Role of serum fibrinogen in patients of ischemic cerebrovascular disease

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ABSTRACT

Fibrinogen is an independent risk factor for coronary events in population-based studies and in patients with coronary heart disease, but there is an uncertainty about its prediction for stroke, particularly in secondary prevention. In view of this uncertainty, study was conducted to establish the role of serum fibrinogen in ischemic stroke. 56 patients with acute ischemic stroke of less than 7 days duration were recruited for the study. 42 age and sex matched candidates served as control. Baseline characteristics and blood pressure were recorded at admission to hospital. Computer tomography head was done in all patients as per protocol. Sampling took place in the early morning (7-9 AM) using all necessary precaution and serum fibrinogen was measured by method of Clauss. Statiscal analysis was performed using student t test and fisher exact test. In present study, mean plasma fibrinogen in patients group was 326.45 mg/dl, which was significantly higher than control group (202.23 mg/dl) ($p< 0.001$). Mean plasma fibrinogen level in lacunar infarct and non-lacunar infarct did not differ significantly (307.47 mg/dl Vs. 333.19 mg/dl). Smoking was found to be a significant predictor of fibrinogen with 36.7% predictability whereas other parameters (risk factors for ischemic stroke) had little or no predictable value regarding serum fibrinogen. After adjustment for other possible ischemic stroke risk factors; plasma fibrinogen levels was found to be still significantly high in patients as compared to controls ($p<0.001$). Mean plasma fibrinogen level between patients who survived and who expired does not differ significantly. Present study concluded that fibrinogen is a powerful predictor of ischemic stroke though it does not predict the type and prognosis of stroke.

Keywords: Fibrinogen - risk factors - stroke prevention –thrombosis –lacunar infarct.

INTRODUCTION

Over the years several modifiable cardiovascular risk factors have been identified that are associated with an increased risk of coronary heart disease or cerebrovascular disease.[1] This has offered ways for treatment and prevention. Several emerging risk factors for CVD are under investigation. Recently interest has focused on novel markers such as lipoprotein (a), apolipoprotein (apo) A-1, apoB-100, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and homocysteine, to evaluate their additive value to traditional risk. Several established and emerging novel biomarkers for vascular risk meet these criteria, although few are ready for clinical practice. With the exception of high-sensitivity C-reactive protein (hsCRP), none has demonstrated additive value over and above Framingham risk scoring, and few are supported by commercial assays that achieve appropriate levels of standardization and accuracy for clinical use.[2]

The current approach to vascular disease risk estimation involves assessment of factors such as age, gender, blood pressure, cigarette smoking, cholesterol, HDL cholesterol, and presence of diabetes. Drawing from the experience of the Framingham Heart Study and similar studies, it is possible to estimate the risk for a future vascular event. Risk equations have been developed along these lines for CHD,[3] intermittent claudication,[4] and stroke.[5] The use of risk scores can provide a more reliable risk estimate, leading to more aggressive care and potential reduction in vascular disease events.[6]

Fibrinogen is involved in primary hemostasis, platelet aggregation, and leukocyte-endothelial cell interactions and is the major determinant of whole blood and plasma viscosity. Elevated levels are associated with atherosclerosis and have been reported in patients with coronary heart disease, peripheral vascular disease, and carotid stenosis. http://stroke.ahajournals.org/cgi/content/full/35/10/2300 - R2-404673http://stroke.ahajournals.org/cgi/content/full/35/10/2300 - R4-404673http://stroke.ahajournals.org/cgi/content/full/35/10/2300 - R5-404673Fibrinogen levels also predict vascular events in many studieas but there is uncertainty about prediction of stroke. Four small cohort studies in patients with transient ischemic attack (TIA) or ischemic stroke have been reported, but all confined analysis to the risk of all cardiovascular events combined.

A number of studies show elevated fibrinogen to be a major risk factor for coronary heart disease (heart attacks) and cerebrovascular disease (strokes), which together account for about 60.0% of deaths in the elderly. In fact, fibrinogen may possibly be the major risk factor, exceeding the “contributions” of homocysteine, cholesterol and other lipids in the pathogenesis of these diseases. Elevated fibrinogen levels have also been associated with a number of other diseases, including cancer, diabetes and hypertension. We in this study did a randomize controlled trial to know the impact of serum fibrinogen level on ischemic

cerebrovascular disease. http://stroke.ahajournals.org/cgi/content/full/35/10/2300 - R24-404673http://stroke.ahajournals.org/cgi/content/full/35/10/2300 - R25-404673

MATERIALS AND METHODS

The present study was conducted in department of Medicine in collaboration with department of Biochemistry in J.N. Medical College Hospital, Aligarh Muslim University, Aligarh. The diagnosis of stroke was confirmed by complete neurological history, examination and neuroimaging. Stroke, defined as rapidly developing clinical sign of focal (at times global) disturbance of brain function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin (Hatono S. *et al*. 1976).

We identified 56 patients with acute ischemic stroke of less than 7 days duration. 42 age and sex matched control were also recruited. Subjects with following features were excluded from study by history, examination and laboratory evidence.

- Pregnancy - Oral contraceptive user - Alcoholic - Diabetes mellitus

Baseline characteristics and blood pressure were recorded at admission to hospital. Routine tests such as complete blood count, blood chemistry (blood urea, serum creatinine, liver function test), blood sugar, fasting lipid profile. Data on baseline computed tomography (CT) brain imaging were collected routinely. We therefore defined presentation with a lacunar stroke or non lacunar stroke on the basis of clinical assessment and lacunar lesion on CT scan of brain.

Number of subjects with systemic hypertension in cases and controls were 17 (40.5%) and 7 (16.7%) respectively. Hypertension was documented by medical record or a subject who had been on anti-hypertensive drug before recruitment.

Number of subjects with current smoker in cases and controls were 18 (42.9%) and 12 (28.6%) respectively. Current smoking was defined as smoking ≥ 1 cigarette a day for ≥ 2 months.

SAMPLINGS

Sampling took place in the early morning (7-9 AM) after over night fast to eliminate circadian rhythm as a confounding element. Coffee drinking and smoking was not allowed on the morning of sampling. Venous blood sample were drown from the anticubital vein without stasis. Plasma fibrinogen was estimated by clotting method of CLAUSS.

STATISTICS

Means and proportions were computed for background variables. Comparisons between patients and controls were made with Students t test for continuous variables. The X^2 or Fishers exact test was used for proportion. Cox proportional hazards models, were used to obtain hazard ratios (HRs; 95.0% CI) for fibrinogen values above versus below the median. HRs were also adjusted for all measured potentially confounding vascular risk factors. There was considerable intraindividual variation in fibrinogen measurements, so correction of risk relations for the effects of regression dilution was necessary. Multiple logistic regression was used to analyse the association between risk of stroke and independent variables, and a value of $P < 0.05$ was considered significant.

RESULTS

We identified 56 patients with acute ischemic stroke of less than 7 days duration. Nine patients with cardiac or cardioembolic cause of ischemic stroke were excluded from further analysis.5 patients were excluded on the basis of raised erythrocyte sedimentation rate (15 mm/hr). Final analysis was done in 42 patients. 42 age and sex matched control were recruited.

Table-1 and fig. 1. Summarizes the baseline clinical charectristics between cases and controls. Fig. 2. summerizes the age and sex distribution of cases and controls

Cases were divided into two groups lacunar infarct and non-lacunar infarct. Non-lacunar infarct group (except cardio embolic stroke as excluded) comprises of other main diagnostic categories as defined by modified TOAST classification as atherothrombotic and undetermined causes.

Adjusted value for fibrinogen (adjusted for age, sex, body mass index, current smoking, hypertension, total cholesterol, LDL-C, HDL-C, triglyceride and blood sugar) still significantly differ between cases and controls ($p<.001$). Before final analysis we excluded 9 patients (21.4%) as a cardiac or cardio embolic cause of ischemic stroke. Fibrinogen is also an acute phase reactant protein. We therefore prospectively excluded patients with any evidence of inflammation or infection as determined by the elevated erythrocyte

sedimentation rate. Fives patients (11.9%) with erythrocyte sedimentation rate > 15 mm/hr were excluded from further analysis.

In the present study mean plasma fibrinogen in patients were 326.45 mg/dl significantly higher than control population (202.23 mg/dl) ($p < 0.001$). Cases were divided into two groups lacunar infarct and non- lacunar infarct. Numbers of patients with lacunar infarct was 11 (26.2%) and non-lacunar infarcts was 31 (73.8%). Mean fibrinogen level in lacunar infarct group (307.47 mg/dl) was low as compared to non-lacunar infarct group (333.19 mg/dl) but it was not significant ($p=0.106$). Difference in mean plasma fibrinogen level between lacunar infarct and non-lacunar infarct does not differ significantly ($p=0.106$). In present study mean plasma fibrinogen level between patients who survived and who expired does not differ significantly (324.51 mg/dl vs. 336.15 mg/dl {$p=0.541$}) suggesting that high fibrinogen levels is a risk factor for ischemic stroke but it does not predict poor prognostic outcome. Stepwise multiple regression analysis was conducted to find out the significant predictors of Fibrinogen. Smoking entered as a significant predictor of fibrinogen with 36.7% predictability. As compared with other established risk factors for ischemic stroke, current smoking was found to be significant predictor of plasma fibrinogen level in cases and controls with 39.5% and 36.7% predictability respectively. While age, sex, body mass index, hypertension, total cholesterol, LDL-C, HDL-C, triglyceride were weakly related but not a significant predictor of plasma fibrinogen After adjustment for other possible ischemic stroke risk factors; plasma fibrinogen levels still significantly high in patients as compared to controls ($p<0.001$).

DISCUSSION

The present study was conducted in department of medicine J.N. Medical College Hospital Aligarh Muslim University Aligarh. The patients with feature of cerebrovascular accident of less than seven days duration, proved to have brain infarct in NCCT- head were included in the study. We identified 56 patients with acute ischemic stroke of less than 7 days duration. 42 age and sex matched control were recruited. In our study before final analysis we excluded 9 patients (21.4%) as a cardiac or cardio embolic cause of ischemic stroke. Out of 9 patients; 4 patients had patent foramen ovale, 2 had atrial septal defect, 2 had mitral stenosis and 1 patient had left ventricle intramural thrombus. Similarly in study of Wessendorf, Thilmann, *et al* 2000, number of patients with cardiac or cardio embolic cause of ischemic stroke was 21 (18.5%).[7] In the present study number of patients on oral anticoagulant and low dose aspirin were 4 and 38 (9.52% and 90.48%) respectively.[8] This study suggest that fibrinogen is a strong risk factor for ischemic stroke and indirectly suggest that person with raised fibrinogen were more prone to ischemic stroke. This was supported by study of Tanne D, Benderly M. *et al*. 2001,[9] mean baseline fibrinogen levels were significantly higher in patients subsequently having a cerebrovascular events than in patients who did not. Risk of ischemic stroke increased from 3.3% in the lowest tertile (baseline fibrinogen <314mg/dl) to 7.0% in the middle tertile (fibrinogen 314-373mg/dl) to 10.0% in the upper tertile (fibrinogen >373mg/dl $P < 0.001$).

Similarly in study of Rothwell PM, Howard SC *et al*. 2004, data from 3 prospective studies of patients with recent transient ischemic attack (TIA) or minor ischemic stroke: the United Kingdom TIA Aspirin (UK-TIA) trial, the Dutch TIA trial, and the Oxford TIA Study, In the UK-TIA trial, mean (SD) fibrinogen was higher in patients with vascular events during follow-up: ischemic stroke, $P=0.005$; coronary event, $P<0.001$; all ischemic vascular events, $P<0.001$. Similar differences were seen in the Oxford cohort: ischemic stroke $P=0.22$, coronary event, $P=0.43$; and all ischemic vascular events, $P=0.02$.[10-12] The risk of recurrent ischemic stroke, acute coronary events, and all ischemic vascular events combined increase linearly with fibrinogen levels.[13]

In our study mean plasma fibrinogen level between patients who survived and who expired does not differ significantly. ($p=0.541$) suggest that high fibrinogen levels is a risk factor for ischemic stroke but it does not predict poor prognostic outcome.[9] In present study high fibrinogen level is found to be a risk factor for lacunar stroke though it does not differ significantly as compared to non lacunar strokes. Our finding was similar to UK-TIA trial. There was no difference between the mean fibrinogen level in patients presenting with a lacunar syndrome versus a non-lacunar syndrome in the UK-TIA trial (3.90[1.10] versus 3.89[1.12], $P=0.89$).[10]

As compared with other established risk factors for ischemic stroke, (age, sex, body mass index, hypertension, current smoking, total cholesterol, LDL-C, HDL-C, and triglyceride) current smoking was found to be significant predictor of plasma fibrinogen level in cases and controls with 39.5% and 36.7% predictability respectively. While age, sex, body mass index, hypertension, total cholesterol, LDL-C, HDL-C, triglyceride were weakly related but not a significant predictor of plasma fibrinogen as shown in linear regression graph in Fig.3,4,5 and 6.

In our study fibrinogen level after adjustment with other risk factor was still significant for ischemic stroke patients. It suggests that there was intra-individual variability of fibrinogen level that was genitically determined, this was supported by study of De Bacquer D. De Backer *et al* 1997.[14]

Several drugs are known to reduce fibrinogen levels, including bezafibrate, ß-blockers, pentoxifylline, and ticlopidine.[15] Moreover, lifestyle modification, including smoking cessation and increased exercise, can reduce fibrinogen levels.[15] Nutritional supplements can reduce fibrinogen levels and the presumably the inherent risk of hyper-fibrinogenemia-related diseases. Ramirez-Bosca's studies in Spain have demonstrated that certain antioxidants are capable of dramatically reducing blood levels of lipid peroxides and oxidized lipoproteins after only 15 days with no adverse effects noted by any of the subjects or adverse changes in any other blood chemistries.

Present study concluded that serum fibrinogen is a powerful predictor of stroke but it does not predict the type of ischemic stroke or the prognosis of the patient with ischemic stroke.

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Table-1: Summarized baseline clinical charectristics between cases and controls.

	Cases		Controls		
	Mean	**S. D.**	**Mean**	**S. D.**	**P**
Age (Years)	58.81	10.20	59.36	10.33	0.808
Male (n&%)	24	57.14	22	52.39	0.661
Hypertension(n & %)	17	40.48	7	16.67	0.016
Current smoking (n& %)	18	42.86	12	28.57	0.172
Body mass index (kg/m^2)	24.75	3.41	23.36	2.43	0.033
Total cholesterol (mg/dl)	227.26	71.30	179.48	52.67	0.001
LDL-Cholesterol (mg/dl)	151.93	67.14	122.05	46.45	0.020
HDL- Cholesterol (mg/dl)	41.24	7.94	48.00	10.06	0.001
Triglyceride (mg/dl)	205.95	61.99	156.86	48.68	0.000
Fibrinogen (mg/dl)	**326.45**	**45.25**	**202.23**	**14.41**	**0.000**

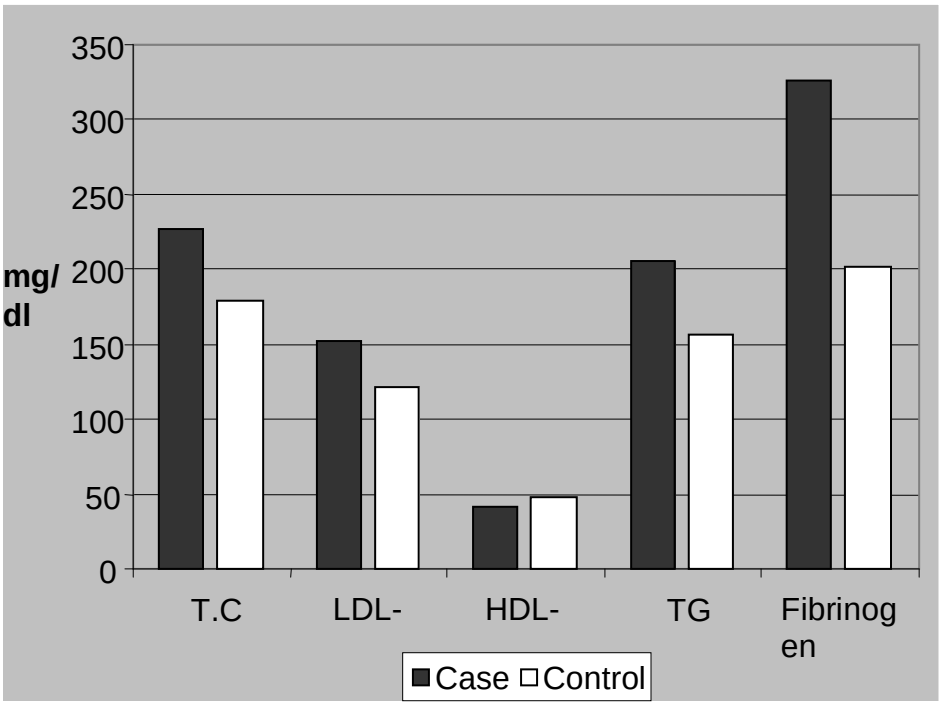

Fig. 1. Baseline characteristics

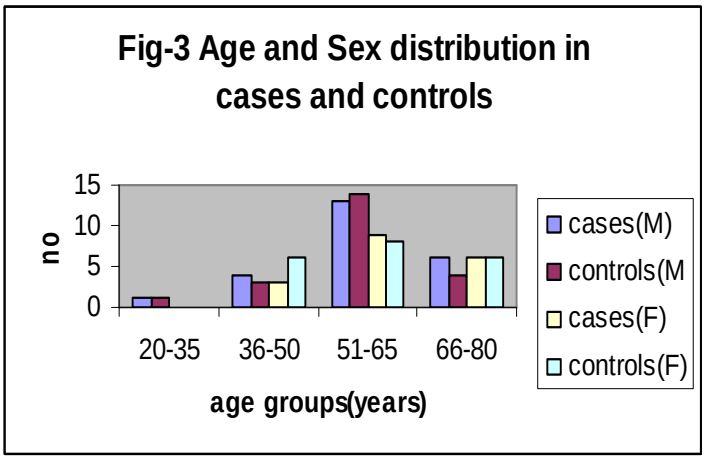

Fig. 2. Age and sex distribution in cases and controls

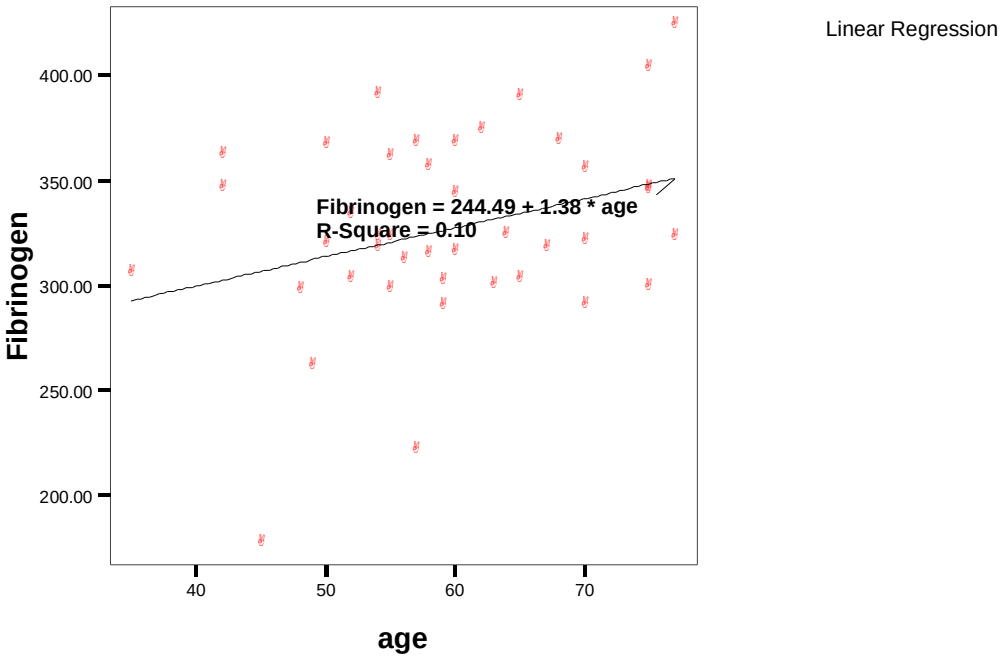

Fig. 3. Showing Linear Regression between age (y) and Fibrinogen (mg/dl)

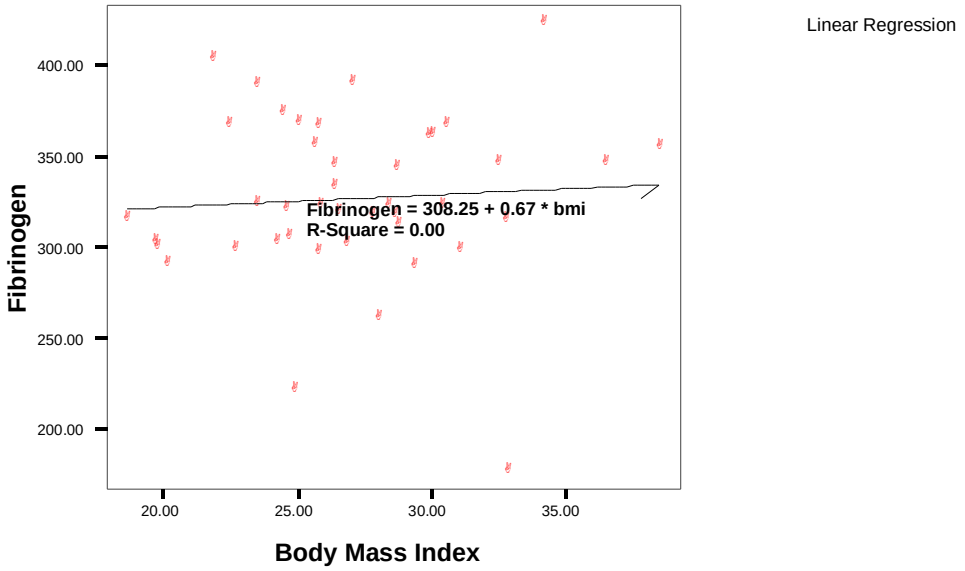

Fig. 4. Showing Linear Regression between Body Mass Index (kg/m^2) and Fibrinogen (mg/dl)

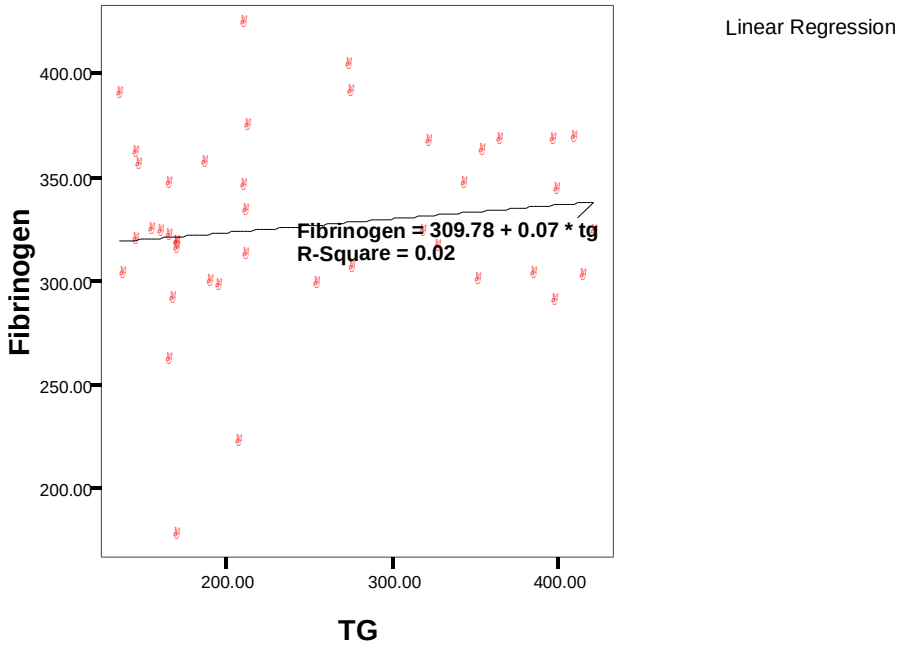

Fig. 5. Showing Linear Regression between Triglycerides (mg/dl) and Fibrinogen (mg/dl)

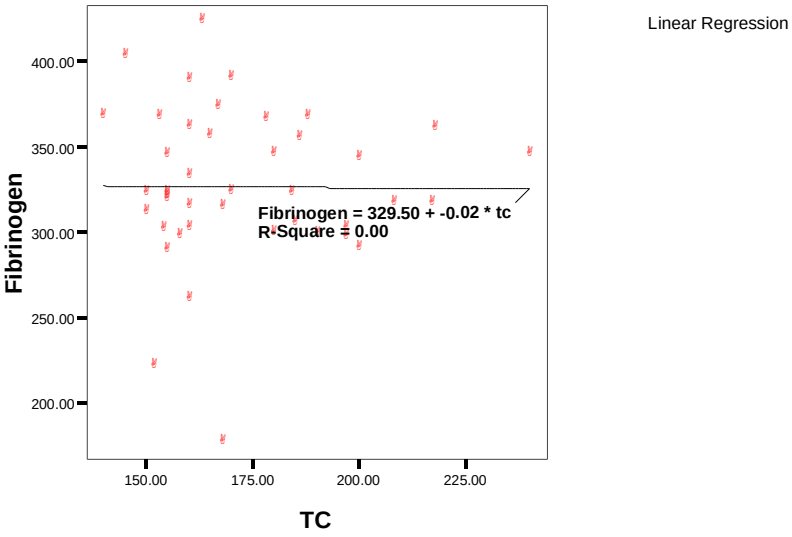

Fig. 6. Showing Linear Regression between Total Cholesterol (mg/dl) and Fibrinogen (mg/dl)