using Friedewald's equation.

2.3. sICAM-1 assay

The laboratory personnel performing the assay were masked of the group identity of the subjects. Stored sera from the subjects were thawed and assayed for sICAM-1 using ELISA kit (Batch 0054-23, Diaclone Research, France). The color developed after the reaction was read using an ELISA Reader (Microspan, India.) A linear curve was obtained by plotting the average absorbance, depicted by optical density (OD) on the vertical axis versus the corresponding sICAM-1 standard concentration on horizontal axis. The amount of sICAM-1 in each sample was determined by extrapolating OD values to sICAM-1 concentrations using the standard curve. The minimal detectable dose of sICAM-1 according to the manufacturer was 0.1 ng/ml. The average normal level of sICAM as given by the manufacturers was 571 ± 168 ng/ml (range: 219 to 1042 ng/ml).

2.4. Definitions

Obesity was defined as $\text{BMI} > 25 \text{ kg/m}^2$ [42]. % BF was defined as indicative of obesity if it was $> 25\%$ in males and $> 30\%$ in females [26,38]. High W-HR was defined as > 0.95 in males and > 0.80 in females [41]. Sigma 4SF was defined as high when the value exceeded 50 mm [40]. A subject was labeled as hypertensive when systolic blood pressure was ≥ 140 mm Hg, and diastolic blood pressure was ≥ 90 mm Hg on two measurements taken ten minutes apart in previously undiagnosed patients, and those patients already on anti-hypertensive treatment. Dia-

betes mellitus was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl) [39]. Hyperlipidemia was defined by the following; serum triglycerides (TG) ≥ 2.26 mmol/l (200 mg/dl), total cholesterol (TC) ≥ 5.20 mmol/l (200 mg/dl), or LDL-c ≥ 3.88 mmol/l (150 mg/dl) [28].

2.5. Statistical analysis

Data were recorded on a pre-designed proforma and managed on Excel spreadsheet. All the entries were double-checked for any possible error by the same person. STATA 7.0 Intercooled version (Stata Corporation, College Station, Houston, TX, USA) was used for the statistical analysis. Anthropometric variables, metabolic profile, and the values of sICAM-1 were considered at quantitative level for purpose of comparison amongst the three groups. The distribution of all the quantitative variables was assessed for approximate normality and after confirmation these were summarized by mean and standard deviation for each group. One-way analysis of variance (ANOVA) was used to compute anthropometric and metabolic parameters amongst the three groups. If the overall significance was shown by the 'F' test, Scheffe's multiple comparison was used as the post-hoc ANOVA to assess which pair(s) of mean values was different. Partial correlation coefficient was computed to assess the strength of relationship between sICAM-1 and various anthropometric and metabolic parameters adjusted for age. Age adjustment was carried out as the subjects in three groups were of different age. The mean values of sICAM-1 for various subgroups in the present study were compared with similar subgroups in other studies by modified student's 't' test with $n_1 + n_2 - 2$ degrees of freedom (used in case of unequal variance) [30]. Stepwise multiple linear regression analysis was used to determine the predictors for the levels of sICAM-1. Value of $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Demographic and anthropometric data

Mean age (years) of subjects in group-1 (42.3 ± 11.1) was significantly higher ($p < 0.001$) as compared to the subjects in group-2 (36.9 ± 13.1) and group-3 (23.0 ± 4.0). The gender distribution of subjects in the three groups was statistically comparable. The proportion of

smokers was 23 (41.1%), 23 (38.3%) and 2 (6.9%) in groups 1, 2 and 3, respectively (Table 1).

Obesity-related variables were analysed in group 1 and group-2 only, since group-3 consisted of non-obese subjects. Group-1 subjects had significantly higher values of BMI as compared to other two groups ($p < 0.01$). Applying BMI ≥ 25 kg/m² as cutoff for the diagnosis of obesity, 4 (7%) males and 15 (25%) females were obese (excluding group-3). The group-wise distribution of obese subjects was as follows: group-1-males: 3 (11.4%), females 10 (33.3%), and group-2-males: 1 (3.3%), females: 5 (16.7%). Biceps skinfolds and triceps skinfolds were significantly higher in group-3 ($p < 0.05$) as compared to other groups. Values of sigma 4SF in the three groups were statistically comparable. Similarly, no significant differences were observed in the values of % BF and W-HR in the three groups. Higher values of W-HR were recorded in 9 (13.6%) males and 33 (44%) females when all the subjects were pooled together. Similarly, 36 (48%) females and 8 (12.3%) males showed higher values of % BF.

3.2. Metabolic profile

The presence of hypertension, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia was observed in 22 (39.3%), 7 (12.5%), 38 (67.8%) and 26 (46.4%) of subjects, respectively, in group-1 (Table 1). Significantly higher mean values of FPG ($p < 0.05$), TC ($p < 0.001$), TG ($p < 0.001$), LDL-c ($p < 0.001$), and ratio of LDL-c/HDL-c ($p < 0.001$) were observed in group-1 as compared to other groups. Mean value of HDL-c was lower in group-1 as compared to the other groups ($p < 0.05$). HDL-c values of < 0.9 mmol/l (35 mg/dl) were recorded in 14 (25%) subjects in group-1, and 9 (15.0%) subjects in group-2.

3.3. Values of sICAM-1 and its correlations with anthropometric and metabolic parameters

Mean levels of sICAM-1, though higher in group-1 (718.5 ± 232.8 ng/ml), were statistically comparable amongst the three groups (Table 1, Fig. 1). Further, the levels of sICAM-1 were higher in the subjects with hypercholesterolemia (720.7 ± 273.3 ng/ml), hypertriglyceridemia (759.2 ± 232.3 ng/ml), diabetes mellitus (878.6 ± 159.5 ng/ml) and hypertension (788.6 ± 274.3 ng/ml) in group-1 as compared to the mean levels in the other groups (Table 1), though the differences were statistically not significant. Further, mean serum

Table 1
Anthropometric and biochemical profile adjusted for age and BMI (all values in mean $\pm$ SD)

Variables	Group-1 (<i>n</i> = 56; M-26, F-30)	Group-2 (<i>n</i> = 60; M-30, F-30)	Group-3 (<i>n</i> = 29; M-13, F-16)	p value
<i>Anthropometry</i>				
Body mass index (kg/m ²)	22.1 $\pm$ 4.5	19.6 $\pm$ 4.5 ^a	20.7 $\pm$ 4.6	< 0.01
Skinfolds (mm) Biceps	6.7 $\pm$ 4.9	8.0 $\pm$ 4.9	9.3 $\pm$ 5.0 ^b	NS
Triceps	13.0 $\pm$ 6.4	12.9 $\pm$ 6.3	16.0 $\pm$ 6.4 ^{b,c}	< 0.05
Subscapular	15.9 $\pm$ 8.1	17.0 $\pm$ 8.0	18.4 $\pm$ 8.1	NS
Suprailiac	18.3 $\pm$ 9.1	19.6 $\pm$ 9.1	17.1 $\pm$ 9.2	NS
Sigma 4SF	53.4 $\pm$ 25.4	56.9 $\pm$ 25.4	60.5 $\pm$ 25.7	NS
Percentage body fat (%)	23.7 $\pm$ 7.5	24.0 $\pm$ 7.4	25.3 $\pm$ 7.6	NS
Waist-hip ratio	0.84 $\pm$ 0.06	0.83 $\pm$ 0.06	0.83 $\pm$ 0.07	NS
<i>Biochemistry (mmol/l)</i>				
Fasting plasma glucose	5.55 $\pm$ 1.74	4.79 $\pm$ 1.73 ^a	4.65 $\pm$ 1.76 ^b	< 0.05
Total cholesterol	5.73 $\pm$ 0.93	4.15 $\pm$ 0.93 ^a	4.16 $\pm$ 0.94 ^b	< 0.001
Serum triglycerides	2.14 $\pm$ 0.82	1.28 $\pm$ 0.81 ^a	1.19 $\pm$ 0.83 ^b	< 0.001
LDL-c	3.94 $\pm$ 1.09	2.62 $\pm$ 1.09 ^a	2.76 $\pm$ 1.10 ^b	< 0.001
HDL-c	0.96 $\pm$ 0.13	1.02 $\pm$ 0.12 ^a	1.01 $\pm$ 0.13 ^b	< 0.05
Ratio of LDL-c/HDL-c	4.2 $\pm$ 1.3	2.6 $\pm$ 1.2 ^a	2.7 $\pm$ 1.3 ^b	< 0.001
sICAM-1 (ng/ml)	718.5 $\pm$ 232.8	696.2 $\pm$ 232.3	688.7 $\pm$ 235.8	NS

a: I Vs II; b: I Vs III; c: II Vs III; statistically different at $p < 0.05$; NS: Statistically not significant. Group-1: Subjects from urban slums having at least one risk factor of coronary artery disease. Group-2: Non-diabetic, normolipidemic and normotensive subjects from urban slums. Group-3: Non-diabetic, non-obese, normolipidemic and normotensive controls from urban non-slum area. Sigma 4SF: sum of four skinfolds; sICAM-1: soluble intercellular adhesion molecule-1. LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

levels of sICAM-1 between the smokers (706.3 $\pm$ 251.7 ng/ml) and non-smokers (704.7 $\pm$ 223.7 ng/ml) were statistically not significant in all subjects combined and in each group. Subjects were categorized into quartiles of sICAM-1 levels (ng/ml) as quartile 1, < 500; quartile 2, 501-730; quartile 3, > 731-850; and quartile 4, > 851 (Fig. 2). Number of subjects in the uppermost quartile was: group-1, 20 (35.1%, $p < 0.05$ as compared to other two groups), group-2, 12 (20%) and group-3, 5 (17.3%). Of note, overall, 37(25.3%) of subjects had sICAM-1 levels in uppermost quartile (Fig. 2).

Partial correlation coefficient R between levels of sICAM-1 and various anthropometric and metabolic parameters adjusted for age showed significant ($p < 0.05$) correlations with BMI in group-1 ($R = 0.27$), with W-HR in group-2 ($R = 0.26$), and with BMI ($R = 0.19$) and FPG ($R = 0.17$) when subjects in three groups were pooled together.

Multiple linear regression analyses with serum sICAM-1 as the dependent variable were used to develop regression equations of all subjects (Table 2). Linear relationship between sICAM-1 levels and BMI was observed when all subjects were analyzed together. To assess the lipid parameters being influenced by the levels of sICAM-1, while keeping the effect of other variables on lipid parameters as constant, we used multiple linear regression analysis with individual lipid pa-

rameters as dependent variables, sICAM-1 as an exposure variable and age, BMI, W-HR, area of residence, and other lipid parameters as co-variables. There was no statistically significant relationship of sICAM-1 with any of the lipid parameters. Subsequently, considering sICAM-1 as the response variable, we assessed the influence of anthropometric variables on sICAM-1 levels. Amongst age, BMI, waist-hip ratio, and area of residence, BMI was observed to be the only independent predictor of levels of sICAM-1. Increment in BMI value by one kg/m² would correspond to an increase in levels of sICAM-1 by 8.5 units ($p < 0.05$) controlling for age and W-HR.

For females, the levels of sICAM-1 were significantly higher (831.3 $\pm$ 247.5 ng/ml) in those with BMI ≥ 25 kg/m² as compared to the subjects with BMI < 25 kg/m² ($p < 0.05$), and in those with high values of FPG (906.6 $\pm$ 154.6 ng/ml) as compared to those with normal blood glucose levels ($p < 0.05$). No significant relationship of sICAM-1 levels and various anthropometric and metabolic parameters was observed in males.

4. Discussion

The observations of similar levels of sICAM-1 in people of low socio-economic strata with and without

Fig. 1. Summary statistics of serum levels of sICAM-1. Group-1: Subjects from urban slums having at least one risk factor for coronary artery disease; group-2: Non-diabetic, normolipidemic and normotensive subjects from urban slums; group-3: Non-diabetic, normolipidemic and normotensive subjects from urban non-slum area; sICAM-1: Soluble intercellular adhesion molecule-1.

Fig. 2. Distribution of subjects according to quartiles of sICAM-1 levels. Group-1: Subjects from urban slums having at least one risk factor for coronary artery disease; group-2: Non-diabetic, normolipidemic and normotensive subjects from urban slums; group-3: Non-diabetic, normolipidemic and normotensive subjects from urban non-slum area; sICAM-1: Soluble intercellular adhesion molecule-1.

coronary risk factors as well as in normal subjects are of significance. Of note, in this study approximately 20–35% subjects displayed levels of sICAM-1 in the highest quartile in all the groups, including the group consisting of young, health-conscious, normotensive, non-obese, non-diabetic medical students. Moreover, the low socio-economic strata group having various risk

factors showed the highest number of subjects in the uppermost quartile of sICAM-1. These observations are of potential importance, since, according to the data in the Physicians Health Study, increasing concentrations of sICAM-1 predict future risk for myocardial infarction (MI). According to Ridker et al. subjects in the highest quartile of sICAM-1 levels (taken as 75th

Table 2
Multiple linear regression analysis with serum levels of sICAM-1 as the dependent variable

Regression equation	R^2 (%)
$TC = +38.5 + 0.009(sICAM-1) + 6.4(SlumRes) - 0.03(Age) + 0.05(BMI) + 0.14*(TG) + 0.76*(LDL-c)$	73.3
$TG = -71.5 + 0.01(sICAM-1) + 20.2(SlumRes) + 0.83(Age) + 167.9*(W-HR) + 1.6*(\%BF) + 0.88*(T.C) - 3.6*(HDL-c)$	33.1
$HDL-c = 36.3 + 0.001(sICAM-1) + 0.39(SlumRes) - 0.009(Age) + 0.04(BMI) - 0.02*(TC) - 0.01*(TG)$	10
$LDL-c = -35.3 - 0.005(sICAM-1) - 1.07(SlumRes) + 0.24(Age) + 0.71(BMI) + 0.88(TC)* - 0.15*(TG)$	71.7
$sICAM-1 = 185.0 + 0.94(Age) + 8.5*(BMI) + 342.0(W-HR) + 5.2(SlumRes)$	5.3

sICAM-1: Soluble intercellular adhesion molecule-1; BMI: body mass index; W-HR: Waist-hip ratio; TC: total cholesterol; TG: serum triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; SlumRes: Area of residence (slum/non-slum);

*: $p < 0.05$; R^2 : coefficient of determination.

percentile of the control distribution of sICAM-1), had a relative risk of 1.6 for developing MI (95% confidence interval 1.1–2.4; $p = 0.02$) [29]. The crude matched-pair analysis revealed that the risk of future MI was 60% higher in subjects having sICAM-1 levels in the highest quartile. The risk increased with the increasing length of follow up, suggesting involvement of sICAM-1 in the initial pathway of atherosclerosis. High levels of sICAM-1 also correlated to high levels of pro-coagulant factors like serum fibrinogen, tissue type plasminogen activator antigen, and plasma homocysteine, augmenting the atherogenic risk several folds [29]. Further, in Atherosclerosis Risk in Communities (ARIC) Study, those with baseline sICAM-1 levels in the highest quartile had five times more risk of CAD as compared to the subjects having the lowest levels (relative risk 5.5, 95% confidence intervals 2.5–12.2) [37].

Levels of sICAM-1 in the slum population and healthy individuals in the present study could be affected due to multiple factors. Besides obesity and hyperlipidemia, myriad infections, as prevalent in northern India, may potentially increase sICAM-1 concentrations in blood and tissues. These include gastrointestinal infection with *Helicobacter pylori*, malaria, tuberculosis etc. All of these, and in particular, *H. pylori*, are common in Indian subcontinent. Prevalence of *H. pylori*, estimated serologically by IgG and IgA antibodies, was approximately 80–90% in the adult Asian Indian population [13]. Potable water and food supply in the hostel setting are frequently contaminated and are likely sources of asymptomatic infection in healthy resident medical students constituting group-3 in the present study. Of relevance, expression of sICAM-1 is increased in gastric epithelial cells in 80% of persons infected with *H. pylori*, decreasing significantly after its eradication [1], and constitutes predominant form of CAMs expressed [20]. Of importance, seropositivity of *H. pylori* has been reported to be associated with higher risk of CAD [21] and its eradication is reported

to be beneficial [21,22]. Interestingly, *H. pylori* DNA was demonstrated in the atherosclerotic plaques in the carotid arteries. Moreover, sICAM-1 was expressed in 75% of such plaques, significantly higher as compared to *H. pylori* negative plaques [36]. Despite these evidences, relationship between *H. pylori* and atherosclerosis needs further support, however, it remains potentially important in context of the current study. In individuals exposed to multiple infectious agents, such as in the current study, ‘aggregate pathogen load’ (pathogen burden due to exposure to multiple infectious agents) is of further interest, since it is reported to correlate to endothelial dysfunction, atherosclerosis, and mortality [35].

None of these issues have been investigated previously in people of poor socio-economic strata in the slums. In a preliminary study in urban population of city of Pune in western India, levels of pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor- α were reported to be the highest in the urban slum dwellers [18]. Frequent respiratory and gastrointestinal infections were cited as the possible causes of increased cytokine expression and endothelial dysfunction. The authors remarked that the role of increased levels of cytokines in the pathogenesis of type 2 diabetes mellitus and dyslipidemia in Asian Indian population remains to be defined [18].

Second, and perhaps an equally important cause of increased levels of sICAM-1 across all the three groups in the present study, may be exposure of the local population to an excessive atmospheric pollution. In New Delhi, one of the world’s 10 most polluted cities, vehicular exhaust contributes mostly to the atmospheric pollution. Interestingly, short-term exposure to the particulate diesel exhaust in healthy human volunteers up-regulates inflammatory mediators, including sICAM-1, in bronchial tissues, indicative of marked systemic and pulmonary inflammatory response [34]. Location of slums and residence of medical students recruited in the present study were close to one of the most pol-

Table 3
Comparative data of levels of sICAM-1 in various ethnic groups and diseases

Author	Ethnic group	Number	Disease	sICAM-1(ng/ml)
Hackman et al. (1996) [2]	Caucasians (USA)	14	Hypercholesterolemia	298 ± 29
		13	Hypertriglyceridemia	342 ± 31
		13	Controls	198.0 ± 14
De Souza et al. (1997) [11]	Caucasians (USA)	11	Hypertension	232.4 ± 16.5
			Controls	189.8 ± 11.1
Ferri et al. (1999) [10]	Europeans (Italy)	16	Impaired glucose tolerance +Hyperlipidemia	268 ± 84.1
		25	Impaired glucose tolerance	268 ± 84.1
		28	Hyperlipidemia	195.1 ± 68
Abe et al. (1998) [42]	Caucasians (USA)	39	Hypertriglyceridemia and low HDL-C	316.0 ± 28.8
			Controls	225.0 ± 16.6
			Type 2 diabetes mellitus	307.71 ± 86.2
Kvasnicka (1998) [16]	Czechs	118	Type 2 diabetes mellitus	307.71 ± 86.2
Ridker et al. (1998) [29] ^a	Caucasians (USA)	474	Cases ^b	59–675 ^d
		474	Controls ^c	59–675 ^d
Kado et al. (1999) [32]	Asians (Japan)	64	Type 2 diabetes mellitus	378.2 ± 70
Romano et al. (2000) [24]	Europeans (Italy)	26	Hypercholesterolemia	264 ± 75
John et al. (2000) [31]	Europeans (Germany)	52	Hypercholesterolemia	196 ± 56
		43	Control group	180 ± 38
Present Study ^e (2001)	Asians (Northern India)	56	Group-1 ^f	705.0 ± 261.4
		60	Group-2 ^f	680.5 ± 226.9
		29	Group-3 ^f	671.0 ± 215.2
			Subgroups	
		9	1. Hypertriglyceridemia and low HDL-c	691.8 ± 263.8
		40	2. Hypercholesterolemia	712.0 ± 250.0
		27	3. Hypertriglyceridemia	784.9 ± 244.5
		21	4. Hypertension	806.8 ± 236.6

^a: Prospective study, all the subjects were divided in four quartiles. Risk of future MI was 80% higher for participants in highest quartile. ^b: Cases-Subjects who developed a first myocardial infarction after 9 years of follow-up. ^c: Controls-Subjects who remained healthy throughout the 9-year follow-up. ^d: Range of sICAM-1 levels in case and control groups. ^e: Normal range of sICAM-1 level given by the manufacturer was 219–1042 ng/ml. ^f: Group-1: Subjects from urban slums having ≥ 1 risk factor for coronary artery disease; Group-2: Non-diabetic, normolipidemic and normotensive subjects from urban slums; Group-3: Non-diabetic, non-obese, normolipidemic and normotensive healthy controls from non-slum area. HDL-C: High-density lipoprotein cholesterol.

luted areas in the city. Upon long-term exposure to diesel exhaust as well as to other atmospheric pollutants, pulmonary and systemic levels of sICAM-1 may even be raised to a higher level. The latter is a potentially important yet unexplored problem for the people chronically living in the heavily polluted environment.

Table 3 shows inter-ethnic and inter-disease comparisons in the levels of sICAM-1 from the published literature [2,11,16,24,32,33,43]. It must be mentioned, however, that sICAM-1 levels were estimated in widely varied clinical situations and using different commercial kits and methodologies in the studies. For example, observation of higher values of sICAM-1 in the current study as compared to other studies could also be to the differences in the normal levels of sICAM-1 provided by the manufacturer of the ELISA kits used by us as compared to those provided by other manufacturers. Hence, data of sICAM-1 in sub-groups of patients in the present study, such as hypertension, diabetes mellitus and dyslipidemia could not be statistically com-

pared to the matched groups from the studies carried out on the other ethnic groups.

The present study has its limitation because of its cross-sectional design and relatively limited number of subjects in each group. Further, temporal relationship between sICAM-1 levels and various factors influencing its expression and its relationship with endpoints of atherosclerosis were not estimated. A prospective study with larger number of subjects, including other inflammatory markers (e.g. C-reactive protein) and pro-coagulant markers (e.g. serum fibrinogen) of atherosclerosis is could yield more meaningful results. The sample population in the present study was also not matched for smoking status. Cigarette smoke is one of the most important factors causing increased sICAM-1 expression [6]. Though this may be one of the confounding factors, however, in the current study sICAM-1 levels in smokers (706.3 ± 251.7 ng/ml) were similar to those in non-smokers (704.7 ± 223.7 ng/ml, $p = ns$) in the pooled data of all subjects. Further, there was no

difference when sICAM-1 levels were compared between smokers and non-smokers in each group. This anomalous observation in the study could be due to the small sample size. Further, uniform high exposure to atmospheric and indoor pollution to smokers as well as the non-smokers, and its potential effects on the levels of sICAM, could also be responsible for the leveling of the difference.

Significant correlations of serum levels of sICAM-1 with BMI and FPG in females were not surprising and consistent with the earlier studies on the same population sample showing higher coronary risk factors in females as compared to males [3,4]. Particularly striking observations were generalized and abdominal obesity and excess % BF, and steep increase in body fat in middle age in females [4]. Of further note, 12–28% of the females in this population were hyperlipidemic [4].

5. Conclusions

Significant observations of the current study were high number of subjects in the uppermost quartile of sICAM-1 levels in all groups, and particularly in group-1 and its significant correlation to parameters of generalized obesity, abdominal obesity, and glycemia, though mean levels of sICAM-1 were not significantly different among the three groups. Such high levels of sICAM-1 could also be due to the frequent infections and high levels of atmospheric pollution. In view of these observations, presence of high levels of sICAM-1 may not be able to predict precisely those prone to atherosclerosis and its complications, as has been reported for other ethnic groups, although it may have a potential role in the pathogenesis of atherosclerosis in Asian Indians. This important research question should be addressed in large prospective studies.

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