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ROLE OF NT-proBNP AMONG CORONARY ARTERY DISEASE SUBJECTS WITH DYSLIPIDEMIA

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Abstract

Coronary artery disease (CAD), the leading cause of mortality globally, is one of the major cardiovascular diseases, which results in the buildup of plaque leading to narrowing of coronary arteries. Genetic, environmental and lifestyle factors have an important role in the development of the disease. Moreover, dyslipidemia is a major focus among the risk factors involved in the pathogenesis of CAD. Early diagnosis and management of the disease can be achieved by analyzing the level of biomarkers like NT-proBNP. The study was conducted among 110 test subjects who were dyslipidemic with CAD and 110 control subjects without any chronic illness. The study revealed that test subjects have an increased concentration of NT-proBNP than the control subjects. Moreover, NT-proBNP can also be used as a biomarker for the early prediction of CAD patients with dyslipidemia.

Keywords: Coronary artery disease, Dyslipidemia, NT-proBNP

INTRODUCTION

Coronary Artery Disease (CAD) is defined as a multifactorial disease of coronary blood vessels caused by atherosclerosis, which results in a restriction of blood flow to the heart defined by Fabian Sanchis-Gomar et al (2016). The World Health Organization (WHO 2017) estimated that, "CAD was responsible for one out of seven deaths in 2015. It is estimated that by the year 2030, cardiovascular disease will be responsible for 40% of deaths". Bhatnagar et al (2016) reported that, "CAD is the largest cause of death in the world".

In 2016, the American Heart Association released an updated report of Heart Disease and Stroke Statistics, which reported that, "in the United States, 15.5 million people above 20 years of age suffer from CAD". Mozaffarian et al (2015) estimated that, "the prevalence was found to be increasing with age in both men and women". In 2016, Krishnan et al pointed out that, "in India, CAD has, of late, gained importance as a major disease". Girelli et al (2000) mentioned that, "genetic and environmental factors have been found to interact with one another to determine the clinical phenotype of cardiovascular diseases".

Lowenstein in 2017 stated that "dyslipidemia is an important risk factor for CAD and stroke". According to WHO (2011), dyslipidemia was associated with more than half of the cases of ischemic heart disease globally and lead to more than 4 million deaths every year. Khashayar & Mohagheghi (2010) reported that, "elevated serum triglyceride (TG) and decreased

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HDL cholesterol levels, the core component of the metabolic syndrome, are also commonly found in many patients with established CAD".

CAD is the most prevalent cardiovascular disease worldwide and thereby its early diagnosis and management can save thousands of lives annually. Several biomarkers are currently used for the diagnosis ease. Among them, "N-terminal pro B-type natriuretic peptide (NT-proBNP) can help to diagnose heart failure and acute coronary syndromes as well as to determine the prognosis of such patients" suggested by Corteville et al (2007). Previously, in 2014 Troughton et al reported that, "Brain natriuretic peptide (BNP) and *N*-terminal proBNP (NT-proBNP) are widely used as significant indicators for the clinical diagnosis of HF and cardiac dysfunction". According to Tsai et al (2010), "BNP is cardiac neurohormone synthesized and released from the cardiac ventricular cells owing to increased wall tension such as volume or pressure overload. BNP has special systemic effects: vasodilatation, increase the excretion of water and sodium, inhibition of SNS and of RAAS".

Costello-Boerrigter et al (2013) explained that, "the precursor of circulating BNP (active peptide) and NT-proBNP (inactive peptide) is a 134 amino acid pre prohormone, which yields a 108 amino acid prohormone molecule, a precursor molecule stored in cardiomyocyte". Bibbins-Domingo et al (2007) mentioned that, "Cardiovascular morbidity and death could be predicted by the raised levels of NT-proBNP in the affected individuals, thereby proving to be markers for high-risk individuals". Current evidence suggests that NT-proBNP rises during myocardial ischemia and therefore it has a potential for the diagnosis of dyslipidemic patients with CAD. Emerging risk markers such as NT-proBNP is necessary to provide specific value when compared to traditional markers. Moreover, clinical implication of NT-proBNP among dyslipidemic subjects with CAD is not well-studied. This study therefore aimed to investigate the correlation between dyslipidemia and the concentrations of NT-proBNP and various risk factors, in CAD patients.

MATERIALS AND METHODS

One Hundred Ten individuals suffering from CAD and dyslipidemia were selected as test subjects. The samples were referred from Hridayalaya, Institute for Preventive Cardiology, Thiruvananthapuram to Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala. One Hundred Ten age and sex matched healthy subjects without any chronic illness was included in control group. Detailed demographic, clinical and lifestyle characteristics were recorded using well-structured proforma. Information about previous infections was also recorded. In this study, NT-proBNP concentration was quantified in each study subject. Five ml of blood was collected in a plain tube and blood was allowed to clot; serum separated immediately. ELISA method was done for estimating NT-proBNP concentration.

OBSERVATIONS AND RESULTS

The age range of study subjects are from 30 years to 55 years. The mean age of test and control subjects was 48.06±4.73 and 47.87±6.56 respectively. No statistical significance difference between the mean age of test and control subjects was observed (t= 0.24748; p= 0.402). The mean NT-proBNP level of test was 134.33±13.25 and for control subjects it was 83.24±24.37. Comparatively an increased mean NT-proBNP level was observed in test subjects than the control subjects. A statistically significant difference was observed between the mean NT-proBNP concentration of test and control group with a p value <0.001 (t=19.311).

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Table: 1 Distribution of mean NT-proBNP according to Demographic characteristics

Variables	Category	NT-proBNP (pg/mL)	
		Test	Control
Age	30-35	126.9	76.73
	36-40	134.16	82.15
	41-45	133.04	89.85
	46-50	136.07	89.08
	51-55	136.4	105.14
Gender	Female	135.22	83.68
	Male	133.41	82.91
Birth order	≤3	135.50	77.92
	>3	132.57	85.05
Residence	Urban	133.91	88.34
	Rural	133.44	75.40
	Coastal	138.51	80.09
Occupational type	Non-sedentary	127.21	82.34
	Sedentary	140.27	84.54
Socioeconomic Status (SES)	High	136.64	81.75
	Average	133.68	83.24
	Low	134.92	83.54

The age of study subjects was categorized into five groups and level of NT-proBNP was analyzed. Subjects with advanced age showed an increased level of NT-proBNP (136.4 pg/mL). Based on the gender of the study subjects, it was observed that among test subjects, females show an increased value of NT-proBNP (135.22 pg/mL) compared to male (133.41 pg/mL). An elevated value of NT- proBNP was observed among test subjects who reside in coastal area when compared to the rest. The occupation type of study subjects was categorized into two (as sedentary and non-sedentary). Test subjects who reported with sedentary type of occupation showed an elevated NT- proBNP value (140.27 pg/mL) than the test subjects reported with non-sedentary type of occupation. Similarly, test subjects reported with high SES showed an increased NT- proBNP concentration when compared to the rest.

Table : 2 Distribution of NT-proBNP according to lifestyle parameters

Variables	Category	NT-proBNP (pg/mL)	
		Test subjects	Control subjects
Habit of smoking	Yes	144.13	81.67
	No	129.95	83.49
Habit of alcohol	Yes	135.33	76.15
	No	134.24	84.36

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consumption			
Regular exercise	Yes	132.93	83.86
	No	135.07	81.96
Physical activity	Good	132.02	82.95
	Average	133.63	82.89
	Poor	135.00	84.38
Obesity	Yes	139.25	72.86
	No	127.50	86.61
Dietary Pattern	Vegetarian	109.18	85.03
	Non-vegetarian	136.85	83.13

An increased level of NT-proBNP (144.13 pg/mL**)** was observed among test subjects reported with habit of smoking. The observed level of NT-proBNP among test subjects reported with habit of alcohol consumption, irregular exercise, poor physical activity and non-vegetarian dietary pattern were 135.33 pg/mL, 135.07 pg/mL, 135.00 pg/mL, 136.85 pg/mL respectively. Obese test subject showed an increased value of NT-proBNP (139.25 pg/mL) when compared to non-obese test subjects.

Table : 3 Distribution of NT-proBNP according to Clinical parameters

Variables	**Category**	**NT-proBNP (pg/mL)**	
		Test (n)	**Control (n)**
H/o Diabetes	Yes	136.74 (65)	96.18 (11)
	No	130.86 (45)	81.80 (99)
H/o Hypertension	Yes	135.21 (66)	83.37 (8)
	No	133.75 (44)	83.23 (102)

The subjects reported with clinical parameters like, H/o Diabetes, H/o Hypertension showed an increased NT-proBNP value when compared to the rest.

Table: 4 Distribution of NT-proBNP according to Biochemical Characteristics

Variables	**Category**	**NT-proBNP (pg/mL)**	
		Test (n)	**Control (n)**
FBS (mg/dL)	≤ 110	127.35 (35)	86.20 (89)
	> 110	137.59 (75)	70.68 (21)
Total Cholesterol (mg/dL)	≤ 200	123.35 (13)	79.48 (107)
	> 200	135.80 (97)	120.83 (3)
HDL-C (mg/dL)	≤ 40	137.98 (91)	83.29 (23)
	> 40	116.86 (19)	83.22 (87)

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LDL-C (mg/dL)	≤ 100	129.05 (46)	78.90 (29)
	> 100	138.13 (64)	85.25 (81)
Triglyceride (mg/dL)	≤ 150	119.07 (19)	83.28 (99)
	>150	137.52 (91)	82.90 (11)
Creatinine (mg/dL)	≤1.2	128.98 (53)	84.30 (95)
	>1.2	139.31 (57)	76.49 (15)

Test subjects with FBS concentration ≤ 110 and >110 mg/dL showed a NT-proBNP level of 127.35 pg/mL and 137.59 pg/mL respectively. Test subjects with total cholesterol level >200mg/dL showed an elevated value of 135.80 pg/mL than the rest. The observed NT-proBNP of test subjects with LDL-C level >100 mg/dL was 138.13 pg/mL and the rest with LDL-C level ≤ 100 mg/dL it was 129.05 pg/mL. Test subjects with creatinine level > 1.2 mg/dL showed an increased level of NT-proBNP 139.31 pg/mL than the rest with creatinine concentration ≤1.2 mg/dL. Whereas, test subjects with decreased levels of HDL-C (≤ 40 mg/dL) showed an elevated NT-proBNP concentration (137.98 pg/mL).

Table: 5 Distribution of NT-proBNP according to Endocrinological factors

Variables	Category	NT-proBNP (pg/mL)	
		Test	Control
T3 (ng/dL)	≤159	134.12	89.27
	>159	134.81	56.10
T4 (µg/dL)	≤11.7	135.08	82.99
	>11.7	132.51	89.79
TSH (µIU/mL)	≤4.5	128.40	84.47
	>4.5	137.72	72.19

The observed NT-proBNP concentration of test subjects with T3 level ≤159 and >159 ng/dL was 134.12 pg/mL and 134.81 pg/mL respectively. Test subjects with T4 level >11.7 µg/dL showed a NT-proBNP level of 15.08 pg/mL and for the rest with T4 concentration ≤11.7 µg/dL it was 135.08 pg/mL. Test subject with TSH value >4.5 µIU/mL showed an increased NT-proBNP of 137.72 pg/mL than the rest with TSH value ≤4.5 µIU/mL (128.40 pg/mL).

DISCUSSION

In the current study, an elevated level of NT-proBNP value was observed among dyslipidemic test subjects with CAD than the control group. Saito et al (1989) reported that, "Natriuretic peptides are biochemically categorized as cardiac hormones which have diuretic and vasodilator responses". Ho et al (2018) showed that, "the protein biomarkers of cardiovascular disorders pointed NT-proBNP as one of the biomarkers for heart failure, all-cause mortality and

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cardiovascular deaths". Mrityunjay & Pallavi (2021) stated that, "dyslipidemia is a major risk factor for CAD that has been widely recognized as an independent risk factor".

In the present study, test subjects with advanced age showed an elevated NT-proBNP concentration than the control group. "Higher levels of NT-proBNP were associated with adverse risk factor characteristics like older age, chronic kidney disease and higher baseline CVD prevalence was reported", in the study done by Welsh et al in 2016.

In the current study, the observed concentration of NT-proBNP among female test subjects was higher than the male test subjects. This was supported by Suthahar et al (2018) who suggested that, "NT-proBNP levels in women are higher than those in men, which may be related to sex hormones which are protective factors of coronary artery". In contrast to the above observation, Franke et al (2015) reported that, "there is no significant difference in NT-proBNP levels between men and women, which may be due to the stimulating effect of female sex hormones on natriuretic peptide gene expression".

In the present study, it was observed that test subjects reported with clinical history of diabetes showed elevated NT-proBNP concentration than the rest. Fang et al (2011) reported that, "NT-proBNP levels are closely related to the severity of CHD (coronary heart diseases) in a Chinese population of diabetic and pre-diabetic patients. The relationship between NT-proBNP and CHD was stronger in diabetic and pre-diabetic patients than normoglycemic controls". Ostovaneh et al (2020) reported that, "patients with lower NT-proBNP at baseline are more likely to be obese and have dyslipidemia and insulin resistance and thus are at higher risk of developing diabetes mellitus and CAD, as well as higher likelihood for greater change in NT-proBNP levels during follow-up".

In the current study, test subjects with a habit of smoking showed an elevated NT-proBNP concentration when compared to the rest. Nadruz et al (2016) reported that, "current smokers showed higher levels of NT-proBNP compared with never smokers in multivariable analysis".

In the present study it was observed that test subjects with increased levels of FBS, TG and LDL-C showed an elevated NT-proBNP concentration. Whereas, test subjects with low HDL-C level showed an increased concentration of NT-proBNP. Simon et al (2010) observed that, "subjects with CAD had higher TC, LDL and TG values with a low level of HDL". Garg et al (2014) found that "TC/HDL and LDL/HDL ratios are better indicators of CAD than only looking at the amounts of TC, TG, LDL-C, and HDL cholesterol alone".

In the current study, "test subjects with TSH value >4.5 µIU/mL showed an increased NT-proBNP of 137.72 pg/mL than the rest". Kim et al (2012) suggested that, "independent of conventional cardiovascular risk factors, thyroid hormones (fT3 and fT4) inversely correlated with coronary artery disease, especially men". In 2013 Yang et al explained that, "high levels of TSH within the reference range were independently associated with the presence of CAD".

In the present study, creatinine level among study subjects was analyzed and it was observed that, test subjects with creatinine level >1.2 mg/dL showed an elevated NT-proBNP

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level than the rest. Bagheri et al (2019), "several mechanisms are involved in the relationship of serum creatinine with the increased risk for CAD".

CONCLUSION

Coronary artery disease is an interwoven phenomenon resulting in the blockage of blood vessels thereby reducing the blood flow to the heart. The incidence of CAD is increasing rapidly in India so understanding the risk factors are necessary for the prevention of CAD morbidity and mortality. Dyslipidemia is one of the major risk factors for CAD, and it may even be a precursor to CAD, occurring before other significant risk factors appear. NT-proBNP can be used as a biomarker for dyslipidemia that effectively correlates with identification of the disease. In the current study, it was observed that the dyslipidemic test subjects with CAD showed an elevated concentration of NT-proBNP than the control subjects. Thus, it can be concluded that, as an emerging risk marker, NT-proBNP provides specific diagnostic and prognostic values when compared to traditional markers among subjects with CAD.

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