Original Article

Journal of Cardiovascular Medicine and Surgery
Volume 4 Number 1, January - March 2018
DOI: http://dx.doi.org/10.21088/jcms.2454.7123.4118.6

Lipoprotein A as an Independent Risk Factor of Coronary Artery Disease in Western Indians

Seema Sharma[1], Pranav Sharma[2]

Authors Affiliation
[1]Assistant Professor, Department of Medicine, B.J. Medical College, Ahmedabad, Gujarat 380016, India.
[2]Professor, Department of CVTS, UN Mehta Institute of Cardiology and Research Center, B.J. Medical College, Ahmedabad, Gujarat 380016, India.

Reprints Requests
Pranav Sharma, Professor, Department of Cardiovascular and Thoracic Surgery, UN Mehta Institute of Cardiology and Research Center, New Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India.
E-mail: realpranav@yahoo.com

Recived on 30.01.2018,
Accepted on 02.02.2018

Abstract

Aims and Objective: To assess the association of lipoprotein a (Lp a) with coronary artery disease (CAD) in Western Indians. *Material and methods:* In this single centric, prospective and case control study 200 subjects (100 patients with CAD & 100 healthy volunteer) were enrolled. Fasting blood sample were collected from the antecubital vein of the subjects under sterile conditions. Lipid profile parameters such as total cholesterol (TC), triglyceride (TG), total lipid (TL), low density lipoprotein (LDL), high density lipoprotein (HDL), and very low density lipoprotein cholesterol (VLDL), Lp (a) were measured. *Results:* The prevalence of cardio-metabolic risk factors was significantly higher in cases as compared to controls ($p<0.05$). Similarly significantly higher mean lipid levels namely total cholesterol, triglyceride, low density lipoprotein and Lp (a) was observed in CAD patients as compared to their counterparts. Lp (a) levels were well correlated with angiographic severity of the disease and overall incidence of the disease was found to be highest in the greatest quartile of Lp (a). *Conclusion:* Lp (a) levels are important markers of CAD in Western Indians and could be effectively used to in clinical setting.

Keywords: Lipoprotein A; Western Indians; Coronary Artery Disease; Lipid Profile.

Introduction

Coronary artery disease (CAD) has become one of the major killers in India. Available evidence in literature has shown that Traditional risk factors like smoking, hyper-tension, diabetes are reported to account for only 50% of prevalence and severity of the disease. This led to studies on newer risk factors like fibrinogen, Lp(a), homocysteine, tissue plasminogen activator etc. Studies on overseas Indians have shown that Lp (a) is an important risk factor of CAD.

Lp (a) levels are not affected by age, sex and environmental factors. Lp (a) values are genetically determined by Lp (a) gene located on chromosome 6q [26-27] and stable lifelong levels are attained by age of two [4,5]. Though earlier studies on relationship between Lp (a) and CAD had shown negative results [6, 7] recently multiple studies have shown that elevated Lp (a) is independently and linearly predictive of future adverse coronary events [8,9]. Lp (a) levels have shown worldwide ethnic variation with different levels associated with CAD occurrencein different populations. This study was carried out to assess that whether the level of Lp (a) are independently associated with risk of CAD in Guajarati people and also its association with various clinical variables and conventional risk factors of CAD.

Materials & Methods

For this case control study100 successive patients of CAD with unstable angina/NSTEMI, acute myocardial infarction (STEMI) and of chronic stable angina who were referred for coronary angiography

© 2017 Red Flower Publication Pvt. Ltd.

were enrolled between January 2013 and July 2014in the department of cardiology, UN MEHTA Cardiology institute. According to the results of angiography, the patients were divided into three subgroups; single, double and triple vessel disease (disease defined by obstruction ≥ 50%).

Hundred healthy, controls were selected from the attendants who were not first degree relatives of the patients. Presence of CAD in controls was ruled out by detailed clinical history, ECG, echocardiography and stress tests like treadmill test or dobutamine stress echocardiography if required. An informed consent was taken from all the subjects. Patients with history chronic liver and kidney disease, thyroid disorders, stroke, Familial hypercholesterolemia, acute/chronic infections and on therapy with sex hormones or anabolic steroids were excluded from the study. Fasting blood samples were drawn from all the participants of the study (cases and controls) 5 ml of venous blood was withdrawn and serum was immediately separated by centrifugation. The serum was stored at -70°C for subsequent analysis. Total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL), Low-density lipoprotein (LDL) cholesteroland Lp (a) were estimated using commercial kits.

Results

Descriptive statistics on study population is presented in Table 1. There was no significant difference in age or sex ratio between cases and controls. Conventional risk factors were common among cases including diabetes, hypertension, tobacco, and smoking. 75% of our patients have STEMI, 15% have NSTEMI/UA and 10% have chronic stable angina (UA). As majority of our patients were established cases of CAD, most of them were on standard doses of lipid lowering drugs, but none of them were on niacin.

In our study population the various lipid components (total cholesterol, LDL cholesterol, HDL cholesterol triglycerides) and Lp (a) had a normal distribution. There was no significant difference in LDL cholesterol between cases or controls but HDL cholesterol was significantly lower in cases compared to controls ($p<0.001$)(Table 1).The triglyceride levels were higher in cases ($p<0.001$). The median Lp (a) levels showed a trend towards higher values with increasing severity of disease (Table 2) and showed a significant difference in Lp(a) levels between controls and patients with DVD or TVD and between patients with SVD and TVD (Table 2). The Lp(a) level was also significantly higher in patients with unstable angina compared to stable angina (Table 2). Age, sex, diabetes mellitus, hypertension, smoking, total cholesterol and triglyceride showed no significant influence on Lp(a) level (data not shown). However Lp(a) was significantly higher in cases with LDL cholesterol >130 mg/dl compared to those with LDL cholesterol <130 mg/dl (Table 2).

The risk of CAD was also assessed using it as a categorical variable. For this purpose Lp(a) was divided into quartiles based on its distribution in the control populations. The Lp(a) concentration showed a graded association with CAD. In the first quartile of Lp(a) (<11.45mg/dl), 16% had CAD as compared to 16% in the 2nd quartile of 11.45–16 mg/dl, 28% in the 3rd quartile of 16.5–31.5 mg/dl and 37% in the 4th quartile.

Table 1: Baseline clinical characteristics and lipid profile of patients and controls

Parameters	Cases N=100	Controls N=100	p-value
AGE	33.73±7.02	33.2±7.6	0.61
Sex (Male/Female)	65/35	59/41	0.47
BMI kg/m2	23.96±4.37	22.65±4.55	0.04
DM	10(10)	2(2)	0.03
TOBACCO	4(4)	13(13)	0.04
HTN	41(41)	11(11)	0.002
SMOKING	11(11)	1(1)	0.004
CHOLESTEROL	172.28±31.77	148.50±40.27	<0.001
TRIGLYCERIDE	131.75±75.10	95.13±47.30	<0.001
HDL	33.82±11.95	41.43±10.17	<0.001
LDLC	92.17±47.12	111.52±22.78	0.005
VLDLC	25.31±14.14	18.43±8.87	<0.001
LDL/HDL	3.07±1.32	2.25±0.87	0.001
TC/HDL	5.11±1.54	3.35±1.34	<0.001
TOTAL LIPID	619.87±101.12	598.17±83.86	0.104
LIPOPROTEIN (a)	34.13±29.49	26.42±23.87	0.018

Table 2: LP (a) levels (mg/dl) in patients with CAD according to clinical presentation, angiographic severity and LDL levels

Variables	Mean ± SD	Median	IQR
UA/NSTEMI (N=15)	38±33.19	20.7	16.9-90
STEMI (N=75)	36.14±30.01	25.2	12.66-60.3
EA (N=10)	23.22±18.42	20.15	12.83-24.44
SVD(N=73)	30.24±26.36	18.8	12.15-37.29
DVD(N=16)	49.23±35.09	35.25	15.88-90.0
TVD(N=11)	47.04±34.24	31.5	13.3-83.7
LDL-C (<130mg/dl) (N=87)	34.46±20.47	29.65	12.7-59.5
LDL-C (≥130mg/dl) (N=13)	39.56±30.04	30.04	16.85-65.65

Table 3: Percentage of patients with CAD according to quartiles of Lp(a) defined from control group

LP (a) Quartiles	LP (a) concentration (mg/dl)	Incidence of CAD
25th	>11.45	18%
50th	11.45-16.55	17%
75th	16.55-31.53	28%
100th	>31.53	37%

Discussion

Lp(a), a circulatory lipoprotein was discovered in 1963 by the Norwegian physician Kaare Berg [16]. Lp(a) levels are influenced by apo(a)polymorphism. Plasma Lp(a) levels are highly heritable. Stable lifelong levels are attained by age two. The rate of secretion by liver determines the Lp(a) levels. Ninety percent of the variation in plasma levels is accounted by the apo(a) gene and 70% by the size of apo(a) isoforms [17-20].

Lp(a) is an LDL like particle which has apolipoprotein (a) attached to apolipoprotein (B) molecule via a disulphide bond. There are 34 different Lp (a) isoforms depending on the size of the apolipoprotein (a). This has resulted in significant variability in measured Lp(a) concentration if assays used are sensitive to variation in number of repeat domain in apo(a) [21,22] Hence in 2003, an expert panel recommended use of assay systems not sensitive to apo(a) isoforms [23] and was accepted by World Health Organization (WHO) in 2003.24 Apolipoprotein(a) has a close homology with plasminogen, which makes this molecule important not only in the process of atherosclerosis but also in thrombosis. While Lp(a) promotes atherosclerosis by increasing smooth cell proliferation and enhancing LDL-C retention in the subintima, it promotes thrombosis by competitively inhibiting plasminogen and up regulating expression of plasminogen activator inhibitor (PAI) [2].

Higher mean Lp (a) levels were observed in patients than controls and difference was statisticallysignificant (P<0.01). This is in agreement with earlier studies conducted in India and abroad. [2-4]. Among Asian Indians worldwide the mean level of Lp (a) is 18-20 mg/dl. The median level is 16 mg/dl in Asian Indians, 22 mg/dl in blacks, 6 mg/dl inwhites and 3 mg/dl among American Indians [38-40]. In our study mean (35.13 mg/dl) and median (20.9 mg/dl) Lp(a) levels were both higher than in Asian Indians which may explain higher prevalenceof CHD reported in western India [11]. Elevated levels of Lp (a) were found to be elevated in 32.15% of 463 apparently healthy gujarati adults by Sahoo et al [48]. The genetic predisposition for CAD in Gujarati population could be partly explained by the early onset of several dyslipidemia and by high prevalence of Lp (a) abnormalities [48].

In our study we found that Lp(a) level assessed by an isoform insensitive assay is an independent risk factor for CAD at a concentration above 31.5 mg/dl corresponding to the 75thpercentile of our control population. Our findings are in agreement with studies carried on the white population in Europe and USA reporting that only high Lp(a) concentration are associated with two to three fold increased risk of CAD [8,28-30]. Similar results were seen in a study involving North Indian population by Jamal Yusuf et al [47]. Accordingly the European Atherosclerosis Society Consensus Panel [31] has defined Lp(a) level above the 80th percentile(-corresponding to the 50 mg/dl) to be independently associated with increased risk of CAD. Our study is the first adequately powered study in the Gujarati population to show that Lp(a) above the 75th percentile is an independent risk factor for CAD, similar to that proposed by the National Heart Lung and Blood Institute for North American Whites based on the Framingham Heart Study [23].

Hoogeveen RC et al27 had proposed a cut off value of Lp (a) of >19 mg/dl on a study in 103 North Indian subjects (57 cases and 46 controls) based on the fact that 25% of the cases compared to 8% of controls in their study had Lp (a) in the highest quartile (>19 mg/dl). However in their study, Lp (a) protein was assessed by enzyme linked immunosorbant assay and value of Lp(a) mass was obtained indirectly by multiplying Lp(a) protein by conversion factor of 3.3. So indirect estimation of Lp (a) may have underestimated the true Lp (a) concentration. Rajasekhar et al, 3 in a study from South India enrolling 151 patients have shown that Lp (a) >25 mg/dl is associated independently with around two fold risk of CAD. Larger studies from various part of the country (Eastern, Western and Central India) are needed to find out the level of Lp (a) associated with increased risk CAD as this will help in better risk stratification of subjects (with or without CAD) and its management. In our study, the median level of Lp(a) in the control group [16.5 mg/dl] is higher than that reported among whites (6 mg/dl), American Indians (3 mg/dl) [32] but similar to Asian Indians residing abroad (16 mg/dl).

In our study, Lp (a) level was significantly higher in patients presenting with acute coronary syndrome as compared to those presenting with chronic stable angina ($p < 0.001$).

Patients presenting with acute coronary syndrome including (NSTEMI/UA and STEMI) comprised 95% of the total cases. Dangas et al [34] have shown that Lp (a) is distributed in larger amounts in the tissues from culprit lesions in the patients with unstable angina compared to those with stable angina. Stubbs et al [35] have also shown that Lp(a) is significantly higher in patients with non ST elevation myocardial infarction. Jamal Yusuf et al [47] also showed the similar reports.

Our study also support the role of Lp (a) in development of acute coronary syndrome justifying the hypothesis of Lp (a) producing prothrombotic state by competing with fibrin binding, inhibiting fibrinolysis and promoting platelet aggregation.

Zampoulkis et al,36 studied the relationship of Lp(a) excess with the extent and severity of atherosclerosis in CAD patients and found that Lp(a) is related to diffuse lesions covering largepart of coronary vasculature. Budde et al [37] showed that Lp(a) levels correlated with the length of coronary lesions as well as the number of diseased vessels especially those with total occlusions. Similarly in our study, higher Lp(a) levels were observed in multivessel disease compared to single vessel disease and similar findings have been reported by Ashfaq et al [13] and Gupta et al [11] and Jamal Yusuf et al [47] studies on North Indian population. Rajasekhar et al [3] in a study from South India also shown Lp(a) levels correlate with the length of coronary lesions as well as the number of diseased vessels. This finding together with the finding of higher Lp(a) values in patients with acute coronary syndrome suggestthe role of Lp(a) in pathogenesis of both atherosclerosis and thrombosis.

Low HDL cholesterol is an independent risk factor for CAD. In our study also, low HDL-C was found to be an independent risk factor for CAD which is in agreement with other Indiansstudies [2,11,38]. Most of our cases were established cases of CAD and were receiving standard doses of lipid lowering drugs. Hence LDL-C levels were lower in cases. In our study, Lp(a) level was significantly higher in patients with LDL cholesterol >130 mg/dl compared to those with LDL <130 mg/dl (median 52.71 mg/dl vs. 30 mg/dl, p ¼ 0.02).

This is due to the fact that LDL cholesterol calculated by Friedewald equation also includes the cholesterol carried in Lp(a). Based on our data, we feel that apart from routine lipid profile, Lp(a) should be assessed in all patients of CAD particularly those presenting as acute coronary syndrome. Statins, the wonder drug for managing dyslipidaemia has no effects on Lp(a) level [39,40]. However niacin in dose of 2 g/day has been shown to decrease Lp(a) by 25% and increase HDL by 40% [41] though it was not effective in reducing clinical end points asreported recently [42,43]. But to answer the question as to whether reduction of Lp(a) per se reduces risk of future adverse coronary events there is a need to develop a drug which selectively decreases Lp(a) only without effect on other lipid factors like LDL, HDL or TG.

We also feel that Lp(a) should be routinely assessed in allour subjects with multiple risk factors for CAD as has been recommended by The European Atherosclerosis Society [31] and The National Lipid Association [46] to better predict the risk of developing CAD.

Limitation of Study

We had enrolled only symptomatic patients of CAD referred for coronary angiography and had not included the entire spectrum of CAD patients. Hence the Lp(a) levels assessed in our study may not be representative of all patients with CAD. Secondly, majority of our patient were established cases of CAD on standard doses of lipid lowering drugs, which may have altered the association of lipids with CAD

in the multivariableregression analysis. However none of our patients were on niacin, which lowers Lp (a) levels.

Conclusion

This study involving Gujarati population showed independent association of Lp(a) with CAD in this ethnic group. Raised Lp(a) level is also associated with increased disease severity.

References

1. Gupta R, Kastia S, Rastogi S, et al. Lipoprotein (a) in Coronaryheart disease: a case-control study. Ind Heart J. 2000;52:407e410.
2. Gambhir JK, Kaur H, Gambhir DS, et al. Lipoprotein (a) as an independent risk factor for Coronary artery disease in patients below 40 years of age. Ind Heart J. 2000;52:411e415.
3. Rajasekhar D, Saibaba KSS, Rao PVLNS, et al. Lipoprotein (a): better assessor of coronary heart disease risk in South Indian population. Ind J Clin Biochem. 2004;19:53e59.
4. Enas EA, Chako V, Senthilkumar A, et al. Elevated lipoprotein (a)-A genetic risk factor for premature vascular disease in people with or without standard risk factors : a review. Dis Mon. 2006;52:5e50.
5. Hobbs HH, White AL. Lipoprotein (a): intrigues and insights. Curr Opin Lipidol. 1999;10:225e236.
6. Jauhiainen M, Koskinen P, Ehnholm C, et al. Lipoprotein (a) and coronary heart disease risk: a nested case-control study of the Helsinki Heart Study participants. Atherosclerosis. 1991;89:59e67.
7. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA. 1993;270:2195e2199.
8. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, et al. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301: 2331e2339.
9. The Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302: 412e423.
10. Geethanjali FS, Luthra K, Lingenhel A, et al. Analysis pf the apo(a) size polymorphism in Asian Indian populations: association with Lp(a) concentration and coronary heart disease. Atheroscelerosis. 2003;169:121e130.
11. Gupta R, Vashisht S, Bahl VK, et al. Correlation of lipoprotein(a) to angiographically defined coronary artery disease in Indians. Intern J Cardiol. 1996;57:265-270.
12. Vashisht S, Gulati R, Srivastava LM, et al. Apolipoprotein (a) polymorphism and its association with plasma lipoprotein (a): a North Indian study. Ind Heart J. 2000;52:165-170.
13. Ashfaq F, Goel PK, Sethi R, et al. Lipoprotein (a) levels in relation to severity of coronary artery disease in North Indian patients. Heart Views. 2013;14:12-16.
14. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation Mi: a method for prognostication and therapeutic decision making. JAMA. 2000; 284:835-842.
15. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.
16. Berg K. A new serum type system in mane the Lp system. Acta Pathol Microbiol Scand. 1963;59: 369-382.
17. Li Y, Luke MM, Shiftman D, et al. Genetic variants in the apolipoprotein (a) gene and coronary heart disease. Circ Cardiovasc Genet. 2011;4:565-573.
18. Kronenberg F, Utermann G. Lipoprotein (a): resurrected by genetics. J Intern Med. 2013;273:6-30.
19. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Apolipoprotein (a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol. 2012;60:722-729.
20. Erqou S, Thompson A, Di Angelantonio E, et al. Apolipoprotein (a) isoforms and the risk of vascular disease: systemic review of 40 studies involving 58,000 participants. J Am Coll Cardiol. 2010;55:2160-2167.
21. Mclean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. Nature. 1987;330:132e137.
22. Marcovina SM, Albers JJ, Gabel B, et al. Effect of the number of apolipoprotein (a) kringle 4 domains on immunochemical measurements of lipoprotein (a). Clin Chem. 1995;41:246e255.
23. Marcovina SM, Koschinsky ML, Albers JJ, et al. Report of the National Heart, Lung and Blood Institute Workshop on Lipoprotein (a) and cardiovascular disease: recent advances and future directions. Clin Chem. 2003;49:1785e1796.
24. Dati F, Tate JR, Marcovina SM, et al, International Federation of Clinical Chemistry and Laboratory Medicine; IFCC Working Group for Lipoprotein(a) Assay Standardization. First WHO/IFCC International reference reagent for lipoprotein (a) forimmunoassay e Lp(a) SRM 2B. Clin Chem Lab Med. 2004;42:670e676.
25. Morrisett JD. The role of lipoprotein (a) in atherosclerosis. Curr Atheroscler Rep. 2000;2:243e250.

26. Vashisht S, Wasir HS, Srivastava LM. Association between incidence of lipoprotein positivity and coronary heart disease. Ind Heart J. 1992;44:223-226.
27. Hoogeveen RC, Ghambir JK, Gambhir D, et al. Evaluation of Lp(a) and other independent risk factors for CHD in Asian Indians and their USA counterparts. J Lipid Res. 2001;42:631-638.
28. Luc G, Bard JM, Arveiler D, et al. Lipoprotein(a) as predictor of coronary heart disease: the PRIME Study. Atherosclerosis. 2002;163:377-384.
29. Sweetnam PM, Bolton CH, Downs LG, et al.Apolipoproteins A-I, A-II and B, Lp(a) and the risk ofischaemic heart disease : the Caerphilly study. Eur J ClinInvest. 2000;30:947-956.
30. Rifal N, Ma J. Apolipoprotein(a) concentration and further risk of angina pretoris with evidence of severe coronary atherosclerosis in men: the Physicians Health Study. ClinChem. 2004;50:1364-1371.
31. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) asa cardiovascular risk factor: current status. Eur Heart J. 2010;31:2844-2853.
32. Wang W, Hu D, Lee ET, et al. Lipoprotein (a) in American Indians is low and not independently associated with cardiovascular disease. The Strong Heart Study. Ann Epidemiol. 2002;12:107-114.
33. Anand SS, Enas EA, Pogue J, et al. Elevated lipoprotein(a) levels in South Asians in North America. Metabolism. 1998;47:182-184.
34. Dangas G, Mehran R, Harpel PC, et al. Lipoprotein(a) andinflammation in human coronary atheroma association with severity of clinical presentation. J Am Coll Cardiol. 1998;32: 2035-2042.
35. Stubbs P, Seed M, Moseley D, et al. A prospective study of the role of lipoprotein(a) on the pathogenesis of unstable angina. Eur Heart J. 1997;18:603-607.
36. Zampoulkis JD, Kyriakousi AA, Poralis KA, et al. Lipoprotein(a) is related to the extent of lesions in the coronary vasculatureand to unstable coronary syndromes. Clin Cardiol. 2000;23:895-900.
37. Budde T, Fechtrup C, Bosenberg E, et al. Plasma Lp(a) levelscorrelate with number, severity, and length-extension ofcoronary lesions in male patients undergoing coronary arteriography for clinically suspected coronaryatherosclerosis. Arterioscler Thromb. 1994;14:1730-1736.
38. Panwar RB, Gupta R, Gupta BK, et al. Atherothrombotic riskfactors & premature coronary heart disease in India: a case econtrol study. Indian J Med Res. 2011 J;134:26-32.
39. Kostner GM, Gavish D, Leopold B, et al. HMG Co A reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels. Circulation. 1989;80:1313-1319.
40. Berthold HK, Berthold IG. Hyperlipoproteinemia(a): clinical significance and treatment options. Atheroscler Suppl.2013;14:1-5.
41. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255-2267.
42. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoprotein A-1 and B and lipoprotein(a) to cardiovascular outcomes in the AIM-High trial. J Am Coll Cardiol. 2013;62:1575-1579.
43. Haynes R, Jiang L, Hopewell JC, et al. HPS2-THRIVE randomised placebo controlled trial in 25673 high risk patients of ER niacin/laropiprant: trial design, prespecified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34:1279-1291.
44. Jaeger BR, Richter Y, Nagel D, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med. 2009;6:229-239.
45. Chennamsetty I, Claude T, Kostner KM, et al. Farnesoid X receptor hepatic human APO A gene expression. J Clin Invest. 2011;121:3724-3734.
46. Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advance lipoprotein testing: advice from an expert panel of lipid specialists. J Clin Lipidol. 2011 Sep-Oct;5(5):338-67.
47. Jamal Yusuf a, Neeraj Yadav, Saibal Mukhopadhyay, Abhishek Goyal, Vimal Mehta, Vijay Trehan a, Sanjay Tyagi. Relook at lipoprotein (A): Independent risk factor of coronary artery disease in North Indian population. Indian heart journal 2014;66:272-279.
48. Prevalence and Profiles of Dyslipidemia in Apparently Healthy Adult Gujarati Population Sahoo et al, Healthline Journal 2015 January-June;6(1).