Original Article

Physiology

Measurement of Plasma Fibrinogen Level in Healthy Smokers to Predict the Risk of Cardiovascular Disease

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ABSTRACT

Objective: To ascertain the association of smoking with high fibrinogen level and to necessitate the inclusion of fibrinogen level measurement in cardiovascular risk profile.

Study Design: cross sectional study.

Place and Duration of Study: This study was carried out in Hematology section of Pathology Department of Government Lady Reading Hospital & Hayatabad Medical Complex Peshawar from June 2011 to December 2011.

Materials and Methods: Plasma fibrinogen level was measured in 250 healthy male smokers & 250 non smokers as controls by Claus method using Coagulation analyzer Sysmex 530. All subjects were in age group between 25-55 years. Smokers were categorized into light, moderate and heavy smokers on the basis of number of cigarettes smoked per day.

Results: Comparison of plasma fibrinogen level of light, moderate & heavy smokers to the plasma fibrinogen level of non-smokers controls showed highly significant results (p-value 0.002, 0.001 & 0.001 respectively) by using t-test. Similarly comparison of plasma fibrinogen level of light to moderate, light to heavy & moderate to heavy also showed highly significant results (p-value 0.001, 0.001 &0.002, respectively)

Conclusion: Smoking is the major factor rising plasma fibrinogen level in smokers and predisposes them to cardiovascular diseases. Fibrinogen level rises as the smoking intensity increases Plasma fibrinogen level assessment should be included in cardiovascular risk profile in general & in smokers in particular.

Key words: Plasma Fibrinogen, Cardiovascular Disease

INTRODUCTION

Cigarette smoking is a major health hazard and largest cause of premature morbidity and mortality worldwide[1]. According to United States Center for Disease Control & Prevention, smoking is the most important preventable risk to human health[2] . WHO estimated that tobacco smoking caused 5.4 million deaths in 2004 which reflects rising mortality when compared to statistics of 1990 showing 400000 deaths worldwide[3]. The cigarettes smoking increased mortality rates by 40% in those who smoke less than 10 cigarettes per day, by 70% in those who smoke 10-19 cigarettes per day, by 90% in those who smoke 20-39 cigarettes per day and by 120% in those smoking 2 packs a day or more [4]. Regular smokers are estimated to live to 2.5 to 10 years fewer than non smokers losing an average of eight years of life[5]. It produces diseases in persons under age of 50 than in those over 50 years of age[6]. According to the WHO about one third of world's male population smokes tobacco. On the average 47.5% of men and 10.3% of women are currently smokers[2]. Tobacco use continues to expand throughout the developing world where currently half of the deaths are due to tobacco smoking[7] .

Out of 1.3 million smokers worldwide, 800 million live in developing countries. Deaths from smoking are projected to increase to 9 to 10 million annually by 2030, by which time 70% deaths will be in developing countries, where tobacco consumption is rising by 3.4% per year. East Asian countries accounting for disproportionately high percentage (38%).In Pakistan 25.4% males are smokers with highest prevalence among middle aged males i.e. 48.6% in 25-44 year age group[8].

Cigarette smoking causes a large number of diseases, among which the cardiovascular disease is the leading cause of death and not the carcinoma lung as commonly perceived by the public[9]. Cardiovascular diseases include coronary heart disease, peripheral vascular arterial disease and stroke (Cerebrovascular disease).

Smoking doubles the incidence of cardiovascular diseases and it increases the mortality among these patients by 50%. In fact half of all cardiovascular risk is attributed to smoking and smoking is called as the 1st modifiable risk factor for cardiovascular disease Overall a smoker has two to three times risk of having heart attack than the non-smoker [10].

Coronary artery disease is a major and growing contributor to morbidity, mortality and disability in the South Asian countries including Pakistan. The total mortality due to cardiovascular disease in Pakistan during 2002, estimated by WHO, was 154,338. Despite this excess disease burden, data are however, sparse from studies investigating the determinants of coronary

heart disease risk in South Asia generally, and in Pakistan in particular [11].

Almost 50% of high risk of cardiovascular disease in smokers is mediated through the effect of smoking on plasma fibrinogen which is found to be high as compared to non smokers[10]. Fibrinogen is an essential plasma protein required for normal coagulation and it becomes hazardous for cardiovascular system when exceeds its normal level of 150-400 mg/dl[12].For each 100mg/dl increase in plasma fibrinogen level over the initial base line there is 2.4 fold greater likelihood of contracting cardiovascular disease.Indeed each cigarette smoked per day increases mean plasma fibrinogen level by 0.35 g/l and the association of fibrinogen level with smoking is much stronger in men [13]. Cigarette smoking is the strongest known environmental influence on plasma fibrinogen level. There is positive and significant dose response relationships between measures of cigarette smoking i.e. cigarettes per day, pack years and elevated levels of fibrinogen [2] and conversely, smoking cessation results in rapid reduction in plasma fibrinogen levels[14]. Fibrinogen has also been positively associated with traditional risk factors for coronary heart disease like advanced age, elevated low density lipids (LDL) and triglycerides, low level of high density lipoproteins (HDL), obesity, physical inactivity, hypertension and diabetes suggesting that elevation of fibrinogen may be a pathway by which these risk factors exert their effects. Fibrinogen is a chemical link between these factors and coronary heart disease. The incidence of heart attack is six times greater in men with high cholesterol and high fibrinogen level as compared to those with high cholesterol and low fibrinogen level[14]. Half of all patients who suffer heart attack and 30% of patients with extensive atherosclerosis have normal blood cholesterol. So fibrinogen may be considered to be a risk factor of equal or higher value than cholesterol. It increases the risk of cardiovascular disease by promoting atherosclerosis, facilitating thrombogenesis through platelet aggregation and inducing vascular endothelial dysfunction by inflammation..

MATERIALS AND METHODS

Present cross sectional study was conducted at Hematology section of Pathology department of LRH & HMC. Subjects comprised of 250 healthy male smokers and 250 non-smokers as controls, in the age group between 25-55 years, were selected randomly from general population of Peshawar. Smokers were divided into light, moderate and heavy smokers on the basis of number of cigarettes smoked per day i.e.5, 6-10 and 10-20& above respectively. Light, moderate and heavy smokers were designated as Group1, 2 & 3, respectively. Plasma fibrinogen level was measured in both smokers and controls by Claus method, using coagulation analyzer Sysmex 530 and Thrombin reagent. The results were analyzed by applying student T test and using SPSS Version 16.Values were expressed as mean ± SD(standard deviation)

RESULTS

Present study comprised of 500 subjects with 250 healthy male smokers and 250 non smokers as controls. Among the smokers 94 (38%) were light, 71 (28%) were moderate and 85 (34%) were heavy smokers. Mean age of smokers was 36.74 years while mean age of controls was 39.44 years. Mean plasma fibrinogen level of light, moderate and heavy smokers and control groups is given in table-1 and graphically presented in figure-1. Comparison of mean plasma fibrinogen level of light smokers to that of controls was found highly significant (p value - 0.002) while comparison of mean plasma fibrinogen level of both moderate and heavy smokers to the mean fibrinogen level of controls also showed highly significant (p value-0.001)difference (table-2).

Table No.1: Mean fibrinogen level in different smoking groups and controls

Smoking status	Number of subjects	Mean (mg/dl)	±SD
Light Smokers	94	253.87	45.68
Moderate Smokers	71	316.71	57.51
Heavy Smokers	85	407.45	80.12
Controls	250	233.67	55.57
Total	500	253.567	98.917

±SD indicates standard deviation

Table No. 2:Comparison of Mean Plasma Fibrinogen Level (mg/dl) of Smokers with Controls

Smoking status	Smokers		Controls		*t*-ratio	P-value
	Mean	±SD	Mean	±SD		
Light	253.87 (94)	45.68	233.67 (250)	55.57	-3.147 *	<0.002
Moderate	316.71 (71)	57.51	233.67 (250)	55.57	-11.026*	<0.001
Heavy	407.45 (85)	80.12	233.67 (250)	55.57	-2.208*	<0.001

The values in brackets are the number of subjects in a group, ±SD represents standard deviation, * significant at 5% level of significance.

Table No.3: Comparison of Mean Plasma Fibrinogen Level Among different groups of smokers

Group	Mean	SD	Group	Mean	±SD	t-ratio	P-value
1*	253.87 (94)	45.68	2*	316.71 (71)	57.51	-7.82**	<0.001
1*	253.87 (94)	45.68	3*	407.45 (85)	80.12	-15.94**	<0.001
2*	316.71 (71)	57.51	3*	407.45 (85)	80.12	-7.97**	<0.001

***- 1, 2and 3 denotes the smoking status (light, moderate and heavy smoker, respectively. ( )-Values in bracket show the number of subjects in the corresponding group. ±SD- stands for standard deviation. ** - indicates significance at 5% level of probability.**

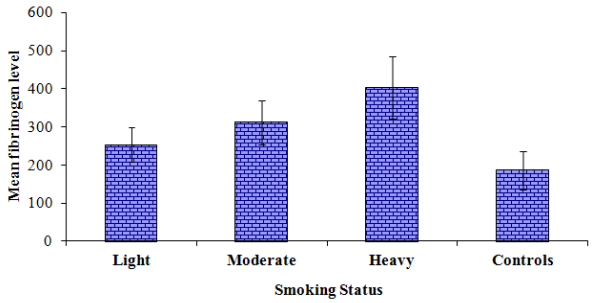

Figure No.1: Average fibrinogen level in different smoking groups and controls

DISCUSSION

During the last decade great progress has been made in the pathophysiology, diagnosis and treatment of the cardiovascular disease. Currently, it is well known that atherosclerotic disease is treatable, that plaque progression can be stabilized and that risk factor identification and modification can influence the clinical expression of cardiovascular disease[15]. The present study was therefore aimed to identify and confirm one of the most important risk factor i.e. high fibrinogen levels in smokers of our population. Fibrinogen has been identified as a major and independent cardiovascular risk factor through several epidemiological studies. At present knowledge about the determinants of plasma level of fibrinogen in health and disease is incomplete.

The present study, like all previous studies has observed a dose dependent association between cigarette smoking and plasma fibrinogen. This association may due to smoking-induced disturbance of vascular endothelium or pulmonary epithelium, inducing release of cytokines such as interleukin-6 which when reaches liver, increases hepatic synthesis of fibrinogen.

When compared the results of this study were found highly consistent with studies conducted earlier. In Framingham study, almost 50% of cardiovascular risk attributable to smoking was found to be mediated through an increase in fibrinogen level requiring the need for such studies to identify and validate the role of high fibrinogen level in smokers of general population[16].

In numerous cross sectional, case control and cohort studies, fibrinogen level has been found to be consistently elevated among smokers compared to non-smoker control[17].

Bruner et al 1993 reported that fibrinogen level is higher among smokers than non-smokers[18].A study done in university of Mauritius in 1999 showed that fibrinogen level was significantly higher in the smokers than in the non-smokers[19].A study done in clinical biochemistry department Copenhagen city showed that among general healthy population, smokers had higher fibrinogen level than non-smokers[20].

In study done in Epidemiology Unit of University of Muenster Germany, fibrinogen levels were found to be higher in smokers as compared to non-smokers[21].

Several prospective studies conducted in recent years confirmed that fibrinogen levels are elevated in smokers.

A study done in "Clinical Epidemiology Unit "Royal Free Hospital London", on smokers also showed that smokers had higher plasma fibrinogen levels as compared to non-smokers[22].Our study shows the difference between mean fibrinogen of smokers and control to be highly significant.

A study conducted in physiology department of Benin University, Nigeria to assess association of fibrinogen level to various risk factors revealed that plasma fibrinogen concentration was significantly higher in smokers than non smoker controls[23]. The results of our study are consistent with all these studies.

A study done in Singapore to assess the cause of increased cardiovascular disease risk in smokers showed higher mean plasma fibrinogen levels in smokers as compared to non-smokers i.e. 2.75g/l in smokers versus 2.6g/l in non-smokers[24] which is consistent with our study and shows elevated level of fibrinogen in all categories of smokers as compared to control.

A study was done in Colombo to assess lipid profile and fibrinogen level in smokers as compared to non-smokers. The results of this study were quite interesting. It showed that total serum cholesterol was high in smokers as compared to non-smokers but there was no association with the degree of smoking. In contrast smokers had significantly elevated fibrinogen levels, showing that smoking may increase the risk of cardiovascular disease by elevating plasma fibrinogen levels and not the cholesterol. Though our study is deficient as compared to this previous study as our

study lacks the assessment of cholesterol level but still the significantly elevated levels of fibrinogen in smoker as compared to non-smokers show resemblance to the study[25].

In a cross sectional study of US general population, self reported current cigarette smoking was associated with elevated levels of fibrinogen as compared to never smokers. There was also positive and significant dose response relationship between numbers of cigarettes smoked per day and elevated levels of fibrinogen[26].

Similarly in another previous study, a dose-effect relationship was reported between the number of cigarettes smoked per day and plasma fibrinogen concentration along with the main conclusion that fibrinogen levels are significantly higher among smokers[27].Our study is exactly consistent with these previous studies regarding increase in plasma fibrinogen level with increase in smoking intensity.

Another previous study conducted on smokers fibrinogen level, in which smokers were divided into light and heavier smokers, fibrinogen levels were found higher in heavier smokers as compared to lighter smokers which is consistent with findings of present study[28].

Results of our study were found consistent with those in previous studies; showing that fibrinogen levels are consistently higher in all three categories of smokers (i.e. light, moderate and heavy smokers) as compared to non-smokers . Also in our study, when light smokers were compared to moderate and heavy smokers, the difference found in mean plasma fibrinogen level was highly significant in both. Similarly comparison of moderate smokers to heavy smokers with regard to the mean fibrinogen level also showed highly significant difference, which is consistent with previous studies[29] i.e. showing positive relation of fibrinogen level to the increasing number of cigarettes smoked.

CONCLUSION

On the basis of present study, it is concluded that plasma fibrinogen level is high in smokers as compared to non smokers among general healthy population. Also it was seen that among the smokers the concentration of fibrinogen increases as the intensity of smoking increases thus reflecting the high risk of cardiovascular disease in heavy smokers as compared to moderate smokers and more risk in moderate as compared to light smokers.

The present study concludes that high fibrinogen level in smokers might be one of the most important variables responsible for the high risk of cardiovascular disease in smokers, as shown by the previous studies as well.

In view of the above conclusions, we thus recommend the following suggestions.

1. Plasma fibrinogen level measurement must be included in cardiovascular risk profile.
2. Emphasis should be put on the need for ban on smoking at public places.
3. Awareness should be raised in general population regarding hazards of passive as well as active smoking through media and aggressive anti smoking campaigns..

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