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Relationship between atherogenic index and oxidative stress among patients presented with coronary artery disease in a tertiary care hospital

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ABSTRACT

CAD is recognized as a multifactorial disease that is influenced by environmental and genetic factors. This study aimed to evaluate the levels of lipid parameters, oxidative stress and antioxidant markers in subjects with CAD compared to their age & sex matched controls and to analyze the relationship between atherogenic Index and oxidative stress among them 62 clinically proved CAD patients and 62 healthy age and sex matched subjects without CAD were selected for this study. 5 ml of fasting venous blood was collected from all the subjects and investigations such as FPG, lipid profile, oxidative markers Malondialdehyde (MDA), F2 isoprostanes (F2iso) and antioxidants glutathione S-transferase (GST), superoxide dismutase (SOD), vitamin-C, vitamin-E were performed. This study showed that levels of lipid parameters total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c) and AI were significantly higher whereas high density lipoprotein cholesterol (HDL-c) were significantly low in CAD patients compared to normal controls. Oxidative stress markers MDA and F2 Isoprostanes level were significantly high, whereas enzymatic antioxidants GST and SOD and non-enzymatic antioxidants Vitamin-C and Vitamin-E levels were significantly low in CAD patients. Oxidative stress markers were found to significantly influence the AI. Results of this study showed that oxidative stress markers F2iso and MDA and antioxidants GST, VIT-C and VIT-E are found to influence the atherogenic index significantly.

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INTRODUCTION

Coronary artery disease is primary disease of cardio vascular diseases consists of multi factorial etiologies, which include various lifestyle and environmental factors. There are many risk factors for CAD some are modifiable such as hypertension, hyperlipidemia, smoking, diabetes, obesity, lack of physical activity, unhealthy diet and stress but some are non modifiable such as age, sex, family history (Hajar, 2017). Dyslipidemia is one of the most critical factors for coronary artery disease. It was determined that atherogenic index of plasma value, which is acquired by logarithmic transformation of the number found by dividing plasma TG value

to HDL value, can be a useful marker for risk of atherosclerosis and cardio vascular disease (Shen *et al.*, 2016). In addition to these risk factors, several experimental and clinical studies have shown that oxidative stress mediated by reactive oxygen

species is involved in pathogenesis of CAD. One of the methods to detect oxidative stress is a measurement of organic molecules that are products of harmful ROS effects on the integrity of biological tissue, e.g., Isoprostanes and malondialdehyde. Isoprostanes are a series of prostaglandin like compounds produced via free radical catalyzed peroxidation of arachidonic acid, independent of cyclooxygenase derived prostaglandins. MDA arises as a result of accepted index of lipid peroxidation (Trachtenberg and Hare, 2009). The imbalance between the generation of reactive oxygen species and intrinsic antioxidant defense system leading to the oxidative stress, has been implicated in the pathogenesis of the cardio vascular disease (Latha *et al.*, 2017).

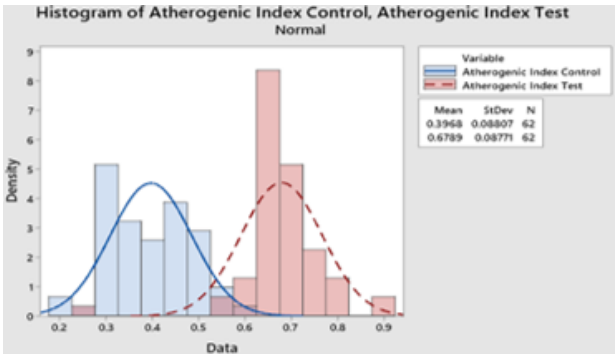

Figure 1: Comparison of atherogenic index of subjects [P=0.000].

Presence of natural antioxidants maintains this balance consists of vitamin A, ascorbic acid (vitamin C) and alpha tocopherol (vitamin E) and antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. Enhancement of lipid peroxidation or decrease of antioxidant protection present in metabolic diseases or bad lifestyle can induce endothelial dysfunction and atherosclerosis (Lubrano and Balzan, 2015). Many studies have conducted to evaluate the role of dyslipidemia and oxidative stress in CAD patients. No systematic studies have been carried out to evaluate the relationship of atherogenic index and oxidative stress in this population. This study was undertaken to investigate the variations of lipid parameters, AI, oxidative stress and antioxidant markers in subjects with CAD compared to their age and sex matched controls and to analyze the relationship between atherogenic index and oxidative stress among patients presented with CAD in a tertiary care hospital.

MATERIALS AND METHODS

62 clinically proved CAD patients referred from the out patient Department of Saveetha Medical College, Tandalam, Chennai were selected for the study. 62 healthy, age and sex matched subjects without CAD formed the control group. Detailed clinical and other relevant data were recorded using proforma. 5 ml of fasting venous blood was collected from all the subjects, and the following investigations were performed. Fasting plasma glucose, total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol (Direct) were estimated in fully automatic chemistry analyzer. The atherogenic index was calculated by using the formula: $\log_{10}$ (TG/HDL-C). Oxidative markers- MDA, F2- Isoprostanes, were estimated using commercially variable ELISA kit [Human Diagnostics, Germany]. Antioxidants enzymatic: - GST and SOD. Nonenzymatic:- Vitamin-C & Vitamin-E were estimated using commercially available ELISA kit [Human Diagnostics, Germany].

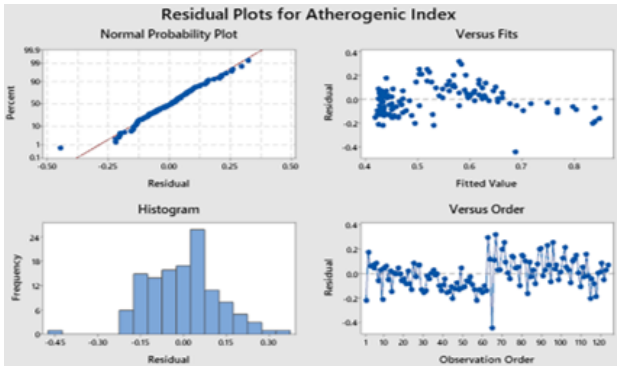

Figure 2: Regression of oxidative stress-Residual plots for atherogenic index.

Statistical Analysis

'*t*' test was performed for comparing the plasma glucose and lipid profile of the study subjects and the control subjects. Mann Whitney test was performed for comparing the oxidative stress and antioxidants of the study subjects and the control subjects. Linear regression analysis was also performed to study the relationship between the atherogenic index and oxidative stress.

RESULTS AND DISCUSSION

In this study, 62 clinically proven CAD patients were selected as test subjects, including 75.0% males and 25.0 % females. Sixty-two normal control subjects were also selected consists of 66.1% males and 43.9% females. All subjects were taken within the age group of 30 to 75 years. The age group of the study subjects ranged from 30 to 71, with a mean

Table 1: Distribution of test subjects and controls according to risk factors.

Subjects		Test		Controls	
		Number	Percentage	Number	Percentage
Family History of CAD	Yes	26	21%	0	0%
	No	36	29%	62	50%
Diabetic	Yes	27	22%	7	6%
	No	35	28%	55	44%
Hypertension	Yes	12	19%	34	55%
	No	50	81%	28	45%
History of MI	Yes	62	50%	3	2%
	No	0	0%	59	48%

Table 2: Comparison of biochemical risk factors of subjects.

Test	Test (n=62)	Control (n=62)	t	P
FPG	141±53.9	90.3±5.5	-7.36	<0.01
T CHOL	230±27.3	176.9±13.8	-13.7	<0.01
TG	175.9±32.5	120.0±19.9	-11.55	<0.01
LDL	157.4±24.7	110.7±10.6	-13.68	<0.01
HDL	36.4±2.9	47.7±4.7	16.07	<0.01

Table 3: Comparison of oxidative stress markers of subjects.

Test	Test	Control	W-Value	P
F2- Isoprostanes	173.4±86.8	28.9±19.4	2007.00	0.000
MDA	25.2±12.2	5.23±6.03	2134.50	0.000

Values are mean ± SD.

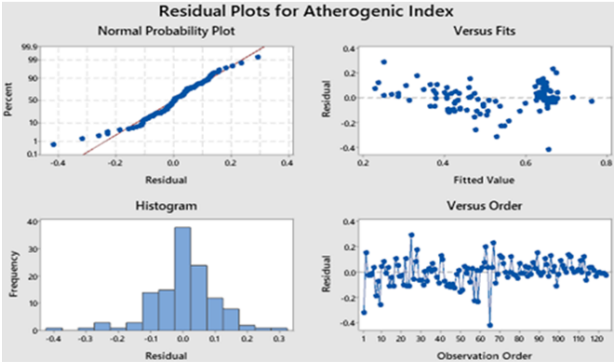

Figure 3: Regression of antioxidants-Residual plots for atherogenic index.

age of 51.9. The observed mean age of the control subjects was 47.43 (age ranged from 35-75). Test and control subjects were distributed according to conventional risk factors of CAD and are given in Table 1. Fasting plasma glucose, total cholesterol (T.C.), triglycerides (T.G.), high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol (Direct) were estimated and compared between the test and control subjects. Results are given in Table 2.

Atherogenic index of subjects was calculated and compared between the test and control subjects. Results are given in Figure 1. Oxidative Markers-M.D.A., F2- Isoprostanes, were estimated and compared between test and control groups and given in Table 3. Enzymatic antioxidants - G.S.T. and S.O.D. and non-enzymatic antioxidants - Vitamin-C and Vitamin-E were estimated and compared between test and control subjects and given in Table 4. Linear regression analysis was performed to study the relationship between atherogenic index and markers of oxidative stress, and the results are given in Tables 5 and 6 and Figure 2. Oxidative stress markers F2iso and M.D.A. are found to significantly influence the atherogenic index as shown by the regression equation.

Regression of oxidative stress

Regression Equation

Atherogenic index = 0.4100 + 0.000911 F2iso (ng/L) + 0.00234 MDA (nmol/mL)

Linear regression analysis was performed to study

the relationship between atherogenic index and markers of antioxidants, and the results are given in Tables 7 and 8 and Figure 3. Antioxidants G.S.T., V.I.T. C and V.I.T. E are found to significantly influence the atherogenic index as shown by the regression equation. No significant influence was observed for S.O.D.

Regression of Antioxidants

Regression Equation

Atherogenic index = 0.6544 + 0.000046 SOD (U/L) + 0.002128 GST (ng/mL) - 0.002994 VIT C (ng/mL) - 0.001999 VIT E (nmol/mL)

Present study explored the relationship between atherogenic index and oxidative stress in CAD. Onset of coronary artery disease is influenced by cardiovascular risk factors that often occur in clusters and may build on one another (Milane *et al.*, 2014). According to Otaki *et al.*, young family history, positive patients have a higher presence, extent, and severity of CAD, which are associated with increased risk for myocardial infarction. In our study, positive FH of CAD was prevalent in CAD patients than in controls. Cardiovascular disease is a major cause of death and disability among people with diabetes (Atlas, 2015).

Our study is in well agreement with above studies. High blood pressure is a major modifiable risk factor for all clinical manifestations of CAD (Weber *et al.*, 2016). Our study is in agreement with the above studies as we found more hypertensive subjects among the CAD patients. Family history of myocardial infarction (MI) is an independent risk factor for MI. (Ranthe *et al.*, 2015) observed risk of M.I.s in first and second degree relatives and by number and age of affected relatives. We also observed more subjects with a family history of MI among the test group. Gui *et al.*, observed that F.P.G. is an independent risk factor for the prevalence and severity of significant angiographic CAD. Lipid parameters also have an essential role in CAD.

(Kumar and Das, 2018) found that the total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides concentrations were significantly higher ($p < 0.05$) in coronary heart disease patients. Studies of (Cai *et al.*, 2017) and (Shen *et al.*, 2016) revealed that the atherogenic index was a significant and independent predictor for CAD risk. We also observed high levels of F.P.G., T.C., triglycerides, LDL cholesterol and low levels of HDL cholesterol in CAD patients compared to normal controls. Our study observed that the atherogenic index is significantly high in CAD patients. According to Chandra *et al.*, biomarkers of reactive oxygen species serve as indicators of oxidative stress in the pathology of cardiovascular diseases. Zhang (2013) found that high levels of F2-isoprostanes in urine or blood may be a non-specific indicator of CVD. Davies and Roberts (2011) found that high levels of F2-isoprostanes are found in many human diseases, such as coronary heart disease. The present findings are also in accordance with a number of studies reporting an increased level of M.D.A. in CAD patients compared with healthy control groups (Pamplona, 2008; Bhat *et al.*, 2012). Amaki *et al.* (2004) identified that the serum levels of circulating MDA modified LDL in patients with CAD were significantly higher than in patients without CAD, indicating the use of this parameter as a diagnostic marker for advanced atherosclerosis. Uzun *et al.* (2013) findings suggest that excessive vascular oxidative stress has been linked to impaired endothelium dependent arterial relaxation in coronary artery disease and antioxidants vitamins C and E improved defective endothelial function.

Mullan *et al.* (2002) reported that Vitamin C prevents low density lipoprotein (LDL) oxidation, either through the recycling of vitamin E or by scavenging free radicals directly. Several studies have found an association between G.S.T. polymorphisms and decreased enzymatic activity and atherosclerosis (Banerjee and Vats, 2014). S.O.D. involved in the disposal of superoxide anions and hydrogen peroxide. Thus, insufficient detoxification of these reactive oxygen species by antioxidant enzymes may lead to an occurrence of imbalance between antioxidant and oxidant systems. The low activity could also attribute to enzyme inactivation by R.O.S. bringing about damage to proteins (Yang *et al.*, 2008). In conclusion, antioxidant enzymes are reduced in the presence of metabolic disease and CAD (Lubrano and Balzan, 2015). Our study is in well agreement with the above studies because we found decreased levels of enzymatic and non-enzymatic antioxidants in CAD patient.

A lot of studies have found that serum M.D.A. is higher in subjects with hyperlipidemia and decrease following dietary supplementation with antioxidants. Similar observations have been reported in animal models of hyperlipidemia (Minhajuddin *et al.*, 2005; Yang *et al.*, 2006). According to Thomas (2000) the alterations in the levels of serum lipid peroxide and antioxidant status in subjects with higher serum T.C., LDL-C, and lower HDL-C levels may increase the susceptibility of LDL to oxidation in the circulation. As a lipid peroxidation process leading to the increased atherogenicity of LDL, it follows that antioxidant status should have a major impact not only on the rate of LDL oxidation but

Table 4: Comparison of antioxidant markers of subjects.

Test	Test	Control	W-Value	P
GST	21.0±17.4	75.9±32.8	5491.50	0.000
SOD	57.1±38.2	485±620	5339.50	0.000
VIT E	7.85±5.11	64.4±21.3	5784.00	0.000
VIT C	11.0±7.32	95.9±40.9	5778.00	0.000

Values are mean ± SD.

Table 5: Coefficients.

Term	Coef	S.E. Coef	T-Value	P-Value	V.I.F.
Constant	0.4100	0.0173	23.73	0.000	-
F2iso (ng/L)	0.000911	0.000158	5.76	0.000	1.83
MDA (nmol/mL)	0.00234	0.00109	2.15	0.034	1.83

Table 6: Analysis of variance.

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	2	1.54076	0.770378	49.88	0.000
F2iso (ng/L)	1	0.51201	0.512005	33.15	0.000
MDA (nmol/mL)	1	0.07108	0.071078	4.60	0.034
Error	121	1.86885	0.015445	-	-
Lack-of-Fit	119	1.85740	0.015608	2.73	0.306
Pure Error	2	0.01145	0.005727	-	-
Total	123	3.40961	-	-	-

Table 7: Coefficients.

Term	Coef	S.E. Coef	T-Value	P-Value	V.I.F.
Constant	0.6544	0.0161	40.58	0.000	-
SOD (U/L)	0.000046	0.000026	1.80	0.074	1.78
GST (ng/mL)	0.002128	0.000704	3.02	0.003	8.18
VIT C (ng/mL)	-0.002994	0.000722	-4.15	0.000	15.93
VIT E (nmol/mL)	-0.001999	0.000883	-2.26	0.025	9.28

Table 8: Analysis of variance.

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	4	2.12911	0.53228	49.47	0.000
SOD (U/L)	1	0.03486	0.03486	3.24	0.074
GST (ng/mL)	1	0.09845	0.09845	9.15	0.003
VIT C (ng/mL)	1	0.18492	0.18492	17.19	0.000
VIT E (nmol/mL)	1	0.05520	0.05520	5.13	0.025
Error	119	1.28050	0.01076	-	-
Total	123	3.40961	-	-	-

perhaps on the development of atherosclerosis. It is possible that a potential risk of atherosclerosis in higher lipid group was associated with LDL oxidation as a result of increased levels of LDL-C and decreased antioxidant enzyme activity.

Results of Yang *et al.* showed that an imbalance in the oxidant/ antioxidant ratio is already present at higher lipid subjects. Their results demonstrated that enhanced lipid peroxidation and decreased antioxidant enzyme activity represent early events in the development of hyperlipidemia in human as they observed a positive correlation between M.D.A. and atherogenic Index (A.I.) (r = 0.61, p<0.05). They also observed decreased activities of S.O.D. and in higher lipid subjects. Our study also in agreement with the studies as mentioned above.

CONCLUSIONS

This study showed that levels of lipid parameters - total cholesterol, triglycerides, LDL- c, were significantly higher, whereas HDL- c were significantly low in CAD patients compared to normal controls. Oxidative stress markers levels were significantly high, whereas enzymatic and non-enzymatic antioxidants levels were significantly low in CAD patients. Oxidative stress markers F2iso and M.D.A. and antioxidants G.S.T., V.I.T. C and V.I.T. E are found to influence the atherogenic index significantly. These data indicate that oxidative stress may be an early event in the evolution of dyslipidemia. Hence in subjects with dyslipidemia, restoring the body's antioxidant status may reduce oxidative stress and may help to prevent or delay the development of CAD.

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The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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