Original Research Article

Study of serum endothelial lipase levels and its gene polymorphism (LIPG 584C/T) in coronary heart disease in Indian population

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ABSTRACT

Introduction: Endothelial lipase is a phospholipase A1 with preference for HDL phospholipids. Previous studies suggest role of EL in negatively regulating HDL-C levels consequently increasing cardiovascular risk. Various factors modulate EL levels and LIPG single nucleotide polymorphism (SNP) is one such factor. LIPG SNP 584C/T is a relatively more prevalent SNP, but its role remains unclear till now warranting further investigation.

Materials and Methods: We conducted a case control study recruiting 160 subjects. The case group included 120 subjects divided into three groups of 40 each, namely myocardial infarction (MI), unstable angina (USA) and stable angina (SA) group. The control group also comprised of 40 subjects. Serum levels of EL and hs-CRP were estimated using ELISA while lipid profile parameters (HDL-C, LDL-C, TAG and total cholesterol) were measured by enzymatic methods on AU-400 autoanalyzer. LIPG 584C/T SNP was studied by DNA extraction from whole blood followed by RFLP-PCR.

Results: EL levels were higher in cases than controls (p value=0.004). Negative correlation was observed between EL and HDL-C levels (r= -0.384; p value<0.001). Multiple logistic regression performed to evaluate effect of EL on CHD gave an Odd’s ratio of 1.017 (p value=0.039). No significant difference was seen in genotypic distribution between cases and controls. Also HDL-C levels did not differ significantly in the different genotypic groups.

Conclusion: Though endothelial lipase levels negatively correlate with serum HDL-C levels, the strength of association between raised EL levels and presence of CHD is weak. Also no significant association was seen between CHD and LIPG 584C/T SNP.

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1. Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally: more people die annually from CVDs than from any other cause. Approximately 17.7 million people died of CVD in 2015 and of these deaths 7.4 million were due to Coronary Heart Disease (CHD).1 The Global Burden of Disease Study 2015 showed that sociodemographic change over the past 25 years has been associated with dramatic declines in CVD in regions with very high sociodemographic index (SDI), but only a gradual decrease or no change in most other regions.2 A decrease in the prevalence of CVDs has been noted in India as well but the CVD mortality continues to be very high (386/100,000) as compared to the global average (286/100,000).2

In 1980s Framingham Heart Study investigators concluded that high levels of HDL-C in blood reduced cardiovascular risk.3 Badimon et al infused cholesterol fed rabbits with HDL plasma fraction and observed regression of established aortic fatty streaks and lipid deposits.4 Jenkins et al confirmed the correlation between HDL-C levels and CH D, observed in epidemiological studies, by performing coronary angiographies. He found a significant association between HDL-C levels and the severity of atherosclerosis.5 In the following years the role of HDL in cardiovascular diseases was extensively studied and low HDL-C levels were accepted as a
cardiovascular disease risk factor. However the lack of effectiveness of HDL-C raising therapies in reducing CVD risk challenged the “HDL hypothesis”. Nevertheless the value of HDL-C as a predictor of cardiovascular risk remains largely unchallenged. Many prospective studies conducted worldwide have confirmed that HDL-C is a strong, consistent, and independent predictor of incident cardiovascular events (myocardial infarction, ischaemic stroke). Endothelial lipase (EL), a relatively new addition to the lipase family, has been shown to significantly influence HDL-C metabolism. EL is a phospholipase A₁ having 40% homology with Hepatic lipase (HL) and 45% homology with Lipoprotein lipase (LPL). Despite the homology it is quite different from HL and LPL as it preferentially acts on HDL phospholipids and has a distinct expression profile (EL is synthesized and expressed by endothelial cells, smooth muscle cells and macrophages in arterial vessel wall). Mature EL is a 68kDa glycoprotein encoded by LIPG gene located on long arm of chromosome 18. Many in vitro and in vivo studies support the role of EL in HDL-C metabolism. EL has been shown to mediate both the selective uptake of HDL-C esters and HDL binding to cell-surface heparin sulphate proteoglycan. Ishida et al conducted a study wherein transgenic introduction of the human LIPG locus in mice was done to modulate the level of EL expression. Fasting plasma HDL cholesterol was increased by 57% in LIPG –/– mice and 25% in LIPG+/– mice and was decreased by 19% in LIPG transgenic mice as compared with syngeneic controls emphasizing inverse relationship between HDL cholesterol level and EL expression. It has been hypothesized that phospholipid hydrolysis by EL may lead to destabilization of HDL particle and shedding of ApoA1 which gets cleared off by the kidneys resulting in increased HDL turnover. Also plasma concentrations of EL have been shown to be upregulated by inflammation, further suggesting its role in pathogenesis of atherosclerosis. Serum EL levels and activity are modulated by LIPG gene polymorphism as well. Many single nucleotide polymorphisms for endothelial lipase gene have been studied, out of which SNP 584C/T is relatively more prevalent (minor allele frequency=0.3). This SNP causes substitution of a threonine residue by isoleucine residue at codon 111 and has been widely studied. However the study results so far have been incongruous; some studies have suggested a protective role for this variant while others propose a lack of association between this variant and CHD risk. In our study we compared serum EL levels in CHD cases and controls. Relationship between serum levels of endothelial lipase and lipid profile parameters (HDL-C, LDL-C, TAG and Total cholesterol) was evaluated. Effect of inflammation on EL levels was assessed by evaluating relationship between blood hs-CRP and EL levels. We also explored the role of LIPG 584C/T gene polymorphism for its possible association with cardiovascular risk.

2. Materials and Methods

This case control study was carried out in the Department of Biochemistry, Maulana Azad Medical College in collaboration with Department of Cardiology, G.B. Pant Hospital, New Delhi. Study population comprised of 160 subjects selected from individuals attending cardiology OPD or admitted in cardiology ward or coronary care unit (CCU) of G.B. Pant Hospital undergoing angiography. The study participants were randomly selected from all those patients who were undergoing angiography. These 160 subjects were divided into 4 groups namely: stable angina (SA), unstable angina (USA), myocardial infarction (MI) and a control group, each comprising of 40 subjects. Cases were divided into SA, USA and MI group on the basis of the following:

1. Clinical history suggestive of stable angina.
2. Findings of various tests like ECG, Stress test, cardiac marker levels in serum (Troponin T levels in serum)

The control group comprised of 40 subjects and included individuals who underwent angiography but were found to have normal coronary arteries. Individuals with heart disorders other than CHD like valvular heart disorders, cardiomyopathies and conduction defects were excluded. 5ml of venous blood sample was collected from each subject in two vials: a plain vial and an EDTA vial. Serum was separated from blood stored in plain vial and stored at -80º Celsius till the time of measurement. EDTA vials were also stored at -80º Celsius. Serum was used for estimation of levels of lipid profile parameters, EL and hs-CRP. Levels of lipid profile parameters (total cholesterol, triglycerides, high density lipoprotein cholesterol and low density lipoprotein cholesterol) were estimated by enzymatic methods on Olympus AU-400 autoanalyser using kits supplied by JAS diagnostics. Endothelial Lipase and hs-CRP levels were estimated using commercially available ELISA kits supplied by Qayee Bio and Calbiotech respectively.

2.1. Genotyping

DNA was extracted from whole blood samples by using Genomic DNA Mini Kit (Geneaid, Taiwan) according to the manufacturer’s instructions and stored at -20ºC. Restriction fragment length polymorphism- Polymerase chain reaction (RFLP-PCR) was performed using extracted DNA for SNP detection. Region of LIPG gene with SNP was amplified by fragment length polymorphism- Polymerase chain reaction (RFLP-PCR) was performed using extracted DNA for SNP detection. Region of LIPG gene with SNP was amplified by using the following primer pair as described by Tang et al. The control group comprised of 40 subjects and included individuals who underwent angiography but were found to have normal coronary arteries. Individuals with heart disorders other than CHD like valvular heart disorders, cardiomyopathies and conduction defects were excluded. 5ml of venous blood sample was collected from each subject in two vials: a plain vial and an EDTA vial. Serum was separated from blood stored in plain vial and stored at -80º Celsius till the time of measurement. EDTA vials were also stored at -80º Celsius. Serum was used for estimation of levels of lipid profile parameters, EL and hs-CRP. Levels of lipid profile parameters (total cholesterol, triglycerides, high density lipoprotein cholesterol and low density lipoprotein cholesterol) were estimated by enzymatic methods on Olympus AU-400 autoanalyser using kits supplied by JAS diagnostics. Endothelial Lipase and hs-CRP levels were estimated using commercially available ELISA kits supplied by Qayee Bio and Calbiotech respectively.
DreamTaq Green buffer, 0.4 mM MgCl₂ and 4 mM each of dATP, dCTP, dGTP and dTTP was used. The amplification protocol consisted of the following conditions: initial denaturation at 94°C for 10 min, amplification for 35 cycles at 94°C for 45s, 57°C for 60s, and 72°C for 60s, followed by a final elongation step at 72°C for 7 min. PCR product so obtained was 254bp long. The amplicon was digested using restriction enzyme NdeI from Thermo Scientific FastDigest enzymes. Presence of T allele created a restriction site and thus Thomozygotes yielded 2 fragments of size 217bp and 36 bp while Chomozygote remained uncleaved yielding a 254bp product. Therefore on performing gel electrophoresis, a single 254 bp band was seen for CC genotype, a single 217bp band was seen for TT genotype (36bp band not seen on agarose gel electrophoresis) and two bands of sizes 254bp and 217bp were seen for CT genotype.

Written informed consent was obtained from all the study participants.

2.2. Statistical analysis

The normality of continuous variables was assessed by using Shapiro Wilk test. Data for all the variables was found to be non parametric except for age and LDL-C. Values of parametric data were expressed in mean and standard deviation while, for non parametric data, it was expressed in median and interquartile range. Values obtained for various continuous variables (like EL and lipid profile parameters) were compared between individual case groups and controls using Man Whitney U test or Students T test. For comparing data obtained for more than 2 groups, Kruskal Wallis test was used. Spearman’s correlation analysis was done for evaluating the relationship between EL, hs -CRP and lipid profile parameters. ROC (receiver operating characteristic curve) analysis was done for analysing the diagnostic efficiency of various biomarkers of CHD like EL, hs-CRP, HDL-C, LDL-C, TAG (triglycerides) and TC (total cholesterol), the state variable being all the subjects with CHD (SA, USA and MI groups). For evaluating the strength of association between various parameters and CHD, multiple logistic regression was performed and variables with p value <0.05 selected. This was followed by adjustment for known CHD risk factors like age, sex, diabetes etc.

3. Results and Discussion

3.1. Characteristics of study participants

Distribution of age and risk factors for the study participants is shown in table I. Mean age of cases and controls was found to be comparable with no significant difference observed by unpaired Students T- test. All the risk factors were found to be much more prevalent in cases than in controls (Table 1). Evaluation of lipid profile parameters in study subjects revealed that cases had a more proatherogenic lipid profile with significantly lower HDL-C levels and higher LDL-C, TAG and TC levels as compared to controls (Table 1).

3.2. Comparison of EL levels in study subjects

Serum EL levels were estimated in all the study groups using ELISA. They were found to be significantly higher in cases than in controls pointing towards association of higher EL levels with CHD (Table 1). Also when each case group was individually compared to the control group, EL levels were found to be significantly raised in MI and USA case groups but not in SA group (Table 1). However no significant difference was seen in EL levels between the different case groups when compared with each other (p value=0.546).

3.3. Correlation between EL and lipid profile parameters

Spearman’s correlation analysis was done to study the relationship between EL and lipid profile parameters. EL was found to negatively correlate with HDL-C levels reinforcing the hypothesis that EL increases HDL-C metabolism and decreases its serum levels. However no significant correlation was seen between other lipid profile parameters and EL (Table 2). Also multiple logistic regression was used to evaluate the effect of EL on HDL-C levels after adjusting for known cardiovascular risk factors like diabetes, hypertension, family history, alcohol consumption and smoking. However after adjustment no significant influence of EL was observed on HDL-C levels (OR= 1.008, p value=0.076).

3.4. Comparison of EL with hs-CRP

Hs-CRP levels were estimated in different study groups and as expected were found to be higher in cases than in controls. All the individual case groups also showed a significantly higher value than controls (Table 1). Further significant positive correlation was observed between serum EL and hs -CRP levels (r=0.169, p value = 0.036).

3.5. 3.5 Comparison of diagnostic efficiency of various markers

To compare the performance of various parameters (EL, hs -CRP, HDL-C, LDL-C, TAG and TC) as biomarkers of CHD, ROC curves were plotted for each and area under the curve (AUC) estimated. Both hs-CRP (AUC = 0.702, p value<0.001) and HDL-C (AUC= 0.75 2, p value<0.001) were seen to have AUC greater than that of EL(AUC=0.699, p value<0.001). But LDL-C, TAG and TC had lower AUCs as compared to that of EL (Table 3). In our study, at a cut off level of 3mg/L, hs CRP was found to be 88.2% specific.
but only 15% specific. EL was found to be 71% sensitive and 55% specific at a cut off of 45ng/L.

3.6. Evaluation of strength of association of EL with CHD

Multiple logistic regression was performed to evaluate the strength of association between various parameters and presence of CHD the results of which are shown in table IV. Only EL and hs-CRP were found to have significant p value (<0.05). These parameters were further adjusted for known CHD risk factors like age, sex, family history, hypertension, diabetes, alcohol intake and smoking. After adjustment, an Odd’s ratio of 1.017 (95% CI 1.001-1.034) for EL and 1.16 (95% CI 1.066-1.261) for hs-CRP were obtained. Since the Odds ratio is very close to 1, it can be surmised that the association between EL and CHD, though significant, is weak.

3.7. Gene polymorphism

Allele frequencies were found to be in Hardy Weinberg equilibrium.

3.7.1 Distribution of LIPG584C>T polymorphism

Evaluation of genotypic distribution of LIPG584C>T polymorphism in cases and controls did not reveal any significant difference (p value=0.299). Similarly, comparisons of polymorphism distribution were made between individual case groups (MI, SA, USA) and control subjects but no significant difference was seen.

3.7.2 Endothelial Lipase levels and LIPG gene polymorphism

No significant difference was seen in EL and HDL-C levels in the different genotypic groups (Table V) (p value=0.581 & 0.422 respectively).

3.7.3 Risk factors and LIPG gene polymorphism

No significant association was observed between LIPG gene polymorphism and presence or absence of risk factors like diabetes mellitus, hypertension and family history of CAD (p value=0.536).

4. Discussion

HDL has long been known as an atheroprotective agent. In 1977, the Framingham Heart study showed a significant inverse correlation between blood HDL-C levels and incidence of coronary heart disease. Consequently HDL-C raising therapies like cholesteryl ester transfer protein (CETP) inhibitors, notably torcetrapib, were developed with the aim of decreasing cardiovascular risk. However torcetrapib, was associated with increased cardiovascular morbidity and mortality, despite substantial increases of HDL levels (by ~60%), leading to a suspension of all further research with this drug. Conventionally HDL cholesterol levels have been estimated but studies have shown that HDL particle number may be a better tool for cardiovascular risk assessment. HDL cholesterol efflux capacity is yet another parameter which has been shown to influence CHD risk. However despite all the controversies, many prospective studies from different racial and ethnic groups worldwide have confirmed that HDL-C is a strong, consistent, and independent predictor of incident cardiovascular events (myocardial infarction, ischaemic stroke).

Endothelial lipase, a relatively new addition to the triglyceride lipase family, has been found to play an important role in HDL metabolism. It is a 68kDa glycoprotein encoded by LIPG gene and expressed by endothelial cells. Though it has considerable molecular homology with hepatic lipase and lipoprotein lipase, it differs from them because of it’s primarily phospholipase A1 activity and preference for HDL. Ma et al conducted a study to evaluate role of EL in both mice model and human subjects. In this study EL gene was inactivated in mice by gene targeting leading to an absence of detectable EL mRNA expression in liver. EL-/− mice showed a significant increase in HDL-C 1 evels probably due to delayed clearance. Also in the same study a significant association was observed between LIPG 584C/T gene polymorphism and HDL-C levels in blood of 372 human subjects. In a study conducted by Badellino et al it was seen that plasma EL levels negatively correlated with HDL-C levels (r = -0.11, p = 0.002) and positively correlated with TAG levels (r = 0.22, p=0.001). The study results also showed that plasma EL levels were associated with metabolic syndrome features and subclinical atherosclerosis. Sun et al also reported an inverse correlation between plasma EL activity and HDL-C levels (r = 0.308, p<0.0001) and association of plasma EL activity with increased cardiovascular risk. Our study findings are in partial agreement with the previous studies. In our study we observed that serum endothelial lipase levels were significantly higher in CHD cases than in controls indicating association between raised EL levels and CHD. However when the strength of association was evaluated by calculation of Odd’s ratio, it was found to be weak (OR=1.017;95% CI 1.001-1.034). Comparison of individual case groups with the control group revealed EL levels to be significantly higher in the MI and USA group. However the SA group did not show any significant difference which might be due to less severe nature of disease in this group. In contrast Trbusic et al 2016 found significantly higher levels in stable CHD patients compared to MI patients. Also on performing correlation analysis, serum EL levels were found to negatively correlate with HDL-C levels and positively correlate with hs-CRP levels. However on performing multiple logistic regression to adjust for known cardiovascular risk factors like diabetes, hypertension, alcohol intake, family history and smoking, no significant influence of EL on HDL-C levels was observed (OR= 1.008, p value=0.076). Therefore from
Table 1: Comparison of baseline characteristics and quantitative parameters in different groups

| Parameter | Controls [n=40] | Cases [n=120] | SA [n=40] | USA [n=40] | MI [n=40] |
|-----------|----------------|---------------|-----------|------------|-----------|
| Age       | 51.25±11.08    | 53.39±9.06    | 54.29±7.2 | 52.23±7.5  | 54.81±10.04 |
| Males     | 21             | 101a          | 35a       | 30a        | 36a       |
| DM        | 2              | 44a           | 14a       | 13a        | 17a       |
| HTN       | 8              | 56a           | 20a       | 20a        | 16a       |
| SMOK      | 5              | 62a           | 20a       | 20a        | 22a       |
| ALC       | 4              | 32a           | 8a        | 10a        | 14a       |
| FH        | 0              | 13a           | 5a        | 2a         | 6a        |
| HDL-C [mg/dL] median & IQR | 40 & 6.75 | 35 & 10a | 31.5 & 10.25a | 38 & 10a | 30 & 9.5a |
| LDL-C [mg/dL] median & IQR | 88.67 & 30.88 | 106.8 & 37.48a | 103.85 & 36.8 | 117.18 & 38.68a | 100.54 & 35.47 |
| TAG [mg/dL] median & IQR | 146 & 25 | 159 & 59a | 163 & 43a | 154 & 53a | 144 & 99 |
| TC [mg/dL] median & IQR | 165 & 55 | 182 & 63.5a | 180 & 58 | 196 & 55a | 174 & 63 |
| EL [ng/L] median & IQR | 44.45 & 9.85 | 55.3 & 29.63a | 54.05 & 21.28 | 60.95 & 59.6a | 58.25 & 67.5a |
| hs-CRP [mg/L] median & IQR | 6.65 & 5.98 | 11 & 8a | 10 & 6.25a | 11 & 9a | 14 & 7.5a |

a: p value < 0.05 when compared to control group using Man Whitney U test [for non parametric data], unpaired T test [for parametric data] and Chi square test [for qualitative parameters] SA: Stable angina; USA: Unstable angina; MI: myocardial infarction; DM: Diabetes mellitus; HTN: Hypertension; SMOK: Smoking; ALC: Alcohol consumption; FH: Family history of CHD; TAG: Triglyceride; TC: Total cholesterol; EL: Endothelial Lipase; hs-CRP: high sensitivity C reactive protein; IQR: interquartile range

Table 2: Correlation between EL, hs-CRP and lipid profile parameters

| Parameter | HDL-C | LDL-C | TAG | TC | hs-CRP |
|-----------|-------|-------|-----|----|--------|
| EL        | -0.391| 0.04  | 0.055| -0.049| 0.169  |
| p value   | <0.001| 0.62  | 0.50 | 0.55| 0.036  |

Using Spearman’s correlation analysis [for non parametric data] and Pearson ’ s correlation analysis [for parametric data] EL: Endothelial lipase; TG: Triglyceride; TC: Total cholesterol; Hs-CRP: High sensitivity C reactive protein

Table 3: ROC curve analysis of EL, hs-CRP and lipid profile parameters

| Parameter | AUC | p value |
|-----------|-----|---------|
| HDL-C     | 0.752| <0.001 |
| LDL-C     | 0.642| 0.008  |
| TAG       | 0.608| 0.044  |
| TC        | 0.637| 0.010  |
| EL        | 0.699| <0.001 |
| Hs-CRP    | 0.702| <0.001 |

Table 4: Multiple logistic regression evaluating influence of different parameters on CHD

| Parameter | p value | Odd's ratio | 95% CI   |
|-----------|---------|-------------|----------|
| EL        | 0.042   | 1.016       | 1.001-1.031 |
| Hs-CRP    | 0.009   | 1.131       | 1.031-1.241 |
| HDL-C     | 0.133   | 0.747       | 0.510-1.093 |
| LDL-C     | 0.519   | 0.886       | 0.612-1.281 |
| TAG       | 0.496   | 0.975       | 0.905-1.050 |
| TC        | 0.438   | 1.158       | 0.799-1.678 |

Table 5: EL and HDL-C levels in different genotypic groups

| Genotype | EL | p value |
|----------|----|---------|
| CC       | 54.4 IQR 24.05|         |
| CT       | 50.6 IQR 24.4 | 0.581   |
| TT       | 47 IQR 33.25  | 0.422   |

| Genotype | HDL-C | p value |
|----------|-------|---------|
| CC       | 36 IQR 10 |         |
| CT       | 37 IQR 12.5| 0.422  |
| TT       | 39 IQR 16.25|         |
Correlation analysis showed significant negative correlation observed between serum EL levels and CHD was weak. Correlation analysis showed significant negative correlation between EL and HDL-C levels but the same was not observed after adjustment for known cardiovascular risk factors. Also EL gene polymorphism, LIPG 584C/T, did not show any association with decreased HDL-C levels and coronary heart disease.

5. Conclusion
From our study it can be concluded that in Indian population as well endothelial lipase levels are higher in CHD cases than in controls. However the strength of association observed between serum EL levels and CHD was weak. Correlation analysis showed significant negative correlation between EL and HDL-C levels but the same was not observed after adjustment for known cardiovascular risk factors. Also EL gene polymorphism, LIPG 584C/T, did not show any association with decreased HDL-C levels and coronary heart disease.

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8. Conflict of interests
The authors declare no conflict of interest.

9. Ethical approval
This study conforms to widely accepted ethical principles guiding human research (such as the Declaration of Helsinki). The Institutional ethics committee of Maulana Azad Medical College, Delhi, India with registration number ECR/329/Inst/DL/2013 approved this study.

10. Contributorship
Dr. Rashmi Verma and Dr. S.K. Gupta researched literature and conceived the study. They were also involved in protocol development, gaining ethical approval and data analysis. Dr. Girish M.P. was involved in patient recruitment.
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