The Relationship of Haemostatic System to the Vessel Wall, Thromboembolism, Atherosclerosis from Pathogenesis and Laboratory Standpoints

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In this review, I am going to discuss the vessel wall in normal and pathologic conditions from Haemostasis and Thrombosis standpoints, and also summarize our laboratory findings related to the Haemostatic System [1,2,4,45,67,68,70,127,128,130,162,163,193,199,200,217,247]. Vessel wall alteration was first time cited by Imhotep of ancient Egypt few thousand years ago. He showed the different apperance of vessels in young and old people during mummification and this was written down on papirus as well on the rocks [146]. The first document related with haemophilia existed almost in the same area; in Babylon Talmut. So bleeding disorders and atherosclerosis and thrombosis were known in ancient times. The alteration was cited as degenerative process by Imhotep. In 1833 J.F. Lobstein and then in 1904 F. Marchand named the disease as "Arteriosclerosis" and "Atherosclerosis" in the last millenium[145]. There are various hypothesis on the pathogenesis of the disease. In recent years many hypothesis, theories and experimental studies on atherosclerosis were published and the pathogenesis of the disease was investigated in biochemical, molecular biologic and molecular genetic perspectives. Most of the studies published in recent years were on lipid changes, genetic defects to receptors; these studies were in strong, correlation between lipoprotein metabolism and development of atherosclerosis.

We are going to present our data related with haemostatic view which really began more than 150 years ago by Rokitansky[147]. This depends

on abnormal deposition of blood components including fibrin in the intima. This view is supported with some addition by Duguid in 1946[71]. He proposed that thrombosis was a factor for the pathogenesis of coronary Atherosclerosis. In 1856 Virchow proposed tissue response to endothelial injury theory and this theory got more support in the following years[148]. Depending on the response to injury theory, in 1976 Ross and Glomset developed this hypothesis and described endothelial injury caused by recurrent denudation of Endothelia Cells (EC) due to smoking, hypertension, hypercholesterolemia, and recurrent mural thrombosis[65,149]. Platelets also activate in this process and release their substances such as growth factors which result in hyperplasia, lipid accumulation as well smooth muscle hyperplasia and smooth muscle migration and finally atheroma formation. These results were also obtained in animal experiments.

This view was followed by "Endothelial Dysfunction" by Gimbrone in 1980 and "hypo/dysfunction of EC with hyperactivity of platelets" by Ulutin in 1986, Depending on our observation we can say that Endothelial dysfunction could be of two types "EC dysfunction that exist genetically" or "EC becoming defective in acquired form"[4,55,119, 133,262]. Endothelium has been recognized as one of the major contributors in initiation and progression of atherogenesis. We are not going to cover related literature extensively, since we already mentioned them in our earlier publications in detail. But I would like to summarize our observations in the cases of atherosclerosis from hemostasis standpoint[1-4,27,45,46,59,68,127,130,164,165,195,201,217,272-274]. Also there are many books and reviews mentioning the historical and scientific developments of the subjects. I am citing some of them[27,54,55,64,65,71,100,119,131,133,142,144,145,149,196,197,209-211].

First I would like to summarize what type of alterations take place in the hemostatic system in this group of cases:

a. Hypo/Dys-function of EC,

b. Decreased and altered fibrinolytic system and its activity; with and without molecular alterations,

c. Increase of some coagulation factors, with and without molecular alterations,

d. Decrease of natural inhibitor activity with/without molecular abnormalities, in vascular system especially in haemostatic mechanism.

e. Hyperactivity of platelets with some functional and biochemical alterations.

f. The role of Monocytes.

A. The role of EC and its function in Hemostasis, Atherosclerosis and Thrombosis have been summarised extensively on the following publications [1,2,4,12, 27,55,59,68,74, 79,89,100,117,119,120,127,128,130-134,139,140,141, 150,164-166,168,194-196,200,203,206,209,217,221, 258] (Table 1). There is increasing evidence that the EC is involved in numereous physiological and pathological processes in the vascular system as well as in the haemostatic mechanism. Its inner surface with TF and its lipid composition and also phospholipid surface have important roles in the activation of hemostatic system. The EC has a strong antithrombotic function due to the substances that it contain and synthesizes. In atherosclerosis these functions and substances are reduced and altered (Table 2). The inner surface of EC has a proteoglycan layer that is a reason to be nonwetable[64,68,119, 133,134,140,196]. Many proteoglycans such as heparan sulfate (HS), dermatan sulfate (DS) and heparin are synthesized in EC. In 1957 Ulutin and Fiestakof developed "Heparin Loading test" and showed, depending on this test there is a resistance to heparin in the cases of atherosclerosis and also in hypercoagulability[4,136,137,156,224]. Karaca and Koşar confirmed these results in 1964[216]. In 1964 Özdamar demonstrated that the cases of atherosclerosis had diminished amount of heparin and these patients also show a resistance to heparin[2,214,215](Table 2). Depending on heparin loading test and its modification, it has been shown that resistance to heparin decreases during intermittant heparin therapy[136,137,156,214,215]. LMW heparin was demonstrated in the heparin fractions in 1974 by Güven et al[303,304]. Now we have many LMW hepa-

Table 1. Summary of the substances contained and produced by the endothelial cells related with haemostosis

- Increase of platelet adhesion with and without other platelet defect
- Alteration of foreign surface activation
Hyperaggregation with aggregating agents
Occasionally spontaneous platelet aggregation
Hypersecretion
Increase of platelet markers in plasma
Increase of platelet alpha 2-Antiplasmin
Decrease of platelet AT-III
Decrease in gamma glutamyl transferase in platelets
Increase in PGF2 alpha, PGE, MDA and TXA2
Defective glucose membrane transport to the platelets and red blood cells
Alteration of membrane phospholipids
Increase of galactose transportation to the platelets and some alteration of membrane glucoproteins
Shortening half life of the platelets
In some cases an “Acquired storage pool deficiency of platelets” occur

rins with different molecular size and slightly different effects. We get similar results with LMW heparins as we showed above with UF heparins. Also LMW heparins show comparatively different effect for the management and therapy in vascular diseases[115]. In the electrically induced thrombosis model LMW and HMW heparins shows different appearance in dogs[254]. We demonstrated that in HMW heparin treated dogs, the larger mass of thrombus rich in red cells were seen. The EC was damaged. In LMW heparin treated dogs the EC was in normal appearance and keeping their unity and only some areas of tiny fibrin layer existed. With LMW heparin fibrinogen levels decrease. On the contrary with HMW heparin fibrinogen levels increased.

EC produces antithrombotic and prothombotic substances as follows: Antithrombotics [HS, tissue plasminogen activator (t-PA), urokinase (UK), Thrombomodulin, Prostacyclin, nitric oxide (NO), 13-HODE, Protease Nexin, etc.] and prothrombotics [plasminogen activator inhibitor 1 (PAI 1), PAI 2, 15-HETE, von Willebrand factor (vWF), TT, Endothelin, platelet activating factor (PAF) etc.].

Tissue factor (TF) (Tissue Thromboplastin) is a low molecular weight integral membrane glycoprotein, few expressed in healthy endothelium, also located in the intima, and some in adventitia[12,55,74,79,100,131,144,150, 164,194, 203,206,208,209]. TF is also located in within the platelets and leucocytes and especially monocytes. Besides EC,

Table 2. Plasma heparin levels in normal controls and in the cases of cerebrosclerosis. Plasma heparin levels were determined using Engelberg’s method (plasma heparin level mg/L). Data obtained from Özdamar’s publication. Ref. No. 214-215

	PE	PS	PI	SPH	PC	Total p/10 PI
Atherosclerotics (n: 32)	4.32 +	0.95 +	0.76 +	2.87 +	5.86 +	14.76 + 1.2
Normals (n: 30)	2.98 +	0.53 +	0.37 +	2.06 +	4.1 +	10.04 + 1.05
Increase %	45	79	24	39	43	44

TF is also released from leucocytes, platelets and especially monocytes[142,222,309]. TF content and its availability increases in the cases of atherosclerosis[12,298]. As known TF and VIIa have a role in the activation of extrinsic system and also TF activates factor IX in the intrinsic system of coagulation mechanism[206, 208]. TF expression increases in atherosclerosis with and without angina and myocard infarction. TF also releases from monocytes in the cases of hypercoagulability associated with angina and myocard infarction[12,79,80, 100,119,120,142,165,166,222]. The procoagulant activity of EC increase after infection with some respiratory viruses or after arterial injury[79,296]. Also some infection promote of development of atherosclerosis such as *Chlamydia pneumoniae*[108]. TF is a lipoprotein and its molecular weight is approximately 45.000, TF is located on chromosome Ip 21-22. Recently it has been published that high level of adhesion moleculs are measured in patients with peripheral arterial disease with impaired EC function[139,150].

A substance produced by the EC named TF Pathway Inhibitor (TFPI) inhibits the action of TF, TF/VIIa and Xa, So coagulation mechanism is inhibited by TFPI in the early stage in the EC and its surface. It was difficult to demonstrate it with standart coagulation tests. This shows another observation about anticoagulant activity in test tubes there are different antithrombotic activity[13-22,75,80,83,109,112,163,166,167,172, 181,264,286]. In blood, Lp(a) bounds TFPI and inactivates it approximately 60-70 percent.

Only free TFPI inhibits certain substance such as TF, TF/VIIa, Xa, elastase etc. In the cases of atherosclerosis Lp(a) levels increase so TFPI activity decreases[63,68,161,163,171, 173,223]. In our patients with atherosclerosis Lp(a) was in normal control 29.3 + 25.01 mg/dL and in patients 97.89 + 77. 92 mg/dL and p< 0.001 (n: 100). Some drugs such as heparin, LMW heparin, defibrotide stimulate the production and release of TFPI[17]. The potentiation of the effect of these drugs is, at least partially, due to increased level of TFPI. Recently it has been shown that a molecular abnormality exist in human TFPI in some cases of thromboembolism especially in the cases with venous thrombosis and also with acute coronary syndrom[13-23,75,80,83,109,112, 198].

Prostacyclin (PGI 2) and NO synthesized by the EC play an important role in the changes related to atherosclerosis. In atherosclerosis PGI 2 production and raelease decrease progressively. Prostacyclin is a very potent anti aggregator and vasodilator substance and stimulates the formation of c-AMP from ATP. PGI 2 decreases significantly in experimental and clinical atherosclerosis[1-5,68,129, 193,278]. The decreased prostacyclin levels in atherosclerotics increases the platelet activation. PGI 2 also decrease in diabetes mellitus, smokers, hemolytic uremic syndrom, lupus anticoagulant, preeclampsia, vit E deficiency and neonatants. In our work we found Plasma 6-keto-PGF 1a levels for normal controls were 96.4 pg/mL and for atherosclorotics 37.7 pg/mL and the difference was p< 0.001 in our patients[193].

EC also produces NO. NO is a vasodilator, decreases the tonus of smooth muscle and also inhibites aggregation and adhesion of platelets and also neutrophil adhesion, and inhibits VSMC proliferation. NO is produced in EC by NO synthase. PGI 2 and NO act synergistically[194,196,220]. It has been shown that the level and production of NO decreases in atherosclerosis[1-7,44,191,193]. The earliest endothelial dysfunction is reduced NO production. Akar et al demonstrated that a significant association exists between ccNOS polymorphism and cerebrovascular accident but not DVT in Turkish patients[44]. Radomski et al showed that endogenous NO inhibits platelets adhesion to endothelium[6]. NO also prevent restenosis after angioplasty[7].

On the other-hand, in 1988 Yanasigawa et al isolatet a polypeptide from EC and named it as “endothelin”[8,9]. Endothelin has a strong vasoconstrictor activity, increases the smooth muscle tonus in atherosclerosis, stimulates platelet and mitogen formations. PGI 2 and NO counteract to endothelin. In the case of atherosclerosis endothelin level is increased and also in ischemic heart disease and possibly in hypertension[7-11,192,194,196]. Endothelin causes vena jugularis thrombosis in rabbits as well other animals experimentally[11].

PAF is a l-o-alkyl-2-acetyl-glycerol-3-phosphoril-choline produced by EC, neutrophils and macrophages and activates the platelets that causes aggregation and secretion. PAF stimulates platelets and facilitates the adherence of neutrophils to the EC by stimulating them. It has been demonstrated that stimulation of EC by thrombin, histamin, bradykinin, leukotriens etc increases the level of PAF.

This increase is more marked in the cases of atherosclerosis[1,2,56]. Thus PAF is involved in vascular alterations and thrombosis formation and has a role in atherosclerotic change by producing platelet activation and endothelial injury[160,229].

It was shown that the production of vWF increases in the cases of atherosclerosis so platelet adhesion increase. At the same time Fibrinogen and factor VIII also increase. Plasma concentration of vWF increase in acute myocard infarction[93,199]. There are few, publications which mention a decrease of vWF in the EC[117]. In atherosclerosis, EC function is altered so antithrombotic role of the EC decreases.

EC produce thrombomodulin. Thrombomodulin bound thrombin and inactivate it. This thrombin/thrombomodulin complex activate Protein C with a cofactor Protein S that inhibits FV and FVIII. Thrombomodulin is in a way a natural anticoagulant on the surface of endothelium. Also binding of the thrombin in the injured area has some protecting role of microcirculation. In collagen vascular diseases the level of plasma thrombomodulin represent a marker of vascular injury[257]. Gene polymorphism was demonstrated in a women with early onset preeclampsia[85].

Using ELT and Fibrin plate methods we demonstrated that there was a clear difference between normal control and atherosclerotics (Table 3). The answer to Cuff test significantly decreases. t-PA, UK and PAI 1 are synthesized in EC. It also has been shown fibrinolytic activity decreases in the cases of atherosclerosis due to decrease of t-PA or increase of PAI-1 sometimes together[69,81,232].

B. Fibrinolytic system activity shows different alterations in the cases of atherosclerosis with and without thrombus formation [1,2,4,25-27,69,81,82,84,89,92,95,97,113,157,163,177,193,200,232,299]. t-PA and PAI 1 synthesized in EC, in one sense control the fibrinolytic activity. There are many reports mentioning reduced fibrinolytic activity in atherosclerosis. The balance between PAI 1 and t-PA is important in the cases of atherosclerosis with/without thrombosis[25,27]. Among 250 cases with atherosclerosis PAI 1 was excess in 207 cases and t-PA decreased in only 24 cases and no change in 19 cases. Also molecular abnormality has been described in PAI 1 and PAI 2. In a group of MI (n= 66) with healthy control (n= 20) a significant difference in PAI 2 was found[42,43]. There are many studies showing the alteration of fibrinolytic system in the cases of atherosclerosis, myocardial infarction and thromboembolism with and without molecular defects[42,43,82, 84,89,92,97,105,113]. There are several studies showing the relation between fibrinolytic system and the devolepment of atherosclerosis[27]. There are many animal experiments showing the inhibition of fibrinolytic system cause atherosclerotic changes in vascular wall and promotes thrombus formation[27,69,72]. On the other hand the activation of fibrinolytic system in animals prevents or decreases EC alteration as well decreased smooth muscle alteration. Berkarda demonstrated that dicoumarol and UF heparin when administrated in therapeutic doses inhibits euglobulin lysis time in 1962[305].

Table 3. The results of ELT and Fibrin plate in normals and atherosclerotics

	Normal control (n: 80)	Atherosclerosis (n: 80)
VIIIc	96 + 16	178 + 64
VIII Ag (vWF)	103 + 22	162 + 43
VIII Ri-co F	592 + 23	159 + 39

C. In the cases of atherosclerosis with and without thrombosis some coagulation factor levels increase and circulate in activated forms and cause hypercoagulability. We can measure their plasma levels immunologically or their procoagulant activity or their activation peptides. In atherosclerosis some factors increase such as Fibrinogen, FVIII, vWF, XII, IX, X, VII, V etc. In this group of cases prothrombin fragments 1 + 2 and "Activation peptide"s of IXa, Xa, XIIa increase[2,32,122].

And also some coagulation factors show molecular alterations[73,116,135,141,143,207,226].

Another vitamin K dependent, calcium ion binding protein is Protein Z[106,213,240]. Molecular weight is 62.000 D, like Protein C, and half life is 2.5 days. Although Protein Z sequence is homolog with IX, Protein C and other serin protease did not show a serine protease activity due to absence of active center aminoacid sequence. In the presence of Protein Z, thrombin bound to phospholipid surface. Protein Z, deficiency causes bleeding tendency. 60% of unexplained mild bleeding tendency might be related to low level of Protein Z as well some thrombus formation[213,241,242]. Protein Z has an important function in maintaining hemostasis and also has a role in the pathogenesis of thromboembolism. On the other hand the presence of Protein Z on macrovascular EC in atherosclerotic lesions has been demonstrated. It seems that Protein Z is also a marker for proliferating activity of the vessel wall.

We observed in our laboratory all vitamin K depended coagulation factors deficiency including prothrombin, factor VII, factor IX, factor X, Protein C, Protein S and also deficiency of fibrinogen, factor V, factor VIII, factor XI, factor XII and vWF etc (Table 4).

Factor VII/VIIa and TF/VIIa has important role in the activation of blood coagulation. They activate extrinsic coagulation mechanism and also through the activation of factor IX effect also the intrinsic system. TFPI inhibits this activation.

Factor VII congenital deficiency causes a bleeding tendency and this clinically resembles a platelet disorder. First congenital factor VII deficiency was published in Turkey in 1958 and followed with others[122,187,292]. Factor VII is a glycoprotein, a single chain with 405 aminoacid and molecular weight is 50.000. Factor VIIa make a complex with TF and activate factor X and factor IX. This interaction increase the catalytic activity of serine protease. Factor VII has many mutations. The clinical symptoms and factor VII activity demonstrated poor correlation[122,186,208]. Recently recombinant VIIa is used in the treatment of the bleeding of severe thrombocytopathia[121,295]. Also rVIIa is used in the Hemophilia A cases with inhibitor succesfully[263,296].

We also have congenital hypoprothrombinemia (Factor II deficiency)[293].

Fibrinogen levels increase significantly in the cases of atherosclerosis with and without thrombosis. A significantly high fibrinogen polymerization curve occurs. Fibrinogen became more sensitive to thrombin compared with normal control.

The clot is comparatively resistant to fibrinolytic substances. This may be related to their content of HMW fibrinogen (Table 5). Also HMW fibrinogen ratio increases in the fibrinogen of patients with atherosclerosis and they have higher risk of thrombosis[28-30,57,99,123]. Also fibrinogen anomaly was shown in the cases of myocard infarction[57]. In this group of cases vWF also increases significantly[197]. From laboratory findings, this type of cases show some similarity with chronic lowgrade DIC[24] (Table 6).

On the other hand, many recent publication indicate high levels of factor VIII is a risk factor of venous thrombosis as well arterial thrombosis. As we mentioned in our earlier publications, fibrinogen level increased significantly in atherosclerosis, in stroke and in- POAD[32,33,93,117,197,225]. The increased levels of D-Dimer and FPA are the indicators of intravascular coagulation. The recognition of specialized membrane receptors and binding of fibrinogen to leucocytes as well as regulation of leucocytes-endothelium interaction by fibrinogen give an additional regulative role to the fibrinogen[28-33,57]. The half-lives of fibrinogen and platelets are decreased in the cases of atherosclerosis[123].

We demonstrated that in leukocyte cultures a

Table 4. The distribution of factor deficiency among 327 patients registered in our division between 1960-1985 (294)

ELT (Min)			
Control (n: 42)	97 + 21	41 + 19	56
Patient (n: 41)	153 + 37	134 + 38	19
F‹BR‹N PLATE			
Control (n: 42)	43.6 + 9.5	93.2 + 16.4	49.6
Patient	26.8 + 11.4	47.2 + 16.6	20.4

substance with factor VIII-like activity synthesize in normal healty donors but not in Hodgkin's[266].

In 1965 and 1967 blood samples taken from coronary sinus by cardiac catheterization, brachial artery and vein were compared from coagulation activity between normal controls and atherosclerotics[276,290,310]. In normal control the coagulation activity between samples showed clear difference and arterial blood showed higher activity than venous blood drawn from coronary sinus. Blood passing the normal myocardium loses some its activity. In normal myocard it has a regulative role. In atherosclerosis there is no difference between samples, so myocardium loss this regulative role in the cases of atherosclerosis. This difference is also clearly demonstrated using thromboelastography.

D. Decrease of natural inhibitors activities with/without molecular abnormalities were seen. In the cases of atherosclerosis, there is a resistance to heparin. The level of heparin decreases. We already demonstrated this using heparin loading tests[136,137]. Heparin is produced by basophils, mast cells and EC and also EC produces HS. The surface of EC covered by HS has a role in nonwetable surface of EC with PGI 2.

As we will discuss later heparin produced by EC has an inhibitory effect on platelet derived growth factor's effect on smooth muscle. Heparin's antithrombotic effect enhances through the activation of AT-III. AT-III and activated AT-III by UF heparin inactivate dose dependently XIa, Xa, VIIa and thrombin. On the other hand, by description, LMW heparin acts through on Xa. But in practice LMW heparin also acts through AT-III but in lesser degree and this is different from one product to other. We can say that LMW heparins are a group of similar proteoglycans but different drugs due to their activities. Heparins obtained from different tissues and different species also show some differences structurally[1,4,34,35,104,115,172, 214-216].

We found that Protein C and S slightly decreases in the cases of atherosclerosis probably due to consumption.

In new born babies some vitamin K dependent factors are in low levels and this is more marked in premature babies but also observed in term. After vitamin K application the majority turn to normal levels. In some low levels persisted for a long time even months up to 6 months even more. This may cause wrong diagnosis[13,73,109,178,230,282-284,301,302]. There are also publications, related with new born thrombosis and haemorrhage with different ca-

Table 5. Fibrinogen levels of normal controls and atherosclerosis

Marker	Control (n: 100)	Atherosclerosis (n: 100)	
PF-4 (IU/mL)	4.4 + 1.4	21.8 + 8.4	p< 0.001
ß-TG (IU/mL)	16.1 + 9.3	82.1 + 21.6	p< 0.001

Table 6. von Willebrand factor levels in normal control and atherosclerotics

	Normal control (n: 260)	Atherosclerosis (n: 260)
Fibrinogen (mg%)	207 + 32	363 + 57
	p< 0.001	

uses[35,73,138,178,185, 190,282,284,302].

Molecular alterations and/or polymorphism are demonstrated in the cases of thromboembolism and vascular disorders in Turkey as well in the literature[23,31,36-44,54,58,76,78,82,84,85,87,89,91,92,95-98,110,111,113,114,151,165,173-176,179,182-184,188,189,191,198,202,207,226,230, 231,233]. Among these Leiden anomaly, PT 21020, methylentetrahydrofolate, NO syntase, angiotension converting enzyme (ACE) gene variants, PAI 2 genetic distribution etc. In 1997 Özbek and Tangün mentioned the existence of FV Leiden in Turkish population[37]. According to Akar et al in the cases of MI, CV infarct and DVT, Leiden anomaly was 25% and PT 21020 9%[38]. Gürgey et al showed that 55 out of 142 adult cases with cerebral thrombosis, pulmonary thrombo-embolism, mesenterium thrombosis and DVT had molecular abnormalities such as 35 heterozygous factor V Leiden (24.6%) 6 homozygot cases (4.2%); 9 cases of PT 20210 (6.3%), 5 cases of combined defect of FV Leiden and PT20210A (3.5%)[39]. Gürgey also demonstrated in Azerbaijan 43 healthy cases (18 heterozygote and 1 homozygote) with methylenetetrahydrofolate reductase C677T mutation (MTHFR C667T) and also 6 cases with FV Leiden. These cases were chosen from the general population and had no history of thrombosis[40].

Akar et al demonstrated endothelial NO synthase polymorphism in a Turkish patient with DVT and cerebrovascular accident[41,44]. In another study, Sayhan et al showed a significant difference observed in the cases of MI comparing with normal healthy people and also a deletion of polymorphism in gene encoding ACE gene variants in patients with MI and normal control existed in certain percentage and also significantly different PAI 2 genotype distribution between MI and control group[42,43]. Also deletion polymorphism at the converting enzyme gene in patient with coronary artery disease, PAOD, and carotide atherosclerosis is published[42,43,84, 173, 204] (Table 7).

In another study made in our clinic 35 patients with thromboembolism had 8 Protein S deficiency, 7 APC-resistance, 4 antiphospholipid antibody syndrome, 3 Protein C deficiency and 2 AT-III deficiency[58]. We also presented a family with 2 cases of homozygot AT-III deficiency. Father and mother were relative and in the family there was 4 heterozygous AT-III deficiency[35]. Recently Akar published the results of pediatric cases with molecular alteration with thrombosis in detail[226]. In some cases of thrombosis a mutation of Protein C gene was demonstrated[114,285].

Some molecular abnormality was observed in some of the cases of Buerger disease causing a risk factor for thromboembolism[135]. Among prothrombotic mutations of prothrombin 20210 G-A is higher than others in Buerger diseases. This combination aggravates vascular pathology and possible thrombus formation. Certainly this observation needs further studies.

Vascular alterations, EC disfunction, thrombus formation and alteration in the haemostatic system are among the findings in the disease originally described by Hulusi Behçet in 1937 as a dermatologic disorder[259]. There are same publication related with the alteration of EC function as well hemostatic system in Behçet's disease[60,129,219,251-256].

Thrombosis and hemostasis in antiphospholipid syndrome[90,102,212,261]: Under this title, there are different clinical and laboratory entities such as Lupus anticoagulant, anticardiolipin antibodies, etc. With these antibodies arterial and venous system thrombotic events occur such as cerebrovascular thrombosis, transient cerebral ischaemic attacks, coronary artery thrombosis, retinal thrombosis, venous thrombosis etc. All are acquired phenomenons.

E. In Table 8 the alteration of platelet function and biohemistry is summarized. The subject of platelet release mechanism has been introdu-

ced to the literature in 1956 by Ulutin and Karaca[45,46,124,159,237-239,270,277]. It has been demonstrated by various methods that platelet adhesion, aggregation and secretion increase in atherosclerotic subjects[45,275]. The increase in the platelet adhesiveness and aggregation were more pronounced in the prethrombotic stage and during transient ischaemic attacks. The alterations of platelet in the cases of atherosclerosis with and without thrombosis are as follows: Hyperaggregation, hypersecretion, hyperadhesion and mitogen formation and release[45-47,59,67,70,130,234]. The alteration of platelets was observed during different osmotic resistance tests[236-239,275,277,306].

Platelets do not adhere to normal endothelium but to injured EC and to subendothelium. Platelets also adhere to functionally altered EC. The continuity of heparan sulfate layer on the surface of EC decreases and also PGI 2 formation of EC decrease so more platelets adhere to the EC surface.

Using platelet retention test, it was shown that, more platelets adhere to the foreign surface.

Using Rebuck technique, we measured the differential counts of platelets on formvar membrane using shadow-casting technique of electron microscope[2,4,45-47]. In normals the majority of platelets were in dendritic form 66% and per hundred single platelets only 4.5% small aggregates observed. On the other hand, in the cases of atherosclerosis 12.6% small aggregates and 5.2% gross aggregates existed (Table 9). This is also shown by Marion Barnhart and her group in the cases of transient ischaemia and cerebrovascular disorders[48]. Certain antiaggregating drugs like aspirin normalize this pathologic alteration. Our results of functional and biochemical alterations of platelets from atherosclerotic patients are summarized in Table 8. And also using thin section methods of electronmicroscopy the ultrastructural alterations were of platelets were shown in normals, in pathologic conditions as well under certain drugs[234,277,281]. When platelets adhere to subendothelium they release growth factors including ß-TG, chemotactic substances, antiheparin (PF-4) and also procoagulants (PF-3) which gives them a role in the pathogenesis of atherosclerosis. In the cases of atherosclerosis, main functions of platelets significantly increase[45,46]. This is observed in congenital or acquired form of atherosclerosis. Mammen described a congenital form and named it as “Sticky Platelet syndrome”[49,50]. Increased spontaneous platelet aggration is a risk factor in the thromboembolic complications in vascular disorders[280]. Platelet shows hyperaggregation to the aggregating agents such as adrenalin, ADP, collagen etc. Platelet secretion due to induction increases significantly in the majority of platelets. In some cases platelets already release their materials before the induction with aggregating agents and in these cases platelets circulate as ghost forms[24]. Among secreted and released factors PF-3 is a procoagulant, PF-4 is an antiheparin factor, Smooth muscle proliferative factor is a mitogen factor, and ß-TG is also a mitogen factor. We showed that there is excessive secretion by measuring ADP, PF-4, ß-TG, Platelet Fibrinogen, Platelet alpha-2-antiplasmin etc[45,270,279] (Table 10). Alteration of platelet membrane phospholipids distribution in atherosclerosis was shown[45,51,158,300]. The total amount of membrane phospholipids was increased, but each phospholipid is increased in different rate. Also different results obtained with different release inducers (Table 11).

Some alterations and amount in the substan-

Table 7. ACE patients with MI & controls. ACE gene variants (42,43)

Control in rest (n: 30)	1.42 + 0.38	TXB_2 (P mol/mL)
Atherosclerosis (n: 62) in rest	2.84 + 1.76	TXB_2 (P mol/mL)
After effort angina or Trait-Mill (n: 60)	7.32 + 2.63	TXB_2 (P mol/mL)

Table 8. Functional and biochemical alteration of platelets in the cases of atherosclerosis

	Aggregation per 100 single platelets					
	R	D	I	S	Small	Gross
Normal (n: 22) %	3.2	66.4	20	10.3	4.5	-
Other (n: 23) %	2.1	24.6	25.1	47.4	12.6	5.2
T-test	p= 0.01	p< 0.001	ns	p< 0.001	p< 0.001	

ces stored in granules of platelets have been demonstrated in these group of cases. It has been shown that the level of platelet AT-III, which is stored in platelet granule and is secreted after induction, is lower in the cases atherosclerosis[1,2,4,227,228,235]. In the cases of atherosclerosis, platelet AT-III and cAMP levels were decreased significantly. The decrease of cAMP in unactivated platelets indicate that platelets were already activated in resting condition. So acquired storage pool deficiency occur like chronic low grade DIC[24].

On the otherhand, platelet a2-antiplasmin increases. Together with the alteration of t-PA and PAI 1 resulted a decrease of global fibrinolytic activity in the cases of atherosclerosis. We may also add alteration of PAI 2 in the cases of MI[1,2,4,27,45,46,124,125].

As we demonstrated in 1985, the synthesis of PGF 2a, PGE 2, MDA, and TXA 2, are increased in atherosclerosis compared to normal after induction with collagen and ADP. At the same time platelet cAMP level decreases[1-5,45,46,169,271]. The importance of eicosanoid metabolism on EC and on platelets is recognized (Table 11).

We demonstrated that the active transport of 14C glucose to the platelet and red cell is defective in the cases of atherosclerosis; both diabetic and nondiabetic patients. In the platelets of normal subjects, 14C-glucose is transported across the membrane both by simple diffusion and active energy dependent mechanisms. The specific glucose binding protein is absent or decreased significantly or molecularly altered in the plateler cell membrane of atherosclerotics[1-4,46, 52,59,67,128,130,236]. On the otherhand juvenil diabetic patients does not exibit this defect.

14C glucose normally binds to the protein peak when osmotic shock is done then supernatant is fractioned by chromatography, but it does not bind to a protein and stays as free glucose in atherosclerotic cases with impaired transport.

And also in our laboratury, was studied on the platelet membrane transport of Arachidonic acid, Leucin transport aminoacids transport palmitic acid transport in normal and patients and also the effectsof certain drugs on membrane transport system[244, 245,267-269,281].

Table 9. Differential count of platelets from normal control and atherosclerotics on formvar membrane using electron microscope with shadowcasting technic

	Parents	Young member	Young control
Defective cuff test (%)	82.6	43.7	11.6
Decreased prostacyclin (%)	72.8	31.9	9.8
Hyperadhesion, hyperaggregation and hypersecretion of platelets (%)	85.2	22.4	8.3
Glucose transport defect (%)	84.2	32.3	4.5
Increase of ß-TG, PF-4	89.9	16.7	5.2

Membrane transport is also found defective in the red cell membrane in the cases of atherosclerosis and diabetes mellitus[107,168, 201]. Some drugs such as defibrotide, metformin, gliclazide partially correct this defect and impaired mechanisms. Insulin receptors also decreases in the case of atherosclerosis with or without diabetes mellitus[203-205] (Table 12).

The membrane transport system of Red cell shows some similarity to platelets in normal and pathologic conditions[107,168,201, 248,289].

We also demonstrated that g-glutamyl transferase activity was 50.78 + 3.37 μ/10^8 Platelet for normal control but platelets obtained from atherosclerotic subject g-GT activity decreased to 24.78 + 3.98 μ/10^8 platelets on the other hand there was no in difference glutathion levels[53,62,249].

Platelets obtained from atherosclertic patient produce more lactate and also platelets of atherosclerotic patients contained less glycogen[155,250].

It also shows that galactose transport to the platelet is normal but the incorporation of galactose to the platelets increases protein and this may explain the changes of pattern of membrane glycoprotein in atherosclerosis[66,243,246].

Some of the defects presented above are also found in the young members of atherosclerotic families. Both parents and families had atherosclerotic disease with thrombotic complications such as MI, stroke, POAD etc. Young members of these families had normal fundus oculy, normal levels of serum lipids with normal distributions, and no hypertension. Some of the haemostatic tests showed some abnormalities such as Cuff test, prostacyclin levels, higher aggregation curves, increase of platelet markers and defective glucose transport compared to the control of same age[52,53]. The preliminary studies suggest that the primary alteration is impairement of function of the EC followed by platelet disfunction in these young members between ages 8 to 18 (Table 13).

We are not going to discuss and summarize, the alteration of leucocytes, smooth muscle cells and others in detail in this short review that mainly depends on ours and collaborators results. They already have been partly discussed and published in our earlier publications[3,4,6,9,11,25,27,43,45,46,51,52,59, 67,70,77,127,158,162,163,168,169,193,200,236,244, 249,250,270,277,279,281].

It is not possible to cover every part of the subject even all our work has been done during the last 50 years on the topic related with hemostasis, thrombosis and atherosclerosis. Coagulation, fibrinolysis, platelets, natural inhibitors and haemorrhagic disorders is not covered in this superficial review.

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Table 10. PF-4 and ß-TG levels in normal control and in atherosclerosis

Group	Receptor no	Insulin bound %	Glucose exchange rate (n.mol/mL cell/min.)
Control n: 20	477.10 + 56.46	11.00 + 0.94	1.01 + 0.02
Athero. n: 20	231.10 + 49.77	8.15 + 1.05	0.35 + 0.08
NIDDM n: 15	186.90 +18.50	4.50 + 1.8	0.65 + 0.09

Table 11. The alteration of platelet membrane phospholids in normal subjects and in the cases of atherosclerosis

VIII deficiency	62.5%
von Willebrand disease	16.5%
IX deficiency	11.0%
V deficiency	11.0%
VWD + thrombopathia	1.5%
VII deficiency	1.5%
II deficiency	0.9%
VII and IX deficiency	0.6%
XIII deficiency	0.6%
I deficiency	0.6%
XII deficiency	0.3%
VWD + thrombasthenia	0.3%
Angiohaemophilia	0.3%
Dysfibrinogenemia	0.6%

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Table 12. Red blood cell insulin receptors and glucose exchange rates. In normal controls, in the cases of atherosclerosis and in the cases of NIDDM

ACE genotypes	Patients (n: 66)	Controls (n: 22)
DD	20 (36.3%)	12 (60%)
ID	29 (49.9%)	7 (35%)
II	13 (19.6%)	1(5%)
D	0.583	0.775
I	0.417	0.225

Table 13. Some observations in the young members of atherosclerotics families

	Nonatherosclerotics	Atherosclerotics	
Endogen heparin level	1.64 mg	1.28 mg	p< 0.01
Postheparin (1 mg/kg)	7.97 mg	1.26 mg	p< 0.001

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