ALTERATIONS IN FIBRIN CLOT RESISTANCE FOR PATIENTS WITH DYSLIPOPROTEINEMIA

H. Matcas [1], *Veronica Sfredel* [2], *Maria Mota* [3], *Anca Rizea* [4], *Dumitru Lacatîş* [5], *Simona Gusti* [2]

[1] Emergency University Hospital of Bucharest, Bucharest, Romania
[2] Department of Physiology and Physiopathology, University of Medicine and Pharmacy of Craiova, Romania
[3] Department of Diabetes and Nutrition Diseases, University of Medicine and Pharmacy of Craiova, Romania
[4] Student, University of Medicine and Pharmacy of Craiova, Romania
[5] Endocrinologie, Diabetologie et Maladies de metabolisme, Geneve, *Suisse*

Abstract

Background. *Hyperlipoproteinemia is associated with an increased incidence of thrombotic complications due to the high thrombotic risk, for example as a result of continuous platelet activation or increased thrombin production.* ***Purpose***. *In this study, we aim to emphasize hemostatic anomalies in patients with hyperlipoproteinemia. Therefore, we have chosen fibrinresistometry as the main method for evaluating hemostatic anomalies, since it measures the breakage resistance of the fibrin clot (BRFC). The major objective of our research is to study the possible correlations between the breakage resistence of the fibrin clot and an increase in plasma lipids.* ***Material and methods***. *We conducted a prospective study, investigating hemostatic anomalies in hyperlipoproteinemic patients using fibrinresistometry, and, concurrently, using classic methods of determining certain parameters of hemostasis, at a 6 months interval between the first and the second evaluation.* ***Results***. *In patients with hyperlipoproteinemia (HLP) the BRFC had a mean value of 296.76±23.37 FU for the initial evaluation versus 248.64±25.71 FU for the control group. By comparison with the control group, we found a significant increase ($p<0.05$) in plasma fibrinogen, platelet count and mean platelet volume. The increase of BRFC is highly associated with an increase in triglycerides ($r=0.585$) and cholesterol ($r=0.574$), moderately associated with LDL ($r=0.551$), and show a weak inverse correlation with HDL values ($r= - 0.246$). A high waist circumference is highly correlated to fibrinresistometric findings ($r=0.576$), and to high fibrinogen values ($r=0.426$). In patients of the subgroup with hypolipemiant treatment, a decrease of 2.85% in BRFC was found, not statistically significant. Plasma fibrinogen had a mean value of 391 ±28.87 mg/dl and after treatment it decreased significantly ($p < 0.05$) to 375.91±21.17 mg/dl.* ***Conclusions***. *Hyperlipoproteinemia produces the alteration of the quality of the fibrin network, which becomes more adherent to the vascular endothelium. The increased breakage resistance of the fibrin clot in the studied patients reveals a thrombogenic potential, thus making BRFC an important marker for this state.*

keywords: *dyslipoproteinemia, fibrinresistometry, haemostasis, thrombogenesis.*

Background and Aims

The causal relationship between dyslipoproteinemia-atherogenesis-thrombogenesis is well documented at the current level of medical knowledge. Numerous experimental studies on animal or human models, as well as a high number of clinical, observational and prospective studies suggest a strong link between hyperlipoproteinemia-coagulation-fibrinolysis-thrombocyte and atherosclerosis pathogeny, along with its vascular complications [1,2,3]. While dyslipidemia is usually associated with atherosclerosis (atherogenesis), thrombogenesis is intimately linked to atherogenesis. Hyperlipoproteinemia is associated with an increased incidence of thrombotic complications due to the high thrombotic risk, for example as a result of continuous platelet activation or increased thrombin production [4].

Classic risk factors, such as hypercholesterolemia, hypertension, smoking and body mass index are weak predictors of coronary and cerebral pathology in cohort studies, while thrombotic factors have proven to be strong predictors of these conditions. It has been shown that fibrinogen, plasma viscosity, vWF, fibrin, D-dimer, tPA antigen are independent predictors of thrombotic vascular pathology [4,5,6).

Having as starting point the complex connections between the thrombocyte-coagulation-fibrinolisis compartment and lipid compartment, in this study, we aim to emphasize hemostatic anomalies in patients with hyperlipoproteinemia. Therefore, we have chosen fibrinresistometry as the main method for evaluating hemostatic anomalies, since it measures the breakage resistance of the fibrin clot (BRFC). We suggest a model of hemostasis evaluation that does not measure the necessary time for the fibrin clot to form, but, rather, its biophysical properties [7]. The major objective of our research is to study the possible correlations between the breakage resistence of the fibrin clot and an increase in plasma lipids.

Material and methods

We conducted a prospective study, investigating hemostatic anomalies in hyperlipoproteinemic patients using fibrinresistometry, and, concurrently, using classic methods of determining certain parameters of hemostasis, at a 6 months interval between the first and the second evaluation. The second evaluation allowed us to observe the changes in clot resistance for the patients on hypolipemiant treatment. The number of study group subjects was 86 adults, with a mean age of 57.31 ±13.01 years, out of which 43 men and 43 women. The control group included 113 clinically and anamnestically healthy subjects, without hemostasis or plasma lipids anomalies, out of which 57 were females and 56 males, with an mean age of 55.6 ±13.76 years.

All patients were assessed with identical clinical and paraclinical protocols. We excluded patients with primary haemostasis pathology, patients treated with any kind of medication that interferes with haemostasis (especially non-steroidal anti-inflammatory, dicumarine, dipiridamol) and patients with hepatic suffering, to exclude the deficit of coagulation factors of hepatic cause.

All the subjects were informed about the details of the study, and those that agreed to

participate signed an informed consent. The present study complies with the Declaration of Helsinki and was approved by the ethics committee of the University of Medicine and Pharmacy of Craiova.

We determined the breakage resistance of the fibrin clot, plasma lipids, plasma fibrinogen, fasting blood glucose, platelet count and other haemostatic parameters, anthropometric parameters (body mass index and **waist circumference**), blood pressure (see table 1). The chosen standards for plasma lipids were as stated in the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III).

Statistics

Continuous data were expressed as mean values ± standard deviation (SD). The comparison of mean value was performed with T-test. Results were considered statistically significant if $p<0.05$. Pearson's coefficient and simple regression analysis were applied for assessing correlation strength. Correlations between BRFC value and plasma lipid concentration were determined by computing the adjusted Odds Ratio (OR) with an accompanying 95 % confidence interval (CI). All statistical analyses were performed with SPSS (Statistical Package for the Social Science) and XLSTAT 7.5.2.

Results

As shown in table 1, the two lots are significantly different, an expected consequence of different selection criteria. Note that for the HPL lot, mean values for cholesterol and LDL concentrations are greater than upper normal limits, while mean values of triglycerides have the same tendency, though not statistically significant. On the other hand, mean HDL is lower than the inferior normal limit (considered to be 45 mg/dl), significantly lower than the control group ($p < 0.05$).

Table 1. Baseline characteristics of the dyslipoproteinemic and control

Parameters	Patients with increased plasma lipids n = 86	Control subjects n = 113	P-value
Mean age (years)	57.31±13.01	55.66±13.76	p>0.05
BMI (Kg/m^2)	28.75±5.08	23.75±2.89	p>0.05
Waist circumference (cm)	99.20±12.28	81.26±4,76	p=0.00523
Breakage resistance of the fibrin clot (FU)	296.76±23.37	248.64±25.71	p=0.00047
Total cholesterol (mg/dl)	259.10±39.02	188.82±12.12	p=0.00026
Total triglycerides (mg/dl)	133.19±38.86	108.53±27.70	p=0.00540
HDL cholesterol (mg/dl)	41.54±10.45	52.11±7.04	p=0.00306
LDL cholesterol (mg/dl)	150.27±22.62	99.47±17.97	p=0.00041
Fasting blood glucose (mg/dl)	5.53±0.49	5. 71±0.57	p>0.05
Plasma fibrinogen (mg/dl)	370.57±52.37	313.47±44.62	p=0.00413
Platelet count-10 $x10^3/mm^3$	379.57±60.20	297±39.32	p=0.00351
VPM*	10.58±1.90	9.87±9.86	p>0.05
APTT (sec.)	30.01±4.95	32.48±3.21	p>0.05
PT (%)	92.02±6.22	86.51±4.29	p>0.05
INR	1.01±0.09	1.01±0.08	p>0.05

We have found that the mean value for BRFC in the control group is 248.64±25.71 Fibrinrezistometric Units (FU). Values in this group range between a minimum of 220 and 280 FU, setting the method's normal limits to a normality interval 95% of 200-300 FU. Mean fibrinresistometric values do not depend on sex (p>0.05): 249.13 ±13.6 FU for men and 248.17 ±14.1 FU for women.

In patients with hyperlipoproteinemia (HLP) the breakage resistance of the fibrin clot, as determined by the fibrinresistometric method, had a mean value of 296.76±23.37 FU for the initial evaluation. Although, this value is in the normal range of the method, it can either be seen as an upper normal value, or a lower limit for pathologic values. By comparison with mean value of the control group (248.64 FU), an increase of 19.35% is noted (p=0.0004). Therefore, the apparently normal result of HLP group is interpreted as close to a hypercoagulable state, many of this lot's patients being undoubtly in the hypercoagulability interval (see figure 1).

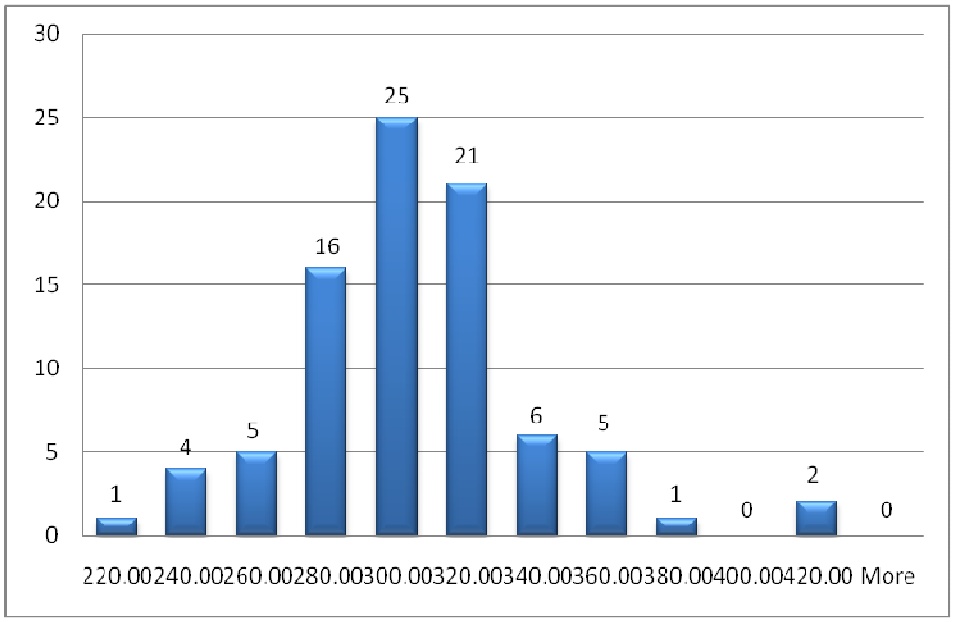

Figure 1. Histogram of fibrinresistometric values in HLP group.

Mean values of BRFC do not vary depending on sex for HLP patients, but they seem to be age-dependent: 285.3 FU < 50 years, versus 310.1 FU>50 years, p=0.0312.

To investigate the relationship between plasma lipids and other conventional parameters of hemostasis, and to identify possible correlations between these and the resistance of the fibrin clot, as determined by the fibrinresistometric method, we took into consideration the following parameters: platelet count, mean platelet volume, plasma fibrinogen concentration, prothrombin time (PT), partial thromboplastin time (PTT) and INR (see table 1). Mean values of the studied temporal coagulation tests are normal, by comparison with both normal ranges and with the control group. Though, the study group, by comparison with the control group, shows a statistically significant increase in mean values for fibrinogen concentration, platelet count, and mean platelet volume (p<0.05) (see figure 2 and 3).

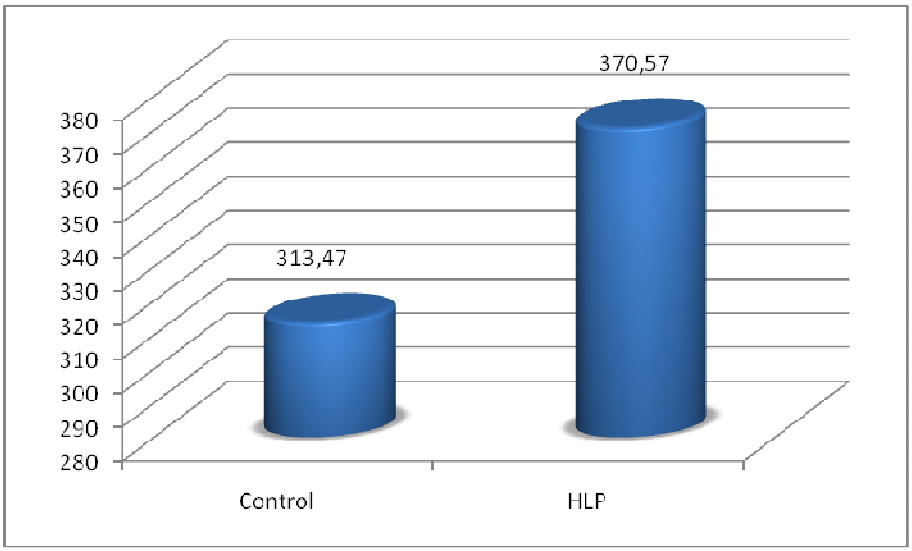

Figure 2. Mean fibrinogen values in the studied groups

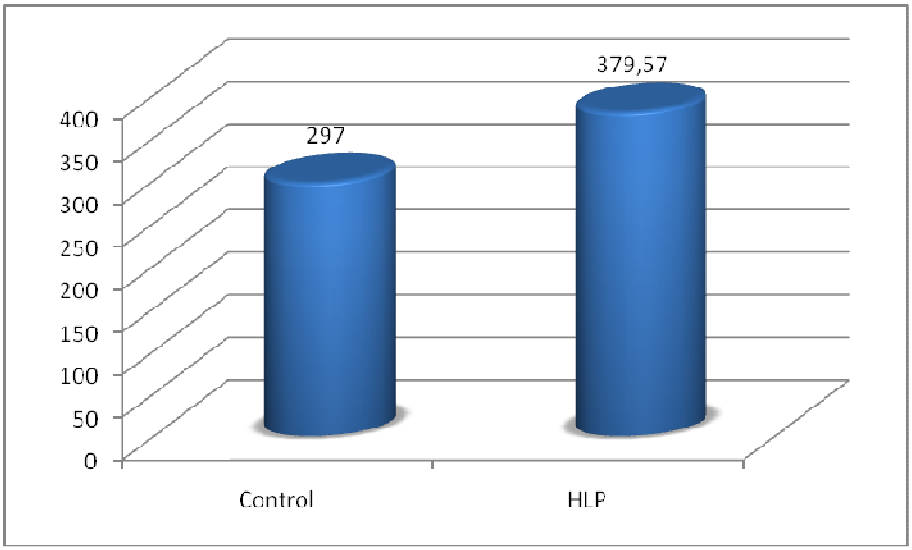

Figure 3. Mean platelet count in the studied groups

We have also found differences between the two lots in BMI and WC mean values. Both parameters are increased in HLP patients versus control group. Also, they are significantly higher than the upper limit of normal values for these parameters, for WC the difference being obvious: 99.20±12.28 cm versus 81.26±4.76cm (p=0.00523).

Results for the six months follow-up

All the patients in the initial HLP group had recommendations for re-evaluation after 6 months of treatment, as part of their follow-up. Unfortunately, the lack of cooperation has led to the exclusion of a large number of patients from this group, even though they benefited from the initial investigations. By the end of the study, the treatment subgroup included only 34 patients, with a mean age of 55.85±3.53 years, out of which 15 women and 19 men. The drop in plasma lipids concentration, following hypolipemiants, was consistent with the normal response to this type of treatment.

Initial values of BRFC showed borderline values for this parameter, relatively close to the limit of hypercoagulability, which indicates a tendency to increased risk of vascular thrombotic complications. This is why we investigated if the treatment had influenced these values and whether the risk for these complications had decreased or not.

Table 2 and picture 4 show that the initial mean value of fibrinresistometry for the HLP lot was 309.55±20,22 FU, droping to 302.26±21,83 FU after treatment. This represents a 2.85% decrease, statistically not significant ($p > 0.05$). According to this result, there is a possibility that the resistance of the fibrin clot may not be influenced by the hypolipemiant treatment. Consequently, the tendency for hypercoagulability present at the initial evaluation of the parameter may remain constant, being unrelated to this type of treatment.

Table 2. Fibrinresistometry before and after hypolipemiant treatment.

Parameter	Before treatment	After teratment	P value
Breakage resistance of the fibrin clot (FU)	309.55±20.22	302.26±21.83	p > 0.05

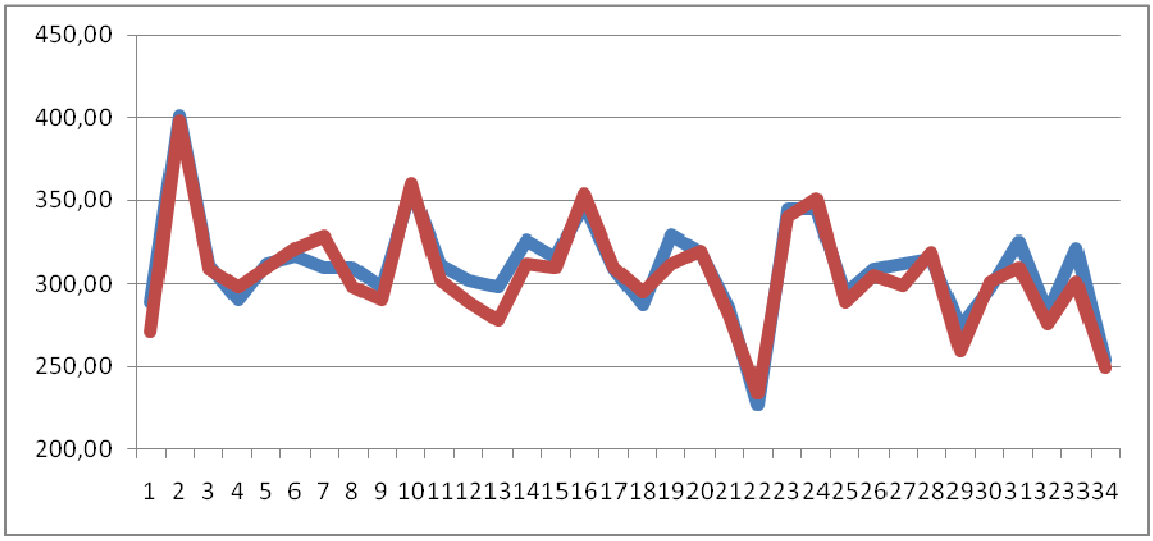

Figure 4. Fibrinresistometry variations depending on treatment: blue-initial values, red-6 moths follow-up.

Post-treatment, a significant decrease in plasma fibrinogen was noted. Initially, it had a mean value of 391 ±28.87 mg/dl and after treatment it decreased significantly ($p < 0.05$) to 375.91±21.17 mg/dl (see figure 5). The other tests used for hemostasis exploration-platelet count, mean platelet volume, PTT, PT, INR did not show statistically significant differences.

Correlations between BRFC, fibrinogen and plasma lipids concentration

The most striking correlations, as seen in table 3, are those between fibrinresistometry and plasma lipids. The increase of BRFC is highly associated with an increase in triglycerides (r=0.585) and cholesterol (r=0.574), moderately associated with LDL (r=0.551), and show a weak inverse correlation with HDL values (r= - 0.246). In

our opinion, this constitutes a convincing evidence that plasma lipids, by multiple actions, determine an alteration in the breakage resistance of the fibrin clot. In fact, an activation of hemostatic systems is the underlying mechanism, leading to a shift in coagulation equilibrium to a state of thrombosis.

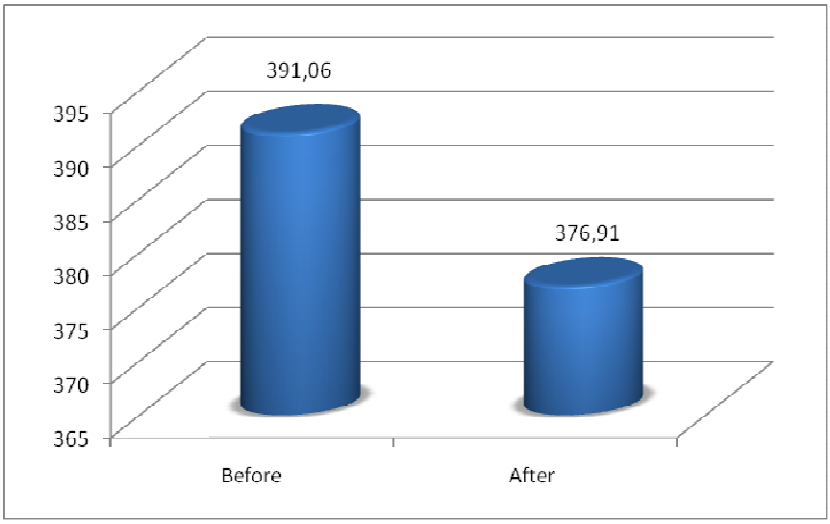

Figure 5. Fibrinogen variations depending on treatment

Table 3. Correlations between BRFC, fibrinogen and plasma lipids concentration

LOT HLP	FBR	W.C.	BMI	COL	TG	HDL	LDL	F-GEN
FBR	-							
W.C.	0.576	-						
BMI	0.401	0.767	-					
COL	0.574	0.551	0.288	-				
TG	0.585	0.431	0.304	0.411	-			
HDL	-0.246	-0.313	-0.044	-0.325	-0.364	-		
LDL	0.551	0.387	0.345	0.547	0.442	-0.371	-	
F-GEN	0.690	0.426	0.284	0.526	0.507	-0.382	0.498	-

Legend. r(84)=0.1786, p<0.05.WC-waist circumference; BMI-body mass index; COL-cholesterol; TG-triglyceride; F-GEN-plasma fibrinogen. Orange: r > 0.6; green: r > 0.5; blue: r > 0.4; yellow: r > 0.3; white: r > 0.2 or lack of correlation

Other important correlations are those between fibrinresistometry and anthropometric characteristics of the evaluated patients. Note that a high waist circumference, indicator of abdominal fat, is highly correlated to fibrinresistometric findings (r=0.576), and to high fibrinogen values (r=0.426), leading us to believe that these three parameters may be risk factors for the onset and development of thrombosis by lipid metabolsim alterations.

Discussions

In this study we aim to establish that the quality of the fibrin clot, along with other

hemostasis parameters, are affected by an altered lipidic profile. Furthermore, we wish to confirm that this parameter can prove to be an important biological marker, which can have predictive value for an increased thrombogenic potential in patients with HLP. The normal values for this parameter have been established in prior studies [9] as ranging between 200 – 300 fibrinresistometric units and the control group was between these limits. No significant differences were found between the men and women of this group, but higher values were found in patients older than 50 years, probably due to endothelial dysfunction generated by an atheromatous condition.

By comparison with the control group, the HLP group had all lipidic fractions altered, all the more since lipidic profile was one of the inclusion criteria. At an initial evaluation of the breakage resistance of the fibrin clot by fibrinresistometric methods, the HLP group had a mean value of 296.76 FU, which is situated in the upper normal range for this method. An increase with 19.35% (p = 0,0004) is therefore noted by comparison with the control group, which has a mean value of 248.64 FU. These results may be interpreted as close to the hypercoagulability risk limit, many of the patients in this lot being in the hypercoagulability interval. A closer look at the distribution of the BRFC values shows that 35 patients, resulting in a percent of 40.7%, have pathologic values of over than 300 FU. This leads us to believe that these subjects have a higher risk for thrombosis.

We believe that an increased resistance of the clot can be associated with the risk for thrombosis. An argument for BRFC as an important marker of the tendency to thrombosis can be the analogy to fibrinogen, another marker currently associated more and more with thrombogenic potential and vascular accidents. As expected, the resistance of the fibrin clot has a higher degree of dependency to the quality and quantity of the coagulation factors, including fibrinogen and platelet count. We consider the quality of the endothelium equally important for clot formation. An endothelium modified by atheromatous plaques becomes more "attractive" for thrombocytes and coagulation factors, therefore making the clot more adherent to the exposed surface. Consequently, the clot becomes harder to break as the opposing resistance is higher. All these considered, we believe that BRFC evaluates not only the quality of hemostasis, in all its steps, but also the prothrombogenic potential of the endothelium. BRFC thus gives us information on both the endothelium and the hemostatic system, clot formation being influenced by the nature of the exposed endothelial surface, as well as local rheology of blood flow [10,11].

As for fibrinogen, many studies, including populational studies, indicate a correlation of fibrinogen with MI, ischemic cardiopathy and stroke [12,13]. This independent association can be due to the major role that fibrinogen plays in coagulation, but also due to its role as biomarker of endothelial inflamatory state. In our research, we have found a strong correlation between fibrinresistometry and fibrinogen (r=0.69), which leads us to believe that the resistance of the fibrin clot has a greater relevance as marker of a thrombogenic potential for patients with this type of pathology. The correlations with thrombo-genic events presented above, lead us to

believe that the resistance of the fibrin clot indicates a tendency to thrombosis for the investigated patients, being a valuable marker in the evaluation of this condition.

Our findings suggest a strong correlation between fibrinresistometric measurements and plasma lipid concentrations. For HLP patients, a strong correlation is found between BRFC and the increase of triglycerides (r=0.585) and cholesterol (r=0.574) and not lastly LDL (r=0.551). On the other hand, the HLP patients show a weak correlation to HDL. We believe that these associations are a convincing proof that plasma lipids lead to an activation of hemostatic systems, shifting the coagulation equilibrium to a state of thrombosis. The increase of fibrinogen concentration mean value, and the positive correlations between fibrinogen and different lipidic fractions correlations (r=0.526 correlation fibrinogen-cholesterol, r=0.507 fibrinogen-TG) indicate a thrombotic potential for these patients. A weaker correlation is found for fibrinogen and LDL. Futher confirmation of hemostatic alterations by means of increase in plasma lipids and hypercoagulability shift is shown by the positive correlations found between platelet count and plasma lipids: platelet count-cholesterol, r=0.466, platelet-LDL, r=0.420. Currently, multiple connections have been identified between plasma lipids and platelet-coagulation-fibrinolysis system. It has been proven that an increase in cholesterol concentration, but especially LDL and oxLDL intensifies the expression of the prothrombogenic properties of the platelets, via the specific receptor for LDL. Though this receptor, LDL transfers cholesterol in membranes, which makes the thrombocyes more sensitive to the action of aggregation inductors [14,15]. Moreover, platelet phospholipase is activated (PLA2) and arachidonic acid is cleaved, by the enzyme cyclo-oxigenase followed by thromboxane syntetase, to TxA2, which has a strong aggregant and vasocontrictor action [16,17]. LDL and oxLDL stimulate coagulation by an extrinsec mechanism and intrinsec mechanism., the base of which lies in the activation of tissue factor (TF). TF is essential for the initiation of coagulation cascade by the extrinsec mechanism or by contact factors, especially F X, which, in turn, initiates the intrinsec mechanism. As a consequence, great quantities of thrombin are generated. Thrombin is the key enzyme of coagulation which will catalyze the formation of fibrin from fibrinogen [18]. It has also been proven that the increase in fibrinogen has a greater degree of complexation in the presence of high concentrations of LDL and oxLDL. Hyperfibrinogenemia, a strong independent risk factor, dyslipidemia and arterial hypertension have a synergictic action in the developement of cardiovascular disease [18,19].

Another argument for the tendency to thrombosis that BRFC indicates is found in the correlations between this parameter and WC and fibrinogen. We found that a waist circumfernce, indicator of the abdomial fat, has a strong correlation with fibrinresis-tometry (r=0,576), as well as fibrinogen (r=0,426), which leads us to believe that these three parameters are risk factors for the onset and development of thrombosis, by lipid metabolism alteration. Weak correlations were found between BRFC and BMI, as well as BMI and plasma lipids. Many studies have reported a positive association between WC

and cardiovascular risk, and especially between WC and the evolution of cardiovascular conditions [21]. By comparison with BMI, WC, making a clearer distinction between fat and lean tissue, seems to be a better indicator of body fat distribution and vascular disease risk [22]. A waist circumference over the normal limits, increase in blood glucose (>100 mg/dl), triglycerides (>150 mg/dl), arterial pressure (>130/85 mm Hg) and decrease of HDL (< 50 mg/dl for women, < 40 mg/dl for men) define the metabolic syndrome or the insulin resistance syndrome, according to National Cholesterol Education Program-Adult Treatment Panel III - NCEP-ATP III and International Diabetes Federation. The characteristics many of our patients depict allow them to fit in these guidelines, especially since 38 of them also having increased blood pressure.

Post-treatment evaluation does not give correlations between BRFC and plasma lipids as strong as the initial evaluation, although plasma lipids have decreased significantly after the hypolipemiant medication. According to this result, the resistance of the fibrin clot may not be influenced by hypolipemiant treatment. The hypercoagulability tendency shown intially may not change in time, and not be affected by this type of treatment. Once initiated, prothrombogenic mechanism and endothelial dysfunction accentuate and further manifest, providing a possible explanation for the thrombotic state under analysis in the current study.

Conclusions

Hyperlipoproteinemia produces the alteration of the quality of the fibrin network, which becomes more adherent to the vascular endothelium. The increased breakage resistance of the fibrin clot in the studied patients reveals a thrombogenic potential, thus making BRFC an important marker for this state.

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REFERENCES

1. Barre D.E. The molecular nature and consequences of lipoprotein (a)'s association with platelets. *Protein Pept Lett*.;14(9):839-42. Review. 2007

2. Blann A.D. Assessment of endothelial dysfunction: focus on atherothrombotic disease. *Pathophysiol Haemost Thromb* 33:256–261. 2003

3. McQueen M.J., Hawken S., Wang X., et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction în 52 countries (the INTERHEART study): a case-control study. *Lancet*; 372 (9634): 224–33. 2008.

4. Rauch H.B., Scholz A.G., Baumgärtel-Allekotte D., Censarek P., Fischer W.J., Weber A.A., Schrör K. Cholesterol Enhances Thrombin-Induced Release of Fibroblast Growth Factor-2 în Human Vascular Smooth Muscle Cells. *Arterioscler. Thromb. Vasc.* Biol; 27;e20-e25. 2007

5. Tracy R.P. Thrombin, inflammation, and cardiovascular disease: an epidemiologic perspective. *Chest*; 124:49S-57S. 2003

6. Mills J.D., Ariëns R.A.S., Mansfield M.W., Grant P.J. Premature Coronary Artery Disease Altered Fibrin Clot Structure în the Healthy Relatives of Patients With Premature Coronary Artery Disease. *Circulation*;106;1938-1942. 2002.

7. Sfredel V., Trăilă A., Moţa M., Dănoiu S. Alterarea hemostazei în diabetul zaharat – o nouă

tehnică de explorare – fibrinrezistometria. *Jurnalul Român de Diabetologie*, vol.7, nr. 1-2, p. 6-9, ISSN 1220-8817. 1999

8. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol în Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002; 106; page 3240.

9. Sfredel V., Moţa M., Trăilă A., Dănoiu S. Disturbances of the coagulating equilibrium of blood in diabetes mellitus, *Romanian Journal of Internal Medicine*, Editura Academiei Romane, vol 37, p.251-269, ISSN 0035-3973. 1999

10. Kim J.A., Tran N.D., Berliner J.A., Fisher M.J. Minimally oxidized low-density lipoprotein regulates hemostasis factors of brain capillary endothelial cells. *J Neurol Sci*; 217:135–141. 2004.

11. Spronk H.M., van der Voort D., ten Cate H. Blood coagulation and the risk of atherothrombosis: a complex relationship. *Thrombosis Journal*; 2:12. 2004.

12. Koenig W. Fibrin(ogen) in cardiovascular disease: an update. *Thromb Haemost*; 89:601-609. 2003.

13. Morange, P.E., Bickel C., Nicaud V., R. Schnabel, H.J. Rupprecht, D. Peetz, K.J. Lackner, F. Cambien, S. Blankenberg, L. Tiret and for the AtheroGene Investigators, 2007. Haemostatic Factors and the Risk of Cardiovascular Death in Patients With Coronary Artery Disease: The Athero Gene Study, Arterioscler Thromb *Vasc Biol*:26;2793-2799. 2007

14. Tselepis A.D., Chapman M.J. Inflammation, bioactive lipids and atherosclerosis: potential roles of a lipoprotein-associated phospholipase A2, platelet activating factor-acetylhydrolase. *Atherosclerosis*; (Suppl 3): 57–68. 2002.

15. Discepolo W., Wun T., Berglund L. Lipoprotein(a) and thrombocytes: potential mechanisms underlying cardiovascular risk. Pathophysiol Haemost Thromb.;35(3-4):314-21. Review. 2006

16. Coleman L.G. Jr, Polanowska-Grabowska R.K., Marcinkiewicz M., Gear A.R. LDL oxidized by hypochlorous acid causes irreversible platelet aggregation when combined with low levels of ADP, thrombin, epinephrine, or macrophage-derived chemokine (CCL22). *Blood* 104:380–389. 2004

17. Reitsma P.H. Is hypercoagulability an issue în arterial thrombosis? No. *J Thromb Haemost*; 2:692-694. 2004.

18. Shen X.G. Oxidatively Modified Low-Density Lipoproteins and Thrombosis in Biochemistry of Atherosclerosis. Sukhinder Kaur Cheema Ed., Springer Science+Business Media, 8:150-170. 2006

19. Shen X.G. OxLDL and Thrombosis in Biochemistry of Atherosclerosis. Sukhinder Kaur Cheema Ed., Springer Science+Business Media, 8:153-157. 2006.

20. Grant P.J. Is hypercoagulability an issue în arterial thrombosis? Yes. *J Thromb Haemost;* 2:690-691. 2004.

21. Mehta L, Devlin W, McCullough PA, O'Neill WW, Skelding KA, Stone GW, Boura JA, Grines CL. Impact of body mass index on outcomes after percutaneous coronary intervention in patients with acute myocardial infarction. Am J Cardiol;99:906–910. 2007.

22. Diercks DB, Roe MT, Mulgund J, Pollack CV Jr, Kirk JD, Gibler WB, Ohman EM, Smith SC Jr, Boden WE, Peterson ED. The obesity paradox in non-ST-segment elevation acute coronary syndromes: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative. *Am Heart J*.;152:140–148. 2006.

Correspondence Data:
Horia Matcas
horiamatcas@yahoo.com
telefon:0766316340