Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

A STUDY OF CORRELATION OF LIPOPROTEIN A LEVEL IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Background:

Common conventional risk factors like Hypertension, Diabetes mellitus, Obesity and smoking do not completely explain the increased prevalence of CAD. Which lead to search of nonconventional risk factors like elevated Lipoprotein(a), Homocysteine, Thrombogenic factors like plasminogen activator inhibitor, Fibrinogen and high sensitivity CRP have gained importance recently.

Aim:

To find out the correlation of lipoprotein a level in patients with acute coronary syndrome and to assess the severity of coronary artery disease.

Materials and methods:

This is a prospective observational study conducted in KIMS, Hubli. The study included 120 patients who presented with acute coronary syndrome. Study subjects were assessed for demographic and risk factors like the age, sex, history of diabetes, hypertension and family history of CAD. Patients are subjected to coronary angiography and necessary investigations including lipoprotein a was studied. Data was analysed using software version SPSS 22. p value of <0.05 was considered as statistically significant.

Results:

In this study it was found that 81(67.50%) patients presented as STEMI, followed by 25(20.83%) patients as NSTEMI, and 14(11.66%) patients as Unstable Angina. From the coronary angiography it was found that 58 (48.33%) patients had SVD then followed by DVD in 33(28.33%) patients, TVD in 14 (11.66%) patients and Insignificant CAD in 14(11.66%) patients. In this study, mean lipoprotein a value with respect to vessels involved is 12.72±6.61mg/dl among the non-CAD (insignificant CAD) patients, 33.55±25.86mg/dl among single vessel disease, 45.87±23.91mg/dl among double vessel disease and 70.03±24.07mg/dl among triple vessel disease.

Conclusion:

Lipoprotein a was found to be significantly elevated in the coronary artery disease patients compared to the non-coronary artery disease patients, it strongly correlates with the severity of coronary artery disease assessed in the form of multivessel involvement.

Keywords- Lipoprotein a; Acute Coronary Syndrome; Coronary angiography.

Introduction:

Cardiovascular disease (CVD) is one of the most serious health problems and one of the leading causes of global death throughout the world. Coronary artery disease (CAD) is the principal cause of mortality and morbidity in the developed countries [1]. But recent evidences show that there is a significant increase in the prevalence of coronary artery disease in South Asians [2]. It presents at a very young age and the presentation is more severe than other population [3]. Common conventional risk factors like Hypertension, Diabetes mellitus, Obesity and smoking do not completely explain the increased prevalence of CAD in younger age group. Which

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lead to search of nonconventional risk factors such as elevated Lipoprotein(a), Homocysteine, Thrombogenic factors like plasminogen activator inhibitor, Fibrinogen and high sensitivity CRP (hs-CRP) have gained importance recently [4]. Higher levels of lipoprotein(a) (Lp[a]) represents as one of the most common genetic dyslipidaemias, affecting 1 in 5 individuals worldwide [5]. It is found to be an inherited independent risk factor for premature CAD in the western countries [6]. Elevated levels of Lp(a) among Asian Indians are highly correlating with the development and progression of coronary atherosclerosis [7]and the incidence of premature myocardial infarction [8]. The relationship of plasma Lp(a) with angiographic severity of CAD may be different in various racial groups. However, Blacks have less dangerous larger isoforms of Lp(a) accounting for the lower prevalence of CAD compared to Asian Indians [9,10,11].

METHODOLOGY

Materials and Methodology:

Source of data:

This is a prospective observational study conducted in Karnataka Institute of Medical Sciences, Hubli. The study was conducted after the Ethical Committee of the Institute approval. The study included 120 patients who presented with acute coronary syndrome. Study subjects were assessed for demographic and risk factors like the age, sex, history of diabetes, hypertension and family history of CAD in the first-degree relatives of the subjects.

The following investigations will be done in the selected patients –

- Complete blood count (CBC),
- Fasting plasma sugar,
- Post prandial plasma sugar,
- Glycosylated haemoglobin (HbA1C),
- Renal function test (RFT)
- Liver function test (LFT) Lipid profile including lipoprotein a
- 12 lead electrocardiograms,
- Echocardiography and Coronary angiography (CAG)

Sample size:120

Type of study: Single centre, Prospective Observational Study.

Sampling: All the patients presenting to KIMS hospital with acute coronary syndrome undergoing angiography included in the study.

Period of study:15/11/2019 to 30/11/2021

Inclusion criteria:

1. All the patients presenting to KIMS hospital with acute coronary syndrome undergoing angiography included in the study**.**
2. Patients who give consent for the study**.**

Exclusion criteria:

1. The presence of neoplastic disease,
2. Heart failure,
3. Recent major surgical procedure,

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4. Women on hormone replacement therapy,
5. Systemic inflammatory conditions, such as infection, liver, or kidney disease.
6. The patients on lipid lowering agents were excluded.

The study subjects who fulfilled the criteria, underwent coronary angiogram. Based on the coronary angiogram study subjects were divided into subjects with significant CAD and insignificant CAD (No vessel involved / normal coronaries). Significant CAD was defined by > 50% luminal stenosis of one of the major vessels (i.e., left anterior descending, circumflex, or right coronary artery) and insignificant CAD includes luminal stenosis of < 50% of the major vessels or its branches. Significant CAD is assessed for the severity in the form of number of vessels affected like single, double or triple vessel involvement which was represented as SVD, DVD and TVD respectively.

Patients were examined while wearing an examination gown. Each measurement was carried out twice, with the average being used in the analysis. For height and weight, we utilised the nearest 0.1 units of measurement. The height of the patients was measured with a tape metre in standing position with the shoulders in a normal alignment. Weight was measured using digital electronic weighing scale and rounded to the nearest 100g. BMI is expressed in kg per m^2 based on corresponding units, i.e., Weight divided by square root of height [128]. The hip circumference is taken at the widest area of the hips at the greatest protuberance of the buttocks, while the waist circumference is taken at midway between the lowest rib and iliac crest.

Waist circumference is considered increased in males and females if it is > 102cms and >88cms respectively. WHR is calculated by dividing the waist circumference by the hip circumference. A ratio of > 0.9 in males and > 0.8 in women is considered to be abnormal and obese. Blood samples were collected early morning after an overnight fast and immediately centrifuged and stored at -70ºC and assessed according to the following methods, Serum creatinine by modified Jaffe's, Triglycerides by glycerol phosphate oxidase (GPO) method, total cholesterol by cholesterol oxidase phenol 4-aminoantipyrine peroxidase (CHOD-PAP) method, LDL-C by precipitation method involving polyvinyl sulfonic acid(PVS) and polyethylene- glycol methyl ether(PEGME) complex, and lipoprotein a by immunoturbidimetry method. According to ATP III criteria for the diagnosis of metabolic syndrome it considers dyslipidaemia, if triglycerides >150 mg/dl, HDL < 40 mg/dl, LDL-C > 100mg/dl, fasting blood glucose ≥ 110mg/dl, waist circumference >102 cm in males and >88 cm in females, additionally in this study the total cholesterol > 200mg/dl and lipoprotein a >30mg/dl is considered abnormal.

Sample size estimation

Considering Lipoprotein level (mg/dl) in four groups (Normal, Grade 1, Grade 2, Grade 3)) as the primary outcome variable, the sample size was calculated for omnibus **one-way ANOVA using G*Power software version 3.1.5**. The results from previous study showed that Mean Lipoprotein level in four groups were 18.95, 39.28, 58.01, 69.22. The calculated effect size was of 0.63 and with alpha error of 1% & power of 90%, the minimum sample size required in each of the four groups is 14 a total sample size of 56. Considering loss to follow up non response final sample size was rounded of to 120 [12].

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data.

Continuous data was represented as mean and SD. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables. **ANOVA (Analysis of Variance)** was the test of significance to identify the mean difference between more than two groups for quantitative data.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram.

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p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyse data [13,14,15].

RESULTS:

In present study out of 120 subjects, 94 (78.3%) were male and 26 (21.7%) were female. Among males, 85 (80.2%) patients had coronary artery disease and 9 patients had Insignificant CAD. Among females, 21 patients had coronary artery disease and 5 patients didn't had coronary artery disease. In the study it had 35 (29.2%) patients falling in between the 51-60 years age group, followed by 32 (26.7%) patients between 41-50years of age group, 29 (24.2%) patients between 61-70 years of age group, 17 (14.2%) patients between <40years of age group and 7 (5.8%) patients between 71-80 years of age group. Among 120 subjects studied, 106 subjects had significant CAD and 14 subjects had insignificant CAD.

Table: 1. Presentation and extent of coronary artery disease among study subjects.

		N (120)	%
Type of ACS	NSTEMI	25	20.83%
	STEMI	81	67.50%
	Unstable Angina	14	11.66%
Number of Vessels	Insignificant CAD	14	11.66%
	SVD	58	48.33%
	DVD	34	28.33%
	TVD	14	11.66%

In present study it was found that 81(67.50%) patients presented as STEMI, followed by 25(20.83%) patients as NSTEMI, and 14(11.66%) patients as Unstable Angina. From the coronary angiography it was found that 58 (48.33%) patients had SVD then followed by DVD in 33(28.33%) patients, TVD in 14 (11.66%) patients and Insignificant CAD in 14(11.66%) patients.

Table: 2. Comorbidities, Personal history and Family history among subjects with and without CAD

		Group						P Value
		CAD (n=106)		Insignificant CAD (n=14)		Total		
		Count	Row N %	Count	Row N %	Count	Row N %	
Hypertension	No	64	88.9%	8	11.1%	72	100.0%	0.816
	Yes	42	87.5%	6	12.5%	48	100.0%	
Diabetes	Yes	35	87.5%	5	12.5%	40	100.0%	0.814
	No	71	88.8%	9	11.2%	80	100.0%	

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Smoking	No	64	85.3%	11	14.7%	75	100.0%	0.186
	Yes	42	93.3%	3	6.7%	45	100.0%	
Alcohol	No	75	91.5%	7	8.5%	82	100.0%	0.117
	Yes	31	81.6%	7	18.4%	38	100.0%	
Family History of CAD	No	87	88.8%	11	11.2%	98	100.0%	0.750
	Yes	19	86.4%	3	13.6%	22	100.0%	

In present study 48 patients had hypertension among whom 42(87.5%) patients had coronary artery disease and 6 (12.5%) patients had insignificant CAD. 40 patients had diabetes mellitus among whom 35(87.5%) patients had CAD and 5(12.5%) patients had insignificant CAD.

45 patients had history of smoking, among whom 42(93.3%) patients had CAD and 3(6.7%) patients had insignificant CAD. 38 patients had history of alcohol consumption, among whom 31(81.6%) patients had CAD and 7(18.4%) patients had insignificant CAD. 22 patients had family history of CAD among whom 19(86.4%) patients had CAD and 3 (13.6%) had insignificant CAD.

There is no significant association between the risk factors among the CAD and insignificant CAD groups.

Table: 3. Laboratory parameters distribution among subjects with and without CAD

	Group						P Value
	CAD (n=106)		Insignificant CAD (n=14)		Total		
	Mean	SD	Mean	SD	Mean	SD	
Cholesterol (mg/dl)	163.60	36.62	144.71	23.09	161.40	35.75	0.063
Triglyceride (mg/dl)	178.48	57.24	151.29	34.27	175.31	55.64	0.086
LDL-C (mg/dl)	100.61	24.30	83.43	13.14	98.61	23.89	**0.011***
HDL-C (mg/dl)	38.59	9.62	42.79	4.06	39.08	9.23	0.111
FBS (mg/dl)	121.01	37.54	101.79	13.33	118.77	36.07	0.061
Total Leucocyte Count(cells/µL)	9995.19	2877.02	8985.71	979.68	9877.42	2741.20	0.197
Hb (gm/dl)	13.43	1.97	21.24	32.79	14.34	11.28	0.014

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Platelet Count (cells/µL)	262764.15	101930.28	259571.43	75430.78	262391.67	98944.88	0.910
Creatinine (mg/dl)	0.97	0.23	0.91	0.24	0.96	0.23	0.379

The mean value of LDL-C in CAD patients is 100.61mg/dl compared to 83.43mg/dl in Insignificant CAD patients. In this comparison the p value is statistically significant.

There is no significant association among the other laboratory parameters like total cholesterol, triglycerides, HDL-C, fasting blood glucose, total leucocyte count, platelet count and creatinine between the CAD and insignificant CAD groups.

Table:4. Lipoprotein and Anthropometric parameters distribution among subjects with and without CAD

	Group						P Value
	CAD (n=106)		Insignificant CAD (n=14)		Total		
	Mean	SD	Mean	SD	Mean	SD	
Lipoprotein (mg/dl)	42.33	27.63	12.73	6.62	38.87	27.74	**< 0.001***
BMI (kg/m2)	22.56	2.75	22.72	2.07	22.58	2.67	0.836
Waist Hip Ratio (WHR)	0.89	0.06	0.85	0.05	0.89	0.06	**0.011**
Waist Circumference (cms)	87.41	9.27	84.64	5.62	87.08	8.95	0.279
Hip Circumference (cms)	97.59	8.33	98.86	5.64	97.74	8.05	0.584

In present study, the mean value of WHR in CAD subjects is 0.89±0.06 compared to insignificant CAD subjects is 0.85±0.06. There is significant association among the CAD and insignificant CAD patients with the p value of 0.011.

The mean value of lipoprotein a is 42.33mg/dl in CAD patients and 12.73mg/dl in insignificant CAD patients. In this comparison the p value is statistically significant.

There is no association for BMI, waist circumference and hip circumference between the CAD and insignificant CAD groups.

Table: 5. Lipoprotein distribution with respect to Number of Vessels affected.

Number of vessels affected	N	Mean(mg/dl)	SD (mg/dl)	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
0	14	12.725714	6.6176614	1.7686444	8.904790	16.546638	2.2400	28.8500
1	58	33.557759	25.8604723	3.3956464	26.758094	40.357423	2.0000	100.0000
2	34	45.874706	23.9119059	4.1008580	37.531447	54.217964	2.0000	100.0000
3	14	70.039286	24.0792673	6.4354549	56.136331	83.942241	24.5000	100.0000

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Total	120	38.873333	27.7399070	2.5322955	33.859135	43.887531	2.0000	100.0000

F Value = 15.727, P value = < 0.001*

In present study, mean lipoprotein a value with respect to vessels involved is 12.72±6.61 among the non-CAD (insignificant CAD) patients, 33.55±25.86 among one vessel involved (single vessel disease), 45.87±23.91 among two vessels involved (double vessel disease) and 70.03±24.07 among three vessel involved (triple vessel disease).

There was a significant positive correlation between the mean value of lipoprotein a among the non -CAD (insignificant CAD) patients and CAD patients and also with severity of CAD in respect to the number of vessels affected with the p value of <0.001.

Table: 6. Correlation between Lipoprotein and Lipid Profile

		Lipoprotein (mg/dl)
Lipoprotein (mg/dl)	Pearson Correlation	1
	Sig. (2-tailed)	
	N	106
Cholesterol (mg/dl)	Pearson Correlation	0.252**
	Sig. (2-tailed)	0.009
	N	106
Triglyceride (mg/dl)	Pearson Correlation	0.120
	Sig. (2-tailed)	0.220
	N	106
LDL-C (mg/dl)	Pearson Correlation	0.321**
	Sig. (2-tailed)	0.001
	N	106
HDL-C (mg/dl)	Pearson Correlation	-0.107
	Sig. (2-tailed)	0.276
	N	106

In this study with respect to Pearson correlation between the lipoprotein a level and lipid profile, the p value is statistically significant between the lipoprotein a with respect to total cholesterol and LDL-C.

Table: 7. Lipoprotein cut off in predicting CAD

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.873
Standard Error[a]	0.0379
95% Confidence interval[b]	0.800 to 0.927
z statistic	9.828
Significance level P (Area=0.5)	<0.0001

a DeLong et al., 1988, b Binomial exact

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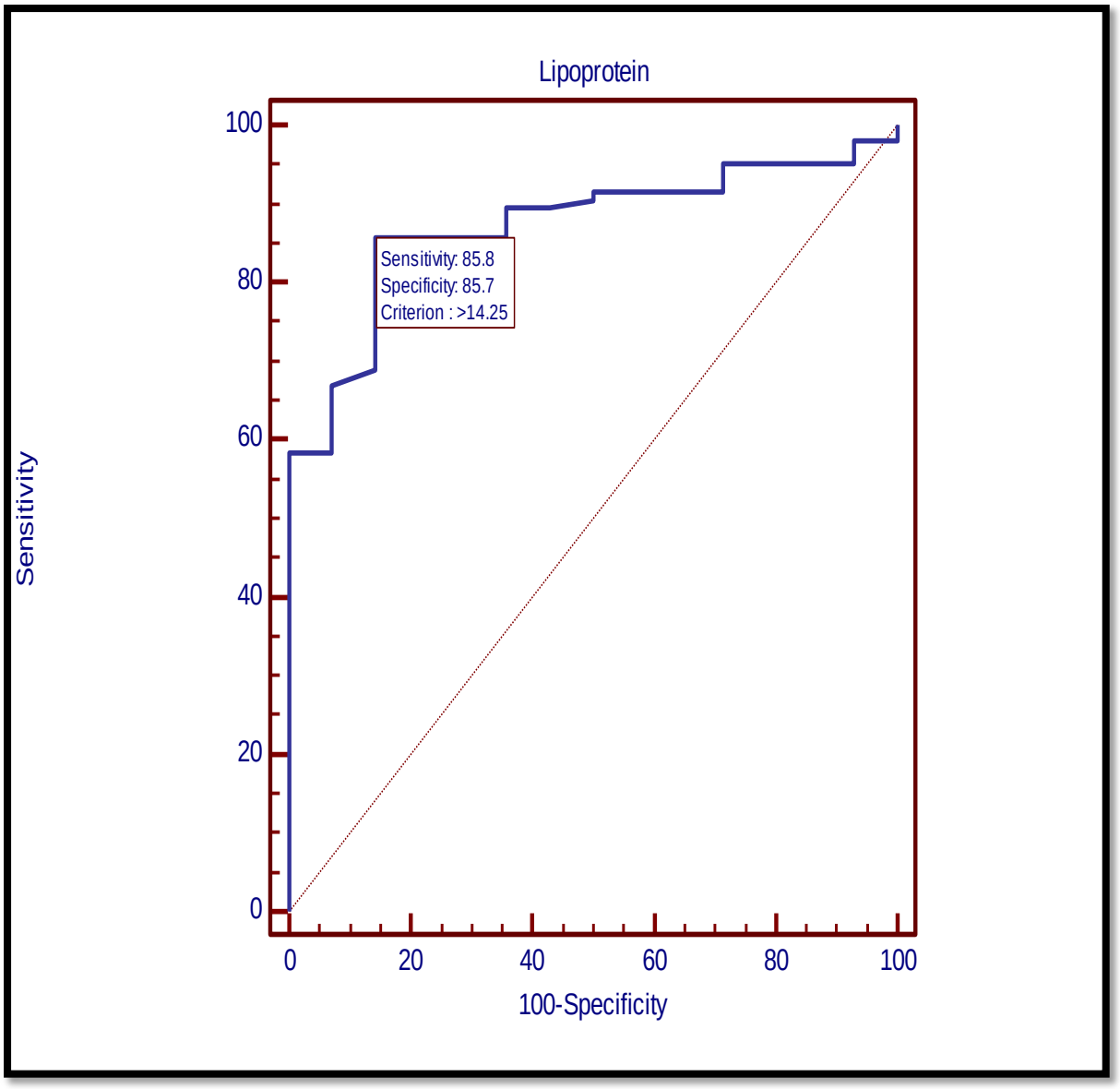

Youden index

Youden index J	0.7156
Associated criterion	>14.25

Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+PV	-PV
≥2	100.00	96.6 - 100.0	0.00	0.0 - 23.2	88.3	
>2	98.11	93.4 - 99.8	0.00	0.0 - 23.2	88.1	0.0
>2.24	98.11	93.4 - 99.8	7.14	0.2 - 33.9	88.9	33.3
>5.39	95.28	89.3 - 98.5	7.14	0.2 - 33.9	88.6	16.7

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>9.5	95.28	89.3 - 98.5	28.57	8.4 - 58.1	91.0	44.4
>10.05	91.51	84.5 - 96.0	28.57	8.4 - 58.1	90.7	30.8
>10.5	91.51	84.5 - 96.0	50.00	23.0 - 77.0	93.3	43.8
>10.86	90.57	83.3 - 95.4	50.00	23.0 - 77.0	93.2	41.2
>10.97	89.62	82.2 - 94.7	57.14	28.9 - 82.3	94.1	42.1
>11.73	89.62	82.2 - 94.7	64.29	35.1 - 87.2	95.0	45.0
>12.57	85.85	77.7 - 91.9	64.29	35.1 - 87.2	94.8	37.5
>14.25	**85.85**	**77.7 - 91.9**	**85.71**	**57.2 - 98.2**	**97.8**	**44.4**
>24.05	68.87	59.1 - 77.5	85.71	57.2 - 98.2	97.3	26.7
>24.5	66.98	57.2 - 75.8	92.86	66.1 - 99.8	98.6	27.1
>28.08	58.49	48.5 - 68.0	92.86	66.1 - 99.8	98.4	22.8
>28.85	58.49	48.5 - 68.0	100.00	76.8 - 100.0	100.0	24.1
>100	0.00	0.0 - 3.4	100.00	76.8 - 100.0		11.7

In the study on plotting the lipoprotein a value, the area under ROC curve with 95% confidence interval and based on the significant p value it was found that lipoprotein a value >14.25mg/dl have 85.85% sensitivity and 85.71% specificity in predicting the coronary artery disease (97.8% positive predictive value).

DISCUSSION:

In the present study, on plotting the lipoprotein a value the area under ROC curve with 95% confidence interval and based on the significant p value it was found that lipoprotein a value >14.25mg/dl have 85.85% sensitivity and 85.71% specificity in predicting the coronary artery disease (97.8% positive predictive value). There is also a significant positive correlation between WHR and number of vessels involved.

A similar study was conducted by Fauzia Ashfaq et al.,[16] in a cross-sectional study done to assess lipoprotein a level in relation to severity of CAD in north Indian patients, among 360 patients BMI and lipoprotein a level was high among CAD patients compared to non- CAD patients ($p<0.001$). The results from the study indicate that lipoprotein (a) level 21.0 mg/dl was associated with presence of CAD.

A similar study done at department of cardiology, GB Pant hospital Delhi by Jamal Yusuf et al.,[17] among 150 patients each of SVD, DVD, TVD with 150 controls, it was established that raised lipoprotein a level ≥ 40mg/dl assessed by isoform incentive assay, was an independent risk factor for CAD. Also raised lipoprotein (a) levels was associated with increased risk of ACS and multivessel CAD.

A case control study done by M.M. Kavitha et al., [18] Serum lipoprotein (a) as a diagnostic marker of coronary artery disease among 120 patients showed a lipoprotein (a) was found to be raised significantly in coronary artery disease patients. The results showed that a lipoprotein (a) level above 23.7mg/dl acts as a predictor for coronary artery disease even when lipid levels are in normal range with an Area under the curve is >0.8 with 78% sensitivity and 86% specificity.

A similar study was conducted by Premtim Rashiti et al.,[19] in Kosovar to assess the correlation between severity of CAD and waist Hip-Ratio, as a measurement of obesity as severity of CAD. The study was conducted on 82 patients. The study compared the two groups, CAD and non-CAD. There was significant

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positive correlation between waist-hip ratio among the CAD patients and it also showed that there is increased severity of CAD in the form of number of vessels affected with increased waist hip ratio.

CONCLUSION:

Lipoprotein a was found to be significantly elevated in the coronary artery disease patients compared to the non-coronary artery disease patients. It strongly correlates with the severity of coronary artery disease, assessed in the form of multivessel involvement and needs close clinical surveillance. In correlation of lipoprotein a with the other lipid profile based on the Pearson correlation it had significant association with total cholesterol and LDL-C in causing the coronary artery disease. We could able to get cut off range of 14.25mg/dl for the lipoprotein a level in coronary artery disease patients with 85.85% sensitivity and 85.71% specificity. Larger prospective studies and randomized trials in individuals with high lipoprotein a are needed to confirm these findings.

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