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Lewis blood group phenotype vis-a-vis biochemical and physiological parameters of coronary artery disease: A study in North Indian population

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Abstract:

BACKGROUND: Many studies have proposed the lack of Lewis antigen as a marker for coronary artery disease (CAD); on the contrary, some of the studies found no association in this regard. This study aims to assess the association of the expression of Lewis antigen as an independent risk factor for CAD separately in males and females.

MATERIALS AND METHODS: In this cross-sectional observational study, patients with angiographically proven CAD were taken as test group, and angiographically, negative patients were included as a control group. The individuals were examined for established CAD risk factor and Lewis antigen expression on red cell. Red cell Lewis phenotyping was done using microcolumn gel agglutination technology. Statistical tests were applied to see the association between lack of Lewis antigen expression and CAD.

RESULTS: Of these 232 patients included in the study, 161 patients had more than 50% luminal stenosis in a major epicardial artery on coronary angiography (Test Group), and 71 were normal on angiography (Control Group). When males and females were considered together, there was an increased frequency of Lewis-negative phenotype among the angiography-positive group (26.7%) as compared to angiography normal control group (16.9 %), though was not statistically significant ($P = 0.19$). When males and females were segregated in multivariate analysis, Le (a-b-) females had a higher incidence of CAD ($P = 0.03$) with the odds ratio of 4.97, though an association was not found significant in males ($P = 0.71$).

CONCLUSION: The association between Lewis phenotypes and CAD was not significant in males and in among the overall study population, but this association was statistically significant in females. Further studies based on a larger sample size may substantiate as well as delineate the possible hypotheses.

Keywords:

Coronary artery disease, Lewis blood group and coronary artery disease, Lewis-negative phenotype

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Introduction

In the past few decades, evidence-based medicine has emerged as a leading tool in explaining the relation between the blood group systems and systemic disorders based on immunological, histological, biochemical, and clinical findings.[1] Several studies have proposed the Lewis blood groups as the genetic marker for epidemiological screening in ischemic heart disease.[2-4] The role of Lewis blood group oligosaccharides in leukocyte-endothelium adhesion has been often thought to be the pivot in the

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pathogenesis of the cardiac disease. Exocrine epithelial cells secrete these fucosylated oligosaccharide antigens into plasma. These antigens are present in plasma as the high- and low-density lipoproteins (LDLs) and adsorbed on to red blood cell (RBC) membrane as glycolipids.[5] The distribution and expression of Le^a and Le^b phenotypes differ based on ethnicity, gender, and demography.[6,7] The gene regulating their synthesis is in close association with LDL receptor gene, insulin receptor gene, and glycogen synthetase gene and may have bearing in the linkage disequilibrium on the 19th chromosome. There are reports showing a strong association between the absence of Lewis antigens and the coronary artery disease (CAD).[2-4,8] On the other hand, some of the studies reported no such association in this regard.[9,10] The present study was aimed to assess the association of Lewis phenotype as an independent risk factor for CAD and its utility as a standard screening test to prevent such occurrences in high-risk individuals.

Materials and Methods

In this cross-sectional observational study, consecutive patients suspected for CAD, based on coronary angiography and catheterization, were enrolled in the study. The study was conducted after obtaining prior informed consent from individual patients and approval from the Institute's Ethics Committee. Those with angiographically proven CAD (defined as ≥50% luminal stenosis of coronary artery)[11] were included as "Test group," and those with normal angiography were included as a control group. Individuals with <25 years of age and pregnant females were excluded from the study. Three hundred healthy voluntary blood donors were included as control group to ascertain the baseline frequency of Lewis phenotypes in the population [Figure 1]. Details about conventional CAD risk factors were recorded, which include smoking, diabetes mellitus, and hypertension, body mass index (BMI), waist–hip ratio, fasting blood sugar, lipid profile, and phenotyping for Lewis blood group systems.

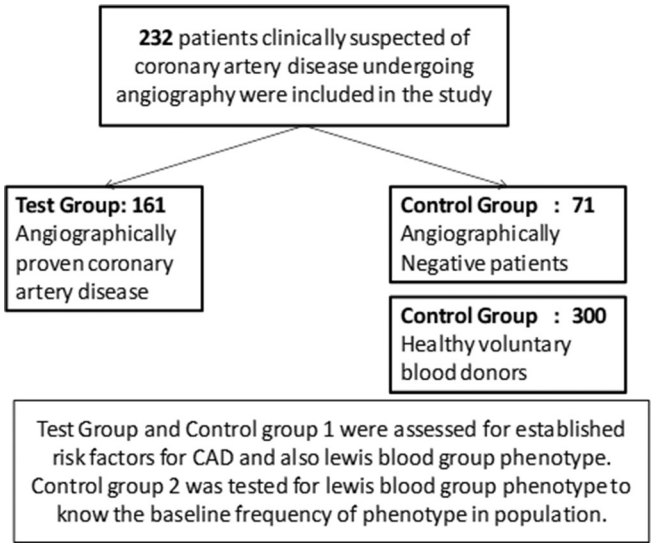

Figure 1: Study design

Red cell Lewis phenotyping was done using microcolumn gel agglutination technology[12] using ID-Card "DiaClon Anti-Le^a" and "DiaClon Anti-Le^b" (Biorad, California, USA). Modular *P* automated clinical chemistry analyzer (Roche, USA) was used to assess the biochemical profile of the individuals.

In a total of 232 consecutive patients subjected to coronary angiography, 161 patients had ≥50% luminal stenosis in a major epicardial artery (Test Group), and 71 had normal coronaries (Control Group).Of the total 232 enrolled patients, 161 were male (124 in the test group and 37 in control Group 1), and 71 were female (37 in the test group and 34 in control group). The study population was analyzed as two groups based on the results of Lewis antigen testing as Lewis-negative (Lewis [a–b–]) and Lewis-positive phenotype (Lewis [a+b–], Lewis [a–b+] and Lewis [a+b+]).

Statistical analysis

Chi-square test was applied to Lewis phenotype data, and logistic regression analysis was used to predict the Lewis phenotype as an independent predictor of CAD. ANOVA was applied for quantitative data comparison.

Results

The frequency of established CAD risk factors was compared in the study population among patients with Lewis-negative and Lewis-positive phenotype separately in males and females to look for any association. Parameters such as fasting blood sugar, mean cholesterol, LDL, high-density lipoprotein (HDL), and triglycerides levels are comparable between Lewis-negative and Lewis-positive phenotype and $P > 0.05$ for both males and females. Physical parameters such as mean BMI and mean waist–hip ratio were also comparable in two groups, as summarized in Table 1. Hence, no association was found between established CAD risk factors and Lewis phenotypes.

There are some known risk factors for CAD as established in the literature.[13-16] These risk factors (hypertension, smoking, diabetes, BMI, waist–hip ratio, and HDL levels) showed significant association with angiographically proven CAD.

The association of Lewis phenotype and coronary artery disease

When males and females were considered together,

Table 1: Comparison of Lewis blood group phenotypes as the risk factor for coronary artery disease among different genders

Parameters	Males			Females		
	Lewis-negative phenotype	Lewis-positive phenotype	*P*	Lewis-negative phenotype	Lewis-positive phenotype	*P*
Fasting blood sugar (mg/dl)	117.05±21.46	120.24±24.91	0.652	112.25±17.92	118.53±27.97	0.327
Hypertension (prevalence) (%)	48.7	50.8	0.819	43.8	34.5	0.501
Smoking (prevalence) (%)	46.2	38.5	0.398	0	0	-
Mean BMI	25.77±2.66	25.86±2.85	0.855	26.37±4.02	25.05±3.29	0.182
Mean waist hip ratio	0.98±0.34	0.979±0.033	0.94	0.956±0.035	0.942±0.028	0.125
Mean total cholesterol (mg/dl)	177.54±31.07	175.52±27.55	0.701	167.25±23.03	169.80±26.61	0.73
Mean HDL (mg/dl)	39.18±5.56	39.43±4.16	0.636	39.19±1.87	40.45±3.88	0.134
Mean LDL (mg/dl)	108.38±35.99	101.05±32.88	0.258	90.25±31.22	92.47±35.31	0.847
Mean triglycerides (mg/dl)	165.13±29.46	171.33±31.55	0.28	158.56±22.33	164.65±29.23	0.444

Values are in mean±1SD. BMI=Body mass index, SD=Standard deviation, HDL=High density lipoprotein, LDL=Low-density lipoprotein

Table 2: Distribution of Lewis phenotypes in the study and control groups

	Lewis-positive phenotype (%)	Lewis-negative phenotype (%)
Angiography-positive CAD patients (test group)	118 (73.3)	43 (26.7)
Angiography normal (control group)	59 (83.1)	12 (16.9)
Donor control group (control group)	215 (71.7)	85 (28.3)

CAD=Coronary artery disease

Table 3: Lewis (a-b-) phenotypes and the risk of coronary artery disease in males and females on multivariate analysis

	Prevalence of Lewis (a-b-) in patients with (%)		*P* (after multivariate analysis)	OR	95% CI
	CAD	Normal angiography			
Males	25	21.6	0.71	1.218	0.4-3.4
Females	32.4	11.8	0.03	4.968	1.2-21.2

OR=Odds ratio, CI=Confidence interval, CAD=Coronary artery disease

there was an increased frequency of lack of expression of Lewis antigen in the angiography-positive group (26.7%) when compared with angiography normal control group (16.9%), but this was not statistically significant (P = 0.19 %) [Table 2].

After applying multivariate analysis for removing the effects of other risk factors, the association of Lewis-negative phenotypes with CAD remained statistically insignificant with the P = 0.13.

When males and females were analyzed separately, Le (a–b–) females had a higher incidence of CAD (odds ratio [OR] 4.97, 95% confidence interval [CI] 1.2–21.2, P = 0.03) [Table 3], though it was not significant in males (P = 0.71).

Discussion

Cardiovascular diseases are attributing to the significant burden of morbidity and mortality in developing countries, especially the urban areas is associated with various modifiable and nonmodifiable risk factors. The modifiable risk factors are such as diabetes, smoking, hypertension, obesity, dyslipidemia, and nonmodifiable risk factors are such as age, sex, race, and family history.[13-16] We found a positive correlation between these risk factors with CAD.

Hein *et al*.[2] found individuals with a lack of expression of Lewis antigen had a higher BMI, a lower HDL level, a higher serum triglycerides level, and a higher risk of diabetes. Clausen *et al*.[4] also found Lewis-negative men had higher BMI, fasting insulin and glucose levels, and systolic blood pressure as compared to Lewis-positive phenotypes. However, in our study, no association was found between known risk factors such as BMI, waist–hip ratio, lipid profile, fasting blood sugar levels, and hypertension vis-a-vis Le (a-b-) phenotype, the observations were in line with the NHLBI Family Heart Study.[6]

The association of Lewis phenotypes with coronary artery disease

It has been observed that the Lewis-negative phenotype is associated with CAD. While some of the earlier studies[3,4,8] supported this association, other studies[9,10] did not find any statistically significant correlation between the two. A study by Hein *et al*.[2,17] showed a higher risk of CAD in males when there is a lack of Lewis antigen expression and showed a two-fold higher prevalence of nonfatal myocardial infarction among the males with Lewis-negative phenotype. In the NHLBI Family Heart Study,[6] the OR for CAD was 2.0 for the Lewis negative than the Lewis-positive phenotype, and the multivariate analysis, including all other risk factors, did not diminish the higher associated risk. Cakir *et al*.[9] evaluated the association of CAD, including the thickness of carotid arteries and presence of Lewis gene and found no association between lack of Lewis

gene and carotid atherosclerosis (OR 1.23, 95% CI 0.70–2.16) compared to individuals with the presence of Lewis gene. These results are consistent with our study which did not find any significant correlation between Lewis-negative phenotypes and CAD. A study by Mansur *et al*.[10] found no association between the expression of Lewis antigen on RBC or saliva with CAD including acute myocardial infarction or abnormal lipid profile. The only study from India by Chaudhary and Shukla[3] found 2.5 times higher prevalence of Le (a−b−) phenotype in CAD patients posted for cardiac surgery as compared to healthy blood donors (29.1% vs. 9.6%, $P < 0.01$). In the present study, we found an increased frequency of Le (a−b−) phenotype in CAD patients compared to normal controls (26.7% vs. 16.9%, $P = 0.194$). However, when males and females were analyzed separately, Le (a−b−) females had a four-fold higher incidence of CAD (OR 4.97, 95% CI 1.2–21.2). If these results are extrapolated to population, Lewis-negative females can have 1.2–21 times higher incidence of CAD as compared to Lewis-positive females. Different results in our study from that by Chaudhary and Shukla[3] may presumably be due to the difference in the genetic makeup of the populations studied (Uttar Pradesh vs. Punjab), sample size, inclusion criteria and the prevalence of Lewis-negative phenotypes in the general population.

Conclusion

The association between Lewis phenotypes and CAD was not significant in the overall population studied. However, it was statistically significant with regard to females, with hitherto unreported observation of higher prevalence of CAD among the females with Lewis-negative phenotype. This has the potential to define an independent risk factor as to devise the screening test to identify high-risk population subgroups. However, further studies on a larger number of patients are required to substantiate the observations as well as delineate possible hypotheses in support of these findings.

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Conflicts of interest
There are no conflicts of interest.

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