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Fibrinogen as a prognostic risk factor for coronary artery disease

Epidemiological studies have shown that high blood concentration of fibrinogen is associated with increased risk of cardiovascular diseases (1, 9). The electrocardiographic exercise treadmill test (EXT) is a noninvasive study used for the assessment of risk of future cardiovascular events in patients with coronary artery disease. The Duke treadmill score (DTS) is a composite index designed to provide survival estimates based on EXT results such as exercise duration, ST-segment depression, presence and severity of chest pain.

The aim of this study was to asses the association between fibrinogen level and severity of coronary artery disease based on DTS and to identify factors that may affect fibrinogen level.

MATERIAL AND METHODS

This study comprised 105 men at the age from 50 to 77 years. Among them 32 had prior myocardial infarction and 32 were diagnosed with hypertension. Patients were excluded if they had any of the following: a history of diabetes, heart failure, tumors, autoimmune and inflammatory diseases, renal and hepatic disorders, steroid treatment, endocrine pathology, and drug or alcohol abuse. Obesity was assessed by calculating: body mass index (BMI) and waist-to-hip ratio (WHI). The lifetime smoking dose (packyears) was calculated by the number of packs (20 cigarettes per pack) smoked daily, multiplied by the number of years of continuous smoking. Educational status was coded as follows: 1 – primary education, 2 – secondary education, 3 – higher education.

Symptom limited EXTs according to Cornell protocol were performed early in the morning on computerized treadmill MAX-1 from Marquette Electronics. The DTS for each patient was calculated according to the formula: DTS = exercise time - (5*ST deviation in mm) - (4*exercise angina coded as 0=none, 1=nonlimiting, and 2=exercise limiting). The score typically ranges from –25 to +15. These correspond to low risk (with a score of ? +5), moderate risk (with scores ranging from –10 to +4) and high risk (with a score of Ł -11) categories (11, 12). Fasting blood samples were taken at 8 in the morning. Leukocyte counts were assessed by hemoanalyzer Cell Dyn 1600 (Abbott). Total cholesterol, triglicerides (TG), high density lipoprotein cholesterol (HDL-cholesterol) and blood glucose were measured using commercially available kit from P.Z. Cormay (Lublin, Poland). Low density lipoprotein cholesterol (LDL-cholesterol) was calculated according to Friedewald formula (6). Fibrinogen concentration was measured using Multifibren U (Dade Behring GmbH, Marburg, Germany). Fasting plasma insulin level was determined by RIA kit (Medgenix, Fleures, Belgium). Insulin resistance (HOMA-IR) was calculated based on fasting plasma insulin and glucose levels according to HOMA model (13).

The study protocol was approved by the University Ethics Committee and written informed consent was obtained from each person before enrollment.

The data were presented as Mean ± SD for all continuous variables. The differences between subgroups were assessed by Student's unpaired *t* test. Associations among variables were evaluated by Pearson's rank correlation test. Trigliceride measurements were logarithmically transformed to fit a linear model. To study the independent contribution of risk factors in the determination of the fibrinogen level, regression analysis was performed. A p value < 0.05 was considered significant in all analyses.

RESULTS

Based on the cutpoints of DTS score the study population was divided into three groups: low risk (n=25), moderate risk (n=65) and high risk group (n=15). The mean values of fibrinogen level in the above risk groups are presented in figure 1. The clear trend of higher fibrinogen levels in groups with higher cardiovascular risk was observed. Patients in low risk group had the lowest level of fibrinogen (328.2±76.1 mg/dl), while those in moderate risk group had intermittent level of fibrinogen (346.1±90.0 mg/dl) and finally patients in high risk group had the highest level of fibrinogen (381.7±80.1 mg/dl). A statistically significant difference was observed between low risk and high risk group (p = 0.042).

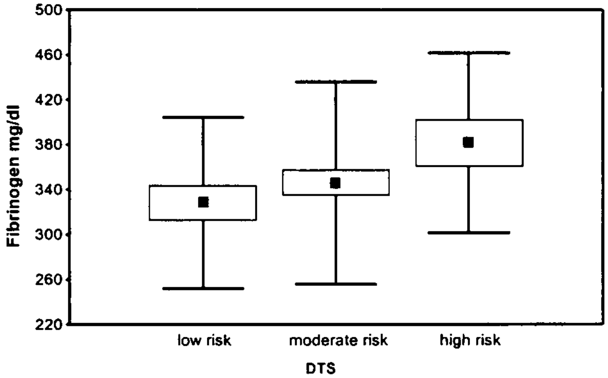

Fig. 1. Fibrinogen levels in subgroups of patients with low, moderate and high cardiovascular risk according to Duke treadmill score

Table 1 presents correlation coefficients between fibrinogen level and selected variables associated with cardiovascular risk. The tendency to lower fibrinogen concentrations was observed in males with higher education level (r=-0.294; p=0.002) and lower HDL cholesterol (r=-0.255; p=0.008). On the other hand, higher fibrinogen concentrations were associated with central obesity, measured using WHR (r=0.322; p=0.001) and higher insulin resistance, according to HOMA model (r=0.222; p=0.022). There was also strong positive correlation between fibrinogen level and white blood cell count (r=0.427; p<0.001). No significant associations were found between fibrinogen and age, tobacco smoking, BMI, insulin concentrations, total cholesterol, LDL-cholesterol and triglyceride levels. Multiple regression analysis revealed that only white blood cell count (β=0.373; p<0.001), insulin resistance (β=0.259; p=0.016), and HDL-cholesterol (β=-0.221; p=0.033) were independently associated with fibrinogen level.

Table 1. Correlation coefficients (r Pearson's) between plasma fibrinogen concentration and other risk factors

Variables	Fibrinogen	
	r	p
Age	-0.073	0.457
Smoking	0.144	0.140
Educational status	-0.294	0.002
BMI	0.120	0.219
WHR	0.322	0.001
Insulin	0.178	0.068
HOMA-IR	0.222	0.022
Leukocytes	0.427	<0.001
Cholesterol	0.020	0.840
HDL-cholesterol	-0.255	0.008
LDL-cholesterol	0.112	0.254
Triglicerides	0.073	0.455

Table 2. Results of multiple regression analysis of fibrinogen and other risk factors

	β	SE	p
Leukocytes	0.373	0.107	< 0.001
HOMA-IR	0.259	0.104	0.016
HDL-cholesterol	-0.221	0.102	0.033

Variables: age, educational status, smoking, HOMA-IR, WHR, leukocytes, HDL-cholesterol, LDL-cholesterol

The non-significant variables ($p>0.05$) are not included in the table

DISCUSSION

Fibrinogen is a liver protein that consists of three pairs of polypeptide chains combined by disulfide bonds. As a fibrin precursor it is the main factor of clotting cascade. It binds to GP IIb/IIIa receptor on the surface of platelets and promotes their aggregation, which subsequently may lead to coronary artery occlusion. In genetic studies baseline levels of fibrinogen shows a clear heritability (16). Epidemiological studies point to its role as an important risk factor for coronary artery disease (1, 9). Our study indicates that fibrinogen concentration may also be a prognostic factor. Its highest levels were observed in the group of men with high risk of cardiovascular incidents, assessed by DTS. The latter parameter is considered as a valuable index of the risk of future cardiac events (15). Our data are indirectly confirmed by other studies. Fibrinogen level is not only elevated in patients with coronary artery disease but it correlates with the exacerbation of the disease, i.e. stable vs. unstable angina (7). It also appears to be independent and one of the strongest risk factors for sudden cardiac death in patients with coronary artery disease (5). Fibrinogen concentrations were associated with education of males in our study group, with the tendency towards lower fibrinogen levels in better educated men. This could be related to a healthier life style of better educated males i.e. different diet, physical activity, and history of tobacco smoking. However, in our study we did not observe any significant association between fibrinogen and tobacco smoking, but such relations were found in much bigger observational studies (10, 14).

Many researchers point to the association between fibrinogen and obesity (10, 14). This phenomenon showed up in our study as a correlation between fibrinogen and WHR, which is a better indicator of central obesity than BMI. Central obesity is characterized by accumulation of visceral fat in abdominal cavity, which consequently leads to insulin resistance and hyperinsulinemia. This was confirmed by our finding of independent association between fibrinogen level and insulin resistance according to HOMA model. A coexistence of high fibrinogen level with insulin resistance may enhance negative consequences of both and lead to atherosclerosis progression (4).

We also observed a positive correlation between fibrinogen and white blood cell count independent of other variables. Fibrinogen, considered as an acute phase protein, is released from liver in response to inflammatory stimuli, just like leukocytes released from bone marrow. Keeping in mind that fibrinogen may serve as a ligand for receptors on the surface of platelets and leukocytes (β2 and β3-integrins), it seems reasonable to believe that fibrinogen may play an important role in platelet-leukocyte interaction (2). Interestingly, adhesion of platelets and leukocytes is markedly increased in patients with unstable angina (8). These observations emphasize the clinical significance of positive correlation between fibrinogen and white blood cell count found in our study.

In accordance with the results of other studies we observed negative correlation between fibrinogen and HDL-cholesterol in the group of aging males. This association was independent of other analyzed factors and it seems to be gender specific. In the study on female-male population, multiple regression analysis revealed fibrinogen-HDL association only in male subjects (3).

CONCLUSIONS

1. Fibrinogen is a factor associated with more pronounced coronary artery disease and increased risk of future coronary events in aging males.

2. Elevated concentration of fibrinogen correlates with higher white blood cell count, increased insulin resistance and lower levels of HDL-cholesterol in aging males.

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SUMMARY

This study evaluated the association between blood fibrinogen level and coronary risk, based on Duke treadmill score, in 105 males at the age from 50 to 77 years. Fibrinogen levels were significantly higher in patients with high coronary risk than in those with low risk. Fibrinogen concentrations correlated positively with waist-to-hip ratio, insulin resistance, and white blood cell count. Negative correlations were found between fibrinogen and level of patients' education as well as between fibrinogen and HDL-cholesterol concentrations. Multiple regression analysis revealed that only white blood cell count, insulin resistance, and HDL-cholesterol were independently associated with fibrinogen level.

Prognostyczna wartość fibrynogenu w ocenie ryzyka w chorobie wieńcowej

U 105 mężczyzn w wieku 50–77 lat badano zależność pomiędzy stężeniem fibrynogenu a poziomem ryzyka wieńcowego ocenianego na podstawie wskaźnika Duke (DTS). Stwierdzono, że stężenie fibrynogenu było istotnie wyższe w grupie wysokiego ryzyka w porównaniu z grupą niskiego ryzyka DTS. Stwierdzono ponadto dodatnią korelację pomiędzy stężeniem fibrynogenu a wskaźnikiem talia biodro, insulinoopornością, liczbą leukocytów oraz ujemną pomiędzy stężeniem fibrynogenu a stanem wykształcenia i cholesterolem HDL. W analizie regresji wielokrotnej utrzymała się zależność – pomiędzy stężeniem fibrynogenu, HOMA-IR i cholesterolem HDL.