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Review Article

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Interplay Among Lipoproteins, Endothelial Cells and Platelets

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Abstract

Epidemiological studies have allowed variables related to coagulation to be implicated in the process of atheromatous plaque formation. These include fibrinogen, factors VIII, VII, and von Willebrand, as well as fibrinolytic activity. It is important to note that the reported changes are reversible and there is a reduction in atherosclerotic disease when hyperlipidemia is corrected. The interference that dyslipidemia makes in the hemostasis system is located in three fundamental points: the endothelial cell, platelets and circulating coagulation factors and fibrinolysis. The lumen of the vessels of the entire cardiovascular system is covered by a single layer of juxtaposed endothelial cells, which are in direct contact with the circulating blood. They separate the blood from the subendothelial matrix, where adhesive proteins important for activating coagulation such as collagen, von Willebrand factor and fibronectin are found. The endothelial cell has multiple functions that, as a whole, protect from the activation of coagulation and thrombus formation. The role of hemostasis in the initial phase of atherogenesis is mainly related to platelet activation. They have a lipoprotein cell membrane containing glycoproteins, which function as important receptors for platelet activation represented by the processes of adhesion, shape change, secretion of granules and aggregation for platelet plug formation.

Keywords: Endothelium, Platelets, Cardiovascular, Blood, Coagulation

Abbreviations

GP: Glycoproteins
IL-1: Interleukin 1
LDL: Low-density lipoprotein
PAI-1: plasminogen activator inhibitor
PGI2: Prostacyclin
t-PA: Tissue-type Plasminogen Activator

1. Introduction

The interference that dyslipidemia makes in the hemostasis system is located in three fundamental points: the endothelial cell, platelets and circulating coagulation factors and fibrinolysis [1].

2. Effects of Hyperlipidemia on Hemostasis

Generation of procoagulant activity in the endothelial cell (activation of the endothelial cell, binding of monocytes to the endothelial cell, expression of tissue factor in the endothelial cell, generation of hypercoagulability, increase of activated factor VII and VII, increase of receptors for fibrinogen in the platelet, increases the binding of platelet to von Willebrand factor) and inhibition of fibrinolysis (production of plasminogen activator inhibitor (PAI-1) and occupation of the plasminogen receptor by lipoprotein(a)).

The role of hyperlipidemia is well known in the genesis of atherosclerotic disease, as well as the participation of the mechanisms of hemostasis in the formation of atheromatous plaque. This interrelationship occurs in two distinct moments: the first, in the early phase of atheromatous formation, where plaque formation begins, and the second, during the secondary development of thrombus at the level of the organized plaque. Hyperlipidemia causes changes in the hemostasis system, which certainly contribute in these two moments, either increasing the formation of atherosclerotic plaque or inducing the formation of thrombi that will occlude arteries. Once the atherosclerotic lesion is established, platelets, coagulation factors and fibrinolysis act to produce the thrombus, which obstructs the artery and interrupts blood flow, causing tissue death [1].

Epidemiological studies have allowed variables related to coagulation to be implicated in the process of atheromatous plaque formation. These include fibrinogen, factors VIII, VII, and von Willebrand, as well as fibrinolytic activity. It is important to note that the reported changes are reversible and there is a reduction in atherosclerotic disease when hyperlipidemia is corrected [2].

3. Endothelial Cell

The lumen of the vessels of the entire cardiovascular system is covered by a single layer of juxtaposed endothelial cells, which are in direct contact with the circulating blood. They separate the blood from the subendothelial matrix, where adhesive proteins important for activating coagulation are found, such as collagen, von Willebrand factor and fibronectin. The endothelial cell has multiple functions that, as a whole, protect from the activation of coagulation and thrombus formation [1].

4. Non-Thrombogenic Endothelial Cell Functions

Heparan sulfate expression, plasminogen tissue activator (t-PA) production, plasminogen receptors, thrombomodulin expression, protein S production, prostacyclin (PGI2) production, nitric oxide production.

Antithrombin III is the main inhibitor of coagulation and heparan sulfate present in the endothelial cell membrane binds to it, increasing its inhibitory effect on thrombin and factor Xa [3].

The endothelial cell secretes and releases t-PA, which transforms plasminogen into plasmin, activating fibrinolysis. In the endothelial cell there are receptors for plasminogen on its surface, being responsible for the localized generation of plasmin, through the action of t-PA at the level of the cell membrane [4].

Thrombomodulin, also present in the endothelial cell membrane, forms with thrombin the complex capable of activating protein C, which inactivates factors Va and VIIIa, limiting thrombin formation. The activation of this system is done in the presence of a cofactor, the S protein, which is also secreted by the endothelial cell. The activated protein C consumes the t-PA inhibitor, called PAI-1, increasing fibrinolytic activity [5].

The endothelial cell produces PGI2 and nitric oxide, which inhibit platelet activation and cause vasodilation [6].

5. Endothelial Cell Activation

Normally the endothelium constitutes a non-thrombogenic surface, but under proper stimulation it can exhibit procoagulant properties. Observations made in human endothelial cell culture demonstrate that interleukins, especially interleukin 1 (IL-1), tumor necrosis factor and bacterial endotoxins are capable of inducing modifications in the endothelial cell membrane, making it thrombogenic. IL-1 and tumor necrosis factor are capable of making the endothelial cell express tissue factor, also called thromboplastin, on its surface [7-9].

Circulating factor VII forms a composite form with the tissue factor present in the activated endothelial cell and initiates the extrinsic thrombin generation pathway. The thrombin formed stimulates the production of adhesive molecules by the endothelial cell, which promote the binding of monocytes and the production of fibroblast growth and differentiation factor and platelet activating factor (PAF).

Studies with cell cultures suggest that hyperlipidemia may alter endothelial cell functions. Exposure of the endothelial cell to high concentrations of cholesterol, usually the predominant component of low-density lipoprotein (LDL), especially when present in oxidized form, leads to the activation of this cell and the binding of monocytes to its surface. The recruited monocytes secrete IL-1, which promotes the expression of tissue factor, which leads to thrombin production. Thrombin and fibrin recruit more monocytes and neutrophils [10].

Monocytes also produce H2O2 superoxide due to their bactericidal properties, which will oxidize cholesterol esters present in LDL. On the other hand, the activated endothelial cell produces free radicals that oxidize the LDL particles and, in this way, they are encompassed by the monocytes, which will constitute the "foam cells" of the atheromatous plaque [1].

The more intense oxidation of LDL degrades apolipoprotein B100 and this modified particle has chemotactic property for monocytes and macrophages, in addition to making the monocyte express tissue factor. This explains why in atheroma plaques macrophages and monocytes express tissue factor [1].

This should be the first step of the genesis of atherosclerotic lesion, which is observed in experimental hypercholesterolemia. Dyslipidemia leads to activation of the endothelial cell, causing it to recruit monocytes and produce thrombin.

6. Platelet

The role of hemostasis in the initial phase of atherogenesis is mainly related to platelet activation. They have a lipoprotein cell membrane containing glycoproteins (GP), which function as important receptors for platelet activation, represented by the processes of adhesion, shape change, granule secretion and aggregation for platelet plug formation. The discontinuity of the endothelium or the modification of the normal characteristics of the endothelial cell causes the adhesion of platelets to the subendothelial structures [11].

GP la-IIa and GP lb-IX are the platelet receptors involved in platelet adhesion to collagen and von Willebrand factor, present in plasma and subendothelial region. These interactions activate the platelet that changes shape and adheres to the endothelium, secretes its granules, synthesizes thromboxane A2, and recruits other platelets. Platelet activation modifies the conformation of GP llb-IIIa, making it able to bind to fibrinogen, which serves as a "bridge" between adjacent platelets, forming the platelet aggregate. It is in this way that fibrinogen participates in the platelet aggregation process, being an indispensable element to its normal function [12].

PGI2 is produced in the epithelial cell and inhibits platelet function by acting on adenylyl cyclase, which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP prevents the release of calcium from the dense tubular system, inhibiting the action of the various enzymes involved in platelet aggregation, which are calcium-dependent. PGI2 is a potent antiplatelet agent of greater physiological importance, as it prevents platelet activation at the level of the normal endothelium [13].

Platelet activation also leads to the exposure of a phospholipid

in the membrane, called platelet factor 3, to which coagulation factors whose synthesis is dependent on vitamin K are attached. This interaction is fundamental for the proteolytic action of these activated factors, leading to thrombin formation [1].

7. Hyperlipidemia and Platelet Activation

Hyperlipidemia causes changes that lead to platelet hyperaggregation. It increases the exposure of fibrinogen receptors on the surface of the platelet activated by adenosine diphosphate (ADP); it also increases spontaneous platelet aggregation and its binding to von Willebrand factor in the endothelial cell, and finally, hyperlipidemia reduces platelet sensitivity to PGI2 [1].

These effects can be detected by sensitive laboratory methods, which identify platelet activation in vivo, such as thromboglobulin measurement, platelet factor 4 (PF4), thromboxane A2 metabolites [14]. However, these measures show no relationship with the status or progression of atherosclerotic disease and are not of clinical use.

8. Coagulation

The presence of fibrin in atheroma results from the gradual effects of activation of coagulation, platelets and reduction of fibrinolysis, during the formation of atherosclerotic plaque. Epidemiological data show a close relationship between hyperlipidemia and coagulation activation, suggesting that there is a direct action of the metabolic abnormality on the mechanisms of hemostasis [1].

Global coagulation tests are not adequate to identify patients with cardiovascular disease. However, the dosage of some factors alone showed a high correlation between the occurrence of thrombotic events and the evolution of atherosclerosis. They are: factor VII, fibrinogen, factor VIII and von Willlebrand factor.

9. Factor VII

Factor VII circulates in the plasma as a zymogen, which is activated in the presence of tissue factor, turning into a two-chain molecule, called factor Vlla. The complex formed by factor VIIa and tissue factor is able to activate factor X, initiating the extrinsic thrombin generation pathway. This should be the most important physiological pathway in the activation of coagulation under physiological conditions. In pathological situations that lead to endothelial injury, the expression of tissue factor is also important for coagulation activation [15].

It is observed that there is an increase in factor VIIa soon after the ingestion of a high-fat diet, which results from the activation of zymogen and not from the increase in the synthesis of total factor VII [1]. On the other hand, the low-fat diet reduces the coagulant activity of factor VII, but does not alter the levels of factor VII measured immunologically [16].

In patients with dyslipidemia, there is a direct correlation between high triglyceride levels and Vlla factor concentration. They increase the activation of the zymogen, but in the presence of prolonged hypertriglyceridemia an increase in the synthesis of this factor is also observed. The same is observed with the other vitamin K-dependent factors. The increase in hepatic synthesis of these factors may be determined by the action of coagulation protein activation peptides induced by hyperlipidemia itself [1].

The activation of factor VII, associated with the expression of tissue factor on the surface of the endothelial cell and activated monocytes, increases the generation of procoagulant activity in plasma and the consequent formation of fibrin. In addition to the effect on factor VII, oxidized lipoproteins incorporated into triglyceride-rich particles offer a negatively charged surface capable of activating the contact phase of coagulation. They also inhibit the action of antithrombin III by binding to its inhibitor interaction site with mucopolysaccharides, such as heparan sulfate and heparin [1].

The treatment and control of hyperlipidemia reduces the level of factor VII, which is also associated with the reduction of markers of coagulation activation, especially of the 1+2 fragment of prothrombin and fibrinopeptide A, indicating a reduction in the state of hypercoaguiability [17].

10. Fibrinogen

Fibrinogen is a risk factor for coronary cardiovascular disease and central nervous system disease, and is independent of other important risk factors, such as hyperlipidemia and hypertension. Fibrinogen level correlates with both recurrence and progression of atherosclerotic lesion. However, it is not clear what exact role the increase in fibrinogen would have on the pathophysiology of atherosclerotic disease, or even if it represents only an epiphenomenon. It behaves as an acute phase protein, whose hepatic synthesis is stimulated by cytokines, especially interleukin [6]. Some other situations are associated with high levels of fibrinogen: smoking, obesity, sedentary life, trauma, use of oral contraceptives, hypertension, diabetes mellitus and infections. The individual response to these factors is genetically regulated, which causes some individuals to present more significant elevations than others, in the face of the same stimulus [18].

The fibrinogen molecule has a number of actions related to the formation and growth of atherosclerotic plaque. There is accumulation of fibrinogen in atheromatous plaques, in direct relation to the concentration of fibrinogen in the plasma. Fibrinogen stimulates the migration of smooth muscle cells in culture, and also in an experimental model of atherosclerosis in rats. The degradation products of fibrin, formed by the action of plasmin, are also able to stimulate the proliferation of smooth muscle cells in vitro [19]. It also plays an important role in the platelet activation process, by binding to the GPllb-llla complex of the platelet membrane and acting as a “bridge” between platelets, a process necessary for platelet aggregation to occur [2].

Finally, fibrinogen is one of the main determinants of blood viscosity. The increase in viscosity favors the aggregation of erythrocytes in the bloodstream, compromising the flow, especially in the microcirculation [18].

11. Factor VIII and Von Willebrand Factor

There is also an increase in factors VIII and von Willebrand in patients with atherosclerotic disease, although this correlation is not as important as it is for factor VII and fibrinogen. The eleva-

tion of these factors is related to endothelial cell dysfunction and vascular injury, being good markers of the so-called "vasculitis" [20].

There seems to be a lower incidence of death from cardiovascular disease in hemophiliacs, who do not synthesize factor VIII [21]. Congenital von Willebrand factor deficiency in a given breed of pigs is also associated with a lower ability to develop experimentally induced atherosclerosis through a hyperlipidemic diet [22].

12. Fibrinolysis

The fibrinolytic system has the purpose of dissolving the clot after the recovery of the integrity of the endothelium, which involves a series of reactions that culminate in the transformation of plasminogen into plasmin, a serine protease that lyses fibrin. t-PA is the main activator of plasminogen and is released into the plasma by the endothelial cell. The t-PA activates only the plasminogen bound to the fibrin network, and the plasmin generated remains attached to it, exerting only there its proteolytic activity. Plasmin acts on specific points of the fibrin molecule, resulting in fragments of different molecular weights, generically called fibrin degradation products. The main role of the fibrinolytic system is to remove fibrin from blood vessels, tissues, ducts and organic fluids. Its action is regulated by two main inhibitors: α2-antiplasmin and PAI-1, produced and released by the endothelial cell. When fibrinogen is converted into fibrin, the mechanism that maintains the hemostatic balance is triggered, with the conversion of plasminogen into plasmin, for the rapid removal of fibrin [23].

13. Hyperlipidemia and Fibrinolysis

An increase in the plasmatic level of PAI-1 is observed in survivors of acute myocardial infarction in relation to the general population and that this increase correlates with the recurrence of the infarction. It is known that PAI-1 behaves as an acute phase protein, being elevated in several situations [24].

Hyperlipidemia is associated with reduced fibrinolytic activity, which may favor the occurrence of thrombotic complications. A reduction in global fibrinolytic plasma activity is observed in obese individuals, suggesting a relationship between dyslipidemia and hypofibrinolysis. t-PA interacts with apolipoprotein B-100 and this interaction with surface-bound LDL particles reduces the action of t-PA, because it occurs precisely through its active site, reducing its ability to activate plasminogen [1].

Lipoprotein(a) is a glycoprotein whose concentration is increased in patients with coronary artery disease. It presents great homology with plasminogen molecule and occupies receptors for plasminogen present in endothelial cells and monocytes. Thus, it competes with it for binding sites, preventing the action of t-PA on the plasminogen bound to the endothelial cell. It is actually present in high concentrations in arteries with arteriosclerosis compared to normal arteries, which contributes to the reduction of fibrinolytic activity in atherosclerotic plaque [25,26].

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None.

Conflicts of Interest

No conflict of interest.

References

1. Miller, G. J. (1994). 14 Lipoproteins and the haemostatic system in atherothrombotic disorders. Baillière's clinical haematology, 7(3), 713-732.
2. Meade, T. W. (1994). Haemostatic function and arterial disease. British medical bulletin, 50(4), 755-775.
3. Bauer, K. A., & Rosenberg, R. D. (1991, January). Role of antithrombin III as a regulator of in vivo coagulation. In Seminars in hematology (Vol. 28, No. 1, pp. 10-18).
4. Wu, K. K. (1992). Endothelial cells in hemostasis, thrombosis, and inflammation. Hospital Practice (Office ed.), 27(4), 145-50.
5. Dahlbäck, B. (1995). The protein C anticoagulant system: inherited defects as basis for venous thrombosis. Thrombosis research, 77(1), 1-43.
6. Palmer, R. M. (1988). Ashton DS, and Moncada S. Vascular endothelial cells synthesize nitric oxide from l-arginine. Nature, 333, 664-666.
7. Bevilacqua, M. P., Pober, J. S., Wheeler, M. E., Cotran, R. S., & Gimbrone Jr, M. A. (1985). Interleukin-1 activation of vascular endothelium. Effects on procoagulant activity and leukocyte adhesion. The American journal of pathology, 121(3), 394.
8. Nawroth, P. P., Bank, I., Handley, D., Cassimeris, J., Chess, L., & Stern, D. (1986). Tumor necrosis factor/cachectin interacts with endothelial cell receptors to induce release of interleukin 1. The Journal of experimental medicine, 163(6), 1363-1375.
9. Colucci, M., Balconi, G., Lorenzet, R., Pietra, A., Locati, D., Donati, M. B., & Semeraro, N. (1983). Cultured human endothelial cells generate tissue factor in response to endotoxin. The Journal of clinical investigation, 71(6), 1893-1896.
10. Pritchard Jr, K. A., Tota, R. R., Lin, J. H., Danishefsky, K. J., Kurilla, B. A., Holland, J. A., & Stemerman, M. B. (1991). Native low density lipoprotein. Endothelial cell recruitment of mononuclear cells. Arteriosclerosis and Thrombosis: A Journal of Vascular Biology, 11(5), 1175-1181.
11. Kroll, M. H., & Schafer, A. I. (1989). Biochemical mechanisms of platelet activation.
12. Hynes, R. O. (1991). The complexity of platelet adhesion to extracellular matrices. Thrombosis and haemostasis, 66(07), 040-043.
13. Moncada, S., Higgs, E. A., & Vane, J. R. (1977). Human arterial and venous tissues generate prostacyclin (prostaglandin x), a potent inhibitor of platelet aggregation. The Lancet, 309(8001), 18-21.
14. Coenen, D. M., Mastenbroek, T. G., & Cosemans, J. M. (2017). Platelet interaction with activated endothelium: mechanistic insights from microfluidics. Blood, The Journal of the American Society of Hematology, 130(26), 2819-2828.
15. Zahavi, J., Betteridge, J. D., Jones, N. A., Galton, D. J., & Kakkar, V. V. (1981). Enhanced in vivo platelet release reaction and malondialdehyde formation in patients with hyperlipidemia. The American Journal of Medicine, 70(1), 59-64.
16. Rapaport, S. I., & Rao, L. V. M. (1995). The tissue factor

pathway: how it has become a "prima ballerina". Thrombosis and haemostasis, 74(07), 007-017.
17. Brace, L. D., Gittler, C., Bowen, P., & Miller, G. (1991, March). FACTOR-VII COAGULANT (VIIC) ACTIVITY IN WOMEN FED A LONG-TERM CHOLESTEROL-LOWERING DIET. In FASEB JOURNAL (Vol. 5, No. 5, pp. A1070-A1070). 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA: FEDERATION AMER SOC EXP BIOL.
18. Wilkes, H. C., Meade, T. W., Barzega, S., Foley, A. J., Hughes, L. O., Bauer, K. A., ... & Miller, G. J. (1992). Gemfibrozil reduces plasma prothrombin fragment F1+ 2 concentration, a marker of coagulability, in patients with coronary heart disease. Thrombosis and haemostasis, 67(05), 503-506.
19. Bini, A., Fenoglio, J. J., Sobel, J., Owen, J., Fejgl, M., & Kaplan, K. L. (1987). Immunochemical characterization of fibrinogen, fibrin I, and fibrin II in human thrombi and atherosclerotic lesions.
20. Mannucci, P. M. (1995). Recent progress in the pathophysiology of fibrinogen. European heart journal, 16(suppl_A), 25-30.
21. WAGNER, D. D., & BONFANTI, R. (1991, June). von Willebrand factor and the endothelium. In Mayo Clinic Proceedings (Vol. 66, No. 6, pp. 621-627). Elsevier.
22. Rosendaal, F. R., Varekamp, I., Smit, C., Bröcker-Vriends, A. H. J. T., Van Dijck, H., Vandenbroucke, J. P., ... & Briet, E. (1989). Mortality and causes of death in Dutch haemophiliacs, 1973–86. British journal of haematology, 71(1), 71-76.
23. Bowie, E. J., Solberg, L. A., Fass, D. N., Johnson, C. M., Knutson, G. J., Stewart, M. L., & Zoecklein, L. J. (1986). Transplantation of normal bone marrow into a pig with severe von Willebrand's disease. The Journal of clinical investigation, 78(1), 26-30.
24. Henkin, J., Marcotte, P., & Yang, H. (1991). The plasminogen-plasmin system. Progress in cardiovascular diseases, 34(2), 135-164.
25. Hamsten, A., Walldius, G., Szamosi, A., Blombäck, M., Faire, U., Dahlén, G., ... & Wiman, B. (1987). Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. The Lancet, 330(8549), 3-9.
26. Chapman, M. J., Huby, T., Nigon, F., & Thillet, J. (1994). Lipoprotein (a): implication in atherothrombosis. Atherosclerosis, 110, S69-S75.