Coagulation factor XIII, impaired fibrinolysis and cardiovascular disease

Factorul XIII al coagulării, reducerea fibrinolizei şi bolile cardiovasculare

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Abstract

This review is based on data in the literature also including clinical and laboratory observations reported by one of the review's authors 38 years ago, demonstrating increased plasma factor XIII activity in patients with hyperlipoproteinemia type IIb and type IV displaying features compatible with the concept of metabolic syndrome. Factor XIII activity was correlated with serum triglyceride levels and also with serum cholinesterase activity, a marker of hepatic protein synthesis. Impaired hepatic protein synthesis subsequent to L-asparaginase therapy in leukemic patients led to an important decrease of both plasma factor XIII and serum cholinesterase activities. It was considered that enhanced hepatic synthesis of factor XIII subunit B occurring in such hypetriglyceridemic subjects would assemble with monocyte-derived subunit A of this factor endowed with transglutaminase activity, thereby stabilizing, transporting and increasing the plasma levels of factor XIII (A2B2) zymogen. Increased plasma factor XIII activity was associated with delayed fibrinolysis in such hypertriglyceridemic patients and in vitro inhibition of factor XIII by parachlormercuribenzoate led to an acceleration of clot lysis. High plasma levels and activity of factor XIII were later reported by British authors in insulin resistant patients. It was also demonstrated that in vivo glycation of fibrinogen occurring in diabetic patients would render a plasmin resistant fibrin clot. The presumptive protection against myocardial infarction exerted by the Val34Leu polymorphism in the subunit A of factor XIII incited many studies with rather controversial results, this protective effect being diminished in insulin resistant patients. Factor XIII exerts bivalent effects on atherogenesis, enhancing thrombotic tendency by reducing fibrinolytic activity, while by the crosslinking of extracellular matrix protein exerted by subunit A in monocytes and histiocytes an atheroma's fibrous cap would be strengthened thereby reducing its vulnerability and preventing plaque's rupture.

Keywords: *factor XIII, impaired fibrinolysis, metabolic disorders, cardiovascular disease, factor XIII subunit A Val34Leu polymorphism*

Rezumat

Referatul se bazează pe date din literatură care includ însă şi observaţiile clinice şi de laborator relatate de către unul din autorii referatului în urmă cu 38 de ani şi semnalând creşterea activităţii factorului XIII al coagulării în plasma pacienţilor cu hiperliproteinemie de tip IIb şi IV având caractere compatibile cu conceptul de sindrom metabolic. Activitatea factorului XIII plasmatic s-a corelat cu nivelul trigliceridelor şi cu activitatea

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colinesterazei serice, un marker al sintezei hepatice de proteine. Perturbarea sintezei hepatice de proteine în cursul terapiei cu L-aparaginază a bolnavilor leucemici s-a soldat cu o importantă scădere a activităţii factorului XIII şi a colinesterazei. S-a considerat că stimularea sintezei hepatice de subunităţi B ale factorului XIII în cazul subiecţilor hipertrigliceridemici ar duce la asamblarea acestei subunităţi cu subunitatea A provenită din monocite şi dotată cu activitate transglutaminazică, asigurându-i-se acesteia transportul şi stabilitatea şi crescând nivelul plasmatic de factor XIII (A2B2) zimogen. Creşterea activităţii factorului XIII în plasma pacienţilor dislipidemici s-a soldat cu o încetinire a fibrinolizei, iar inhibarea in vitro a acestui factor cu paraclormercuribenzoat a dus la scurtarea timpului de liză. Creşterea nivelului de factor XIII în plasma pacienţilor insulinorezistenţi a fost semnalată ulterior de către autori britanici. S-a mai arătat că glicarea in vivo a fibrinogenului survenită în cazul bolnavilor diabetici se soldează cu creşterea rezistenţei faţă de plasmină a cheagului de fibrină. Posibilul efect protector faţă de infarctul miocardic, conferit de polimorfismul Val34Leu în subunitatea A a factorului XIII a stimulat elaborarea a numeroase studii cu rezultate destul de controversate, rezistenţa la insulină diminuând în mare măsură presupusul efect protector al alelei Leu 34. Factorul XIII exercită efecte bivalente asupra aterogenezei, pe de o parte contribuind la încetinirea fibrinolizei, iar pe de altă parte, subunitatea A din monocite şi histiocite ar lega transversal proteinele din matricea extracelulară întărind capsula fibroasă a ateromelor, scăzându-le astfel vulnerabilitaea şi prevenind ruptura plăcii ateromatoase.

Cuvinte cheie: *factor XIII, reducerea fibrinolizei, anomalii metabolice, boli cardiovasculare, polimorfismul Val34leu al subunităţii A a factorului XIII*

Introduction

Increasing incidence of necroptically documented myocardial infarction (1) as well as histopathologic studies providing evidence that mural thrombi may be incorporated into the arterial wall (2-4) were suggesting that thrombosis could be involved in the pathogenesis of not only acute coronary syndromes but also in the development and especially in the progression of atherosclerotic lesions. A possible role played by a systemic prothrombotic condition was also suspected, and an inhibition of fibrinolytic activity could be emphasized in hyperlipidemic patients with or without clinically detectable atherosclerotic lesions (5), although plasma lipoproteins were not found to be themselves inhibitors of fibrinolysis (6).

Differences between clot lysis time in hypertriglyceridemic patients and in controls were less obvious when the investigated plasma was substituted by serum added fibrinogen (7,8). Also, because factor XIII had been reported to be involved in the control of fibrinolytic activity (9), the behavior of this factor's activity in hyperlipidemic patients and in several other disease states was studied.

Behavior of plasma factor XIII in several pathologic conditions

By assessing factor XIII activity according to a semiquantitative procedure (10), decreased activities were found in patients with decompensated cirrhosis of the liver and in women with septic abortion, displaying disseminated intravascular coagulation and acute renal failure, while hyperlipidemic patients with or without clinically detectable atherosclerosis displayed values significantly higher than those found in normal weight normolipidemic control subjects (11). Data on low factor XIII activity occurring in liver failure and in consumption coagulopathy were merely confirming the previously reported ones obtained by this procedure (10). By investigating plasma factor XIII activity in relation to the type of hyperlipoproteinemia an increased activity could be noted in patients with type IIb and type IV, in whom increased plasma triglyceride levels were accompanied by high serum cholinesterase activity, a marker of hepatic proteosynthesis. The same results were later obtained when measuring factor XIII activity by a quantitative procedure based on the incorporation of the fluorescent dansylcadaverine into cassein (12). To our knowledge, these studies (11,

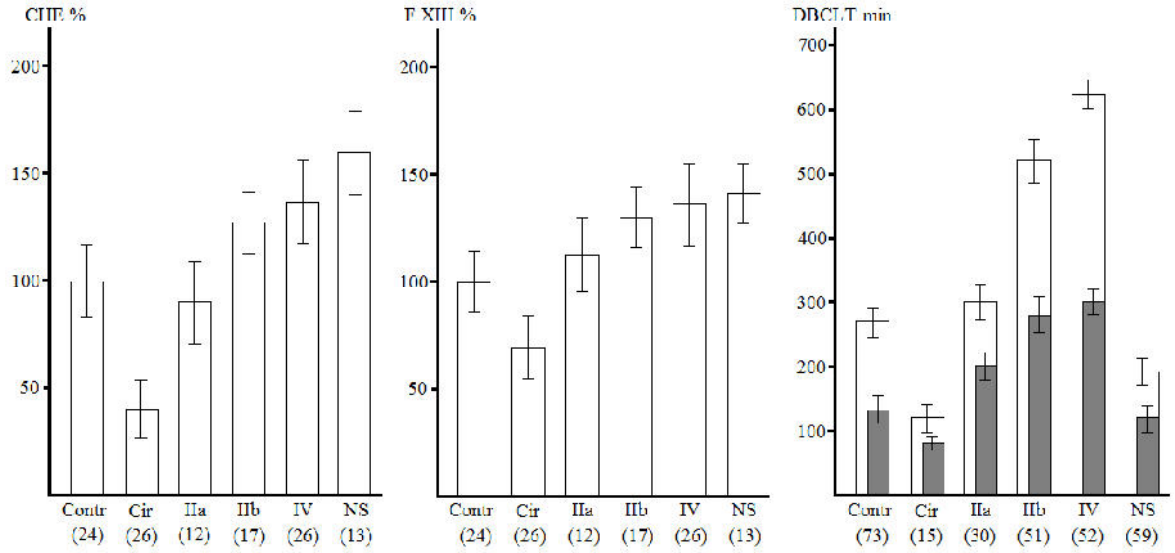

Figure 1. Behavior of serum cholinesterase (CHE) and of plasma factor XIII activities as well as of dilute blood clot lysis time (DBCLT) in healthy, normal weight normolipidemic control subjects (Contr), in patients with decompensated liver cirrhosis (Cir), in various types of hyperliperproteinemia (HLP) and in patients with the nephrotic syndrome (NS). Serum CHE and plasma factor XIII are represented as a percentage of mean normal values, while DBCLT is given in minutes. Mean ± SEM. Number of investigated patients in brackets. The filled gray squares indicate DBCLT in the presence of parachlor-mercuribenzoate (PCMB), an inhibitor of factor XIII activity. According to Cucuianu et al (1979, 1985, 1989).
In a previously published paper (Cucuianu et al 1973) both CHE and factor XIII activities were moderately decreased in patients investigated 4 days after major surgery, while the lowest values of plasma factor XIII were recorded in the 16 women with septic abortion and acute renal failure, in whom a consumption coagulopathy could be documented. Unfortunately DBCLT was not investigated in 1973 in these patients.

13, 14) were among the first ones to report the behavior of a hemostatic variable in relation to the type of hyperlipoproteinemia, emphasizing that the increase of factor XIII occurred mainly in patients with endogenous hypertriglyceridemia known to be associated with an enhanced hepatic synthesis of VLDL and compatible with the concept of metabolic syndrome. High factor XIII activity was found also in patients with the nephrotic syndrome in whom a compensatively accelerated hepatic synthesis of VLDL and of liver secreted proteins is developing (14) (F*igure 1*).

Increased factor XIII levels and activity were later reported in relation to insulin resistance (15-17).

A reduction in factor XIII concentration was reported during the first days of an acute myocardial infarction (18,19), these findings being more recently confirmed in a study assessing factor XIII activity by a photometric procedure (20,21). Noteworthy the rather modest decrease of factor XIII occurring in such patients as well as in postoperative ones were accompanied by a decrease of liver secreted cholinesterase (11,21). A decrease of this serum enzyme which is not involved in hemostasis and is not inactivated or consumed during blood clotting had been reported by other authors (22). Because both acute myocardial infarction and major surgery are known to trigger the acute phase reaction, one may suspect that such a reaction might have led

to a commuted hepatic protein synthesis, when the accelerated synthesis of acute phase proteins reactants is associated with a reduced production of other liver secreted proteins. Actually the acquired factor XIII deficiency occurring during an exacerbated ulcerative colitis or Crohn's syndrome was associated with an increase of C-reactive protein, and a negative (inverse) correlation between this marker of the acute phase reaction and plasma factor XIII levels could be established (23). Noteworthy, efficient thrombolysis attenuating pain and necrosis thereby reducing the acute phase reaction, led to a lesser decrease of factor XIII activity in patients afflicted by a myocardial infarction (24).

The above mentioned findings are supporting the important role played by the liver in the regulation of plasma factor XIII levels. Severe liver disease was actually reported to be one of the main causes of acquired factor XIII deficiency (25,26).

It was also noted that impaired hepatic protein synthesis caused by L-asparaginase therapy in leukemic patients led to an associated decrease of plasma factor XIII and of serum cholinesterase activities, which recovered in an almost parallel manner when this therapy was discontinued (27). It was later specified that this decrease affected especially the factor XIII subunit B (28). Noteworthy orthotopic liver transplantation was followed by a transient decrease of factor XIII activity during the anhepatic phase, this activity progressively recovering after the reperfusion of the grafted liver, the highest activity being however obtained in a sample of perfusate harvested from the graft's vein and taken prior to opening hepato-caval anastomoses (29).

All the above mentioned clinical studies provided circumstantial evidence that plasma factor XIII is produced in the liver. Some more advanced and sophisticated investigations however demonstrated that plasma factor XIII has a complex structure, is synthesized in several types of cells and acts not only on fibrin but also on many other substrates (30).

Factor XIII structure, sites of synthesis and substrates

Factor XIII is the zymogen form of a blood coagulation factor, present in plasma and in cells, whereas activated factor XIII (FXIIIa, plasma transglutaminase, fibrinoligase, fibrin stabilizing factor) belongs to a group of Ca2+ dependent enzymes called endo-γ-glutamine: ε lysine transferases (E.C. 2.3.2.13).

Zymogen exists in two molecular forms. One form is intracellular, found in platelets and monocytes as a dimer of two identical A chains (A2), while the other is extracellular, being found only in the plasma and having two subunits A and two subunits B, the heterotetrametric F XIII(A2B2) zymogen. Subunit A is endowed with enzymatic activity, being provided with cysteine in its active centre. Subunit B has no sulfhydril groups and is lacking enzymatic activity acting as a carrier of F XIII(A2B2) zymogen, increasing its affinity for fibrin and preventing the more labile subunit A from chemical modification (30).

Studies on cultured hepatocytes demonstrated that these cells synthesize subunit B (31), while subunit A appears to be produced in cells originating within bone marrow such as monocytes and megakariocytes (32- 34). Noteworthy the factor XIII (A2B2) is the only sulfhydril enzyme known to function extracellularly. Because the liver secreted B2 subunits bind subunit A, it appears that the liver plays indeed an important role in the regulation of activable factor XIII (A2B2) zymogen plasma levels. It is worth noting that the circulating plasma factor XIII (A2B2) is the first to attach itself to the fibrin of parietal thrombi and be activated by thrombin thereby exerting its activity and preventing a precocious fibrinolysis, and when in excess it would continue to bind α2plasmin inhibitor from the circulation into the fibrin network thus promoting the persistence of the thrombotic material (35). Cellular factor XIII subunit A would be later released from the progressively degrading platelets trapped into thrombi. To be mentioned that at high concentra-

tions of activated factor XIII, resistance to plasmin of highly cross-linked alpha chains of polymerized fibrin may proceed along with the inhibiting effect of α2plasmin inhibitor, thereby enhancing endovascular persistence of fibrin (36).

Intracellular factor XIII subunit A, as well as other intracellular transglutaminases, the most important one being TG2, would preferentially act on protein substrates of the extracellular matrix. It was actually demonstrated that factor XIII subunit A as well as TG2 may crosslink fibronectin to fibrin (37) and fibronectin to collagen (38). Thrombospondin and vitronectin are also substrates for factor XIII A subunit (39, 40). Through these activities transglutaminases including cellular factor XIII would limit the effects of extracellular matrix metalloproteinases (MMPs), which tend to proteolytically degrade the above mentioned matrix.

Transglutaminases and atherosclerosis

By incorporating α2plasmin inhibitor (α2PI) into fibrin and thereby inhibiting fibrinolysis, activated factor XIII favors the persistence of mural thrombi, which would be subsequently incorporated into the arterial wall (2-4).

Evidence was recently provided that activated factor XIII (XIIIa) and TG2 are also involved in "coated platelet" formation which have a higher surface content of α granular proteins including fibrinogen, factor von Willebrand, coagulation factor V and thrombospondin. Such platelets are more adhesive and also acquire a procoagulant activity (41).

Intracellular factor XIII subunit A appears to be involved in another more direct and rather interesting atherogenic mechanism. Evidence was actually provided that angiotensin II would stimulate a factor XIIIA subunit mediated crosslinking of angiotensin receptor type 1 (AT-1 receptor), thereby producing a dimerization of this receptor in human monocytes. The AT-1 dimers are hyperactive and would activate the monocytes which would become more adhesive to endothelium at sites predisposed to atherosclerosis; the penetration of such activated monocytes into the arterial wall is considered to be involved in the onset of atherosclerosis (41). The above mentioned experimental study provides biochemical evidence for the rather popular concept of pathogenically associated diseases linking arterial hypertension and atherosclerosis. More importantly, inhibition of angiotensin converting enzyme (ACE), subsequently reducing the generation of angiotensin II, or blocking the angiotensin receptors as well as inhibition of factor XIII by certain peptides may delay and limit the development of atherosclerosis. Such an effect had been actually achieved in hyperlipidemic apoE deficient mice (42). The above mentioned factor XIII inhibitors were some peptides derived from factor XIIIa and their use is limited to experimental research (43). In contrast to the proatherogenic effects of angiotensin stimulated cellular factor XIII subunit A, the expression of transglutaminase 2 (TG2) into monocytes was found to limit the extension of atherosclerotic lesions (44).

Such different effects on atherogenesis exerted by two enzymes catalyzing the same transglutaminase reaction are surprising. Effects of an enzymatic activity may however differ in relation to different substrates, different sites of action or different stages of a pathological process. Actually TG2 is not activated by angiotensin II and is not effective in forming dimers of AT1 receptors. Also activated factor XIII subunit A would increase the adhesion of monocytes to vascular endothelium favoring their penetration into the arterial wall, being thereby involved in the onset of atherogenesis, while TG2 acts at a later stage and its main action consists in phagocytosis of apoptotic cells and of atheromatosus gruel resulting in a scavenging effect (44).

As previously mentioned circulating factor XIII (A2B2) preferentially acts on fibrin in mural thrombi increasing fibrin crosslinking and inhibiting fibrinolysis by incorporating α2plasmin inhibitor into the fibrin network, while cellular factor XIII A subunit and TG2 from monocytes, Kupffer cells and connective tissue histiocytes are crosslinking extracellular matrix proteins (30, 34).

An impaired transglutaminase activity or a disproportionate increase of metalloproteinases may reduce the fibrous cap's strength of an atheroma thereby increasing its vulnerability and favoring plaque rupture, a main cause of myocardial infarction (45,46).

Evidence was provided that cellular factor XIII subunit A improves endothelial barrier reducing endothelial permeability (47) and would also promote angiogenesis (48). Apparently, cellular factor XIII A subunit's beneficial effects prevail favoring myocardial healing after an infarction. On the other hand, plasma factor XIII activities are mainly related to hemostasis and in certain condition would become prothrombotic.

Impaired clot lysis in type 2 diabetes mellitus

Fibrinogen was isolated and purified by affinity chromatography from plasma of 150 diabetic patients and of 50 healthy control subjects. It could thus be demonstrated that factor XIII mediated incorporation of α2 plasmin inhibitor (α2 PI) into the fibrin resulted by clotting the fibrinogen purified from the diabetic plasma was higher than that recorded in clots prepared from fibrinogen purified from normal plasma added to same amounts of factor XIII, α2 PI thrombin and Ca2+. In a similarly performed experiment it was found that binding of both t-PA and Glu-plasminogen was lower in clots prepared with fibrinogen purified from plasma of patients with type 2 diabetes mellitus. It is of note that impaired fibrinolysis was significantly correlated with the degree of fibrinogen's glycation, as assessed by its content in fructosamine (49). This study demonstrates that fibrin clots are not passive substrates, as they are centrally involved in both activation and regulation of fibrinolysis. Evidence was also provided that increased plasma levels of plasminogen activator inhibitor 1 (PAI-1) may not be the only mechanism responsible for impaired clot lysis in diabetic patients, and that inadequate glycemic control actually contributes to impaired fibrinolytic activity.

Comparative behavior of plasma factor XIII activity and of dilute blood clot lysis time in several selected pathologic conditions

According to clinical observations the main pathogenic link between increased plasma factor XIII activity and thromboatherosclerosis appears to be impaired fibrinolysis. Actually, as shown in fig.1, decreased plasma factor XIII activity occurring in patients with decompensated cirrhosis of the liver was accompanied by an accelerated clot lysis time (50), while the increased activity recorded in patients with hyperlipoproteinemia type IIb and IV was associated with a delayed clot lysis time (50). Neither factor XIII activity nor dilute blood clot lysis time were abnormal in subjects with familial hypercholesterolemia mainly caused by impaired removal of LDL particles and not by an accelerated synthesis of VLDL.

A striking discrepancy between increased plasma factor XIII activity and of plasma fibrinogen (4,42g/l) on one side, and of the significantly accelerated dilute blood clot lysis time on the other side was noted in nephrotic patients. It had however been shown that a potent activation of fibrinolysis as assessed in vitro by using higher concentrations of urokinase (u-PA) would override the inhibitory effect of factor XIII on clot lysis (51). Only moderately increased plasma t-PA antigen and activity were noted in nephrotic patients (52). A better explanation of the accelerated clot lysis recorded in nephrotic patients was provided by data emphasizing that albumin may sterically hinder the formation of the ternary complex

t-PA- fibrin-plasminogen, thereby interfering with plasmin generation. Such interference would not occur in severely hypoalbuminemic nephrotic patients (53).

Role of the Val34 Leu polymorphism within factor XIII subunit A

A common genetic polymorphism represented by the substitution of valine by leucine in position 34 of the factor XIII A subunit (54) was reported to exert a protective effect against

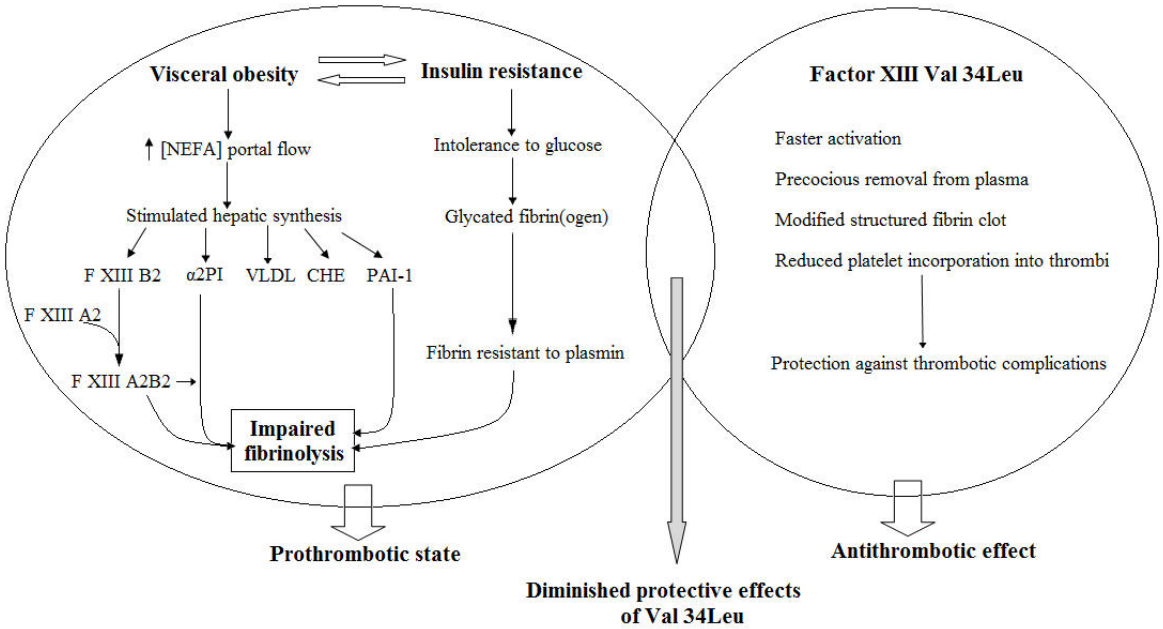

Figure 2. Schematic representation of presumed mechanisms leading to a diminished protective effect of factor XIII Val34Leu polymorphism in insulin resistant patients. Visceral obesity and insulin resistance are accompanied by an enhanced hepatic secretion of VLDL, CHE, factor XIII B2 subunit, plasminogen activator inhibitor-1 (PAI-1) and α2plasmin inhibitor (α2PI), while intolerance to glucose may lead to an in vivo glycation of fibrinogen, so that the resulting fibrin clot becomes resistant to plasmin. Details in text. According to Kohler and Schroder (2002) slightly modified.

myocardial infarction (55). Actually the 34 Leu allele led to accelerated activation of factor XIII by thrombin and produced a fibrin clot, which at high plasma fibrinogen concentrations was characterized by thicker loosely packed fibrin fibers, therefore being more permeable. Such thrombi would be more easily perfused in the circulation and may be more prone to fibrinolysis (56-58). Also a faster activated factor XIII may be precociously inactivated, resulting in a decreased plasma level (59). It was also suggested that a fast and efficient activity of cellular factor XIII A subunit within monocytes and histiocytes would strengthen an atheroma's fibrous cap thereby reducing a plaque's vulnerability and would also favor the sealing and healing of impending plaque fissures. The repeated process of sealing and healing may however incite plaque progression and negative remodeling. It was claimed that fatal rupture may represent an ongoing process of arterial wound healing (60).

Another potentially beneficial effect of an intracellular factor XIII faster activation could be represented by a quicker and more efficient binding of parietal microthrombi to the arterial wall thereby preventing or at least reducing downstream embolization.

The presumed protective effect of the Val 34Leu polymorphism against the thrombotic complications of atherosclerosis stimulated research in this field and among the many publications there were several that did not support this concept. Actually a meta-analysis surveying the results of sixteen studies including 5346 cases and 7053 control subjects showed that the overall risk for coronary heart disease was 18% less in carriers of 34 Leu allele. There was however a considerable heterogeneity among the various

studies that is rather difficult to explain. It was however noted that some of the negative results came from Mediterranean countries (Italy, Spain, Southern France) in which the prevalence of environmental risk factors (climate, diet) is lower than in other populations, so that, presumably in such cases no further protection could be provided by a relatively moderate protective genetic factor (61). It was also noted that the protective effect of the 34 Leu allele in factor XIII A subunit was efficient only at high plasma fibrinogen concentrations (62). Most importantly the presumed protective effect of the Val 34 Leu polymorphism was diminished or even abolished in insulin resistant patients displaying the features of the metabolic syndrome (63) (*Figure 2*).

The development of coronary heart disease involves life-long interactions between genetic and environmental factors that influence an individual's risk for such a disease. The combination of multiple genes effects and environmental factors determine factor XIII level and fibrinolytic activity. The importance of a rather modest effect of a coagulation factor's polymorphism on the thrombotic component of vascular disease should therefore be considered with circumspection (61-65).

Perspectives

There is still much work to be done in order to unravel the more intimate mechanisms leading to increased plasma factor XIII activity and impaired fibrinolysis. A more stringent problem pertains to the possible therapeutic means able to modulate factor XIII activity towards the beneficial effects, while preventing the development of the prothrombotic ones.

Presumably even the most enthusiastic supporters of the factor XIII A subunit 'Val 34Leu polymorphism would not seriously consider a genetic engineering approach. Also because of the bivalent effects of coagulation factor XIII it would be risky to resort to a thorough inhibition of this factor's activity. Because circulating factor XIII (A2B2) zymogen is increased in insulin resistant subjects, a rather widespread pathologic condition, and because plasma factor XIII is more closely related to inhibition of fibrinolysis, a therapy aimed at reducing insulin resistance seems to be more adequate, as it would attenuate the enhanced secretion of liver-derived factor XIII subunit B, thereby normalizing factor XIII (A2B2) zymogen levels, and would also reduce the production of plasminogen activator inhibitor-1 (PAI-1).

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