Hemostasis in chronic renal failure

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Introduction

Hemostasis is a process of blood clot formation at the site of vessel injury. When a blood vessel wall breaks, the hemostatic response must be quick, localized, and carefully regulated. Bleeding or a thrombosis may occur due to missing or dysfunctional moieties of the coagulation or fibrinolytic factors. The pathways of thrombin-stimulated fibrin clot formation and plasmin-induced clot lysis are linked and commonly regulated. When they work in coordinated harmony, a clot is laid down to stop bleeding, followed by eventual clot lysis and tissue repairing. Abnormal bleeding can result from diminished thrombin generation (e.g., due to factor VIII deficiency) or enhanced plasmin formation (e.g., due to alpha-2-antiplasmin deficiency). Conversely, excessive production of thrombin (e.g., due to an inherited thrombophilia) can lead to thrombosis. Clot formation and its subsequent lysis may be decided in the four steps: initiation and formation of the platelet plug, propagation by the coagulation cascade, termination of the clotting by antithrombotic control mechanisms and removal of the clot by fibrinolysis.

In a variety of slowly progressive renal diseases such as chronic glomerulonephritis, diabetic nephropathy, and polycystic kidney disease, it is at present, not possible or very difficult to correct the underlying disease. Eventual progression to renal failure is common in patients with various kidney diseases once the serum creatinine exceeds 1.5 to 2.0 mg/dL. This may occur even if the underlying disorder is "cured". After a certain point, a reduction in the number of functioning nephrons eventually leads to loss of the more normal remaining nephrons. Renal failure may be associated with a variety of signs and symptoms that are collectively referred to as the uremic state. However, the is no predictable correlation between the development of these problems and the severity of renal disease. Loss of renal function results in the accumulation of metabolic waste products and alters the normal homeostatic mechanisms. Potential consequences of these abnormalities are the signs and symptoms of uremia. Using renal replacement therapy in a form dialyses or kidney transplantation, the physician can treat these disturbances and improve the quality of life in many patients with chronic, end-stage renal disease.

Platelet dysfunction in uremia

Platelets are activated at the site of vascular injury to form a platelet plug that provides the initial hemostatic response to stop bleeding. The functional response of activated platelets involves: adhesion – a sticking of platelets to the subendothelial matrix, aggregation – platelet-platelet cohesion, secretion – the release of platelet granule proteins (serotonin, ADP, thrombospondin, fibrinogen, thromboxane A2, growth factors) and procoagulant activity – the enhancement of thrombin generation.

It is likely that multiple factors are responsible for the platelet dysfunction in uremia. Three of the factors that may contribute are the retention of uremic toxins, anemia, and nitric oxide [1]. Platelet dysfunction is observed mainly in advanced uremia before starting dialysis treatment. It is probably related to uremic toxins present in the circulation. The importance of circulating toxins is suggested by commonly seen a beneficial effect of acute dialysis on platelet dysfunction, although the bleeding time is rarely normalized [1]. Urea alone, however, is probably not the major platelet toxin and there is no correlation between blood urea nitrogen and the bleeding time in patients with renal failure [2]. Other potential toxins include guanidinosuccinic acid, phe-

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nolic acid, and middle molecules (mol wt 500 to 3000 Daltons). However, no single compound accumulating in end-stage renal failure has been unequivocally identified as being responsible for platelet dysfunction. *In vitro* studies in which normal platelets are incubated with uremic serum suggest that a dialyzable factor interferes with the binding of fibrinogen to GPIIb-IIIa [3]. Several authors reported that platelet aggregation induced by different stimuli in PRP was depressed in chronic uremia [4,5] whereas other studies provide evidence of hyperaggregability [6-8]. In our previous study, in hemodialyzed (HD) and peritoneally dialyzed (CAPD – chronic ambulatory peritoneal dialysis) patients platelet aggregation in PRP induced by 5 agonists was significantly depressed, whereas platelet aggregation in whole blood (considered as more physiological) did not differ from that in the healthy volunteers. So far, there have been no comprehensive data on platelet aggregation in CAPD subjects. In one report of Arends et al. [9] it was stated that treatment by means of peritoneal dialysis can at least partially correct platelet dysfunction and reverse the bleeding tendency. Kim et al. [10] found that there was a direct link between hypoalbuminemia and increased platelet aggregation in CAPD, which confirmed eaarlier observation of Sloand et al. [11]. Kozek-Langenecker et al. [12] found a decreased expression of fibrinogen binding sites on resting uremic platelets (from hemodialyzed patients) compared with normal platelets as measured by reduced binding of activation-independent monoclonal antibody against platelet GPIIIa. It has been hypothesized that fibrinogen fragments may occupy a percentage of platelet fibrinogen receptors, thus preventing binding of fibrinogen to platelets, a step considered to be essential for aggregation. On the other hand, Himmelfarb et al. [13] found that HD patients had a marked increase in circulating reticulated platelets compared to PD patients or controls, indicating accelerated platelet turnover. Increased platelet activation and turnover may contribute to the qualitative platelet dysfunction in uremia.

Degree of anemia appears to correlate relatively closely with the degree of prolongation of the bleeding time [14], which reflects the impaired platelet-vessel wall interactions. The prolongation of the bleeding time is a common feature of chronic renal failure. It has been proposed that rheologic factors play an important role in the relationship between anemia and platelet dysfunction [14]. At a hematocrit above 30 percent, the red cells primarily occupy the center of the vessel, while the platelets are in a skimming layer at the endothelial surface. This close proximity allows the platelets to adhere and then form a platelet plug when there is an endothelial injury. With anemia, on the other hand, the platelets are more dispersed, thereby impairing adherence to the endothelium. Correction of anemia with blood transfusions or erythropoietin often improves platelet function.

Moreover, nitric oxide (NO; endothelium-derived relaxing factor) produced by endothelial cells and platelets, is a potent inhibitor of platelet aggregation. It has been reported that platelet NO synthesis is increased in uremic patients and that uremic plasma stimulates NO production by cultured endothelial cells [15]. It may be due to elevated blood levels of guanidinosuccinic acid, a uremic toxin that may be a precursor for nitric oxide [16]. Noris et al. [17] suggested that increased NO biosynthesis may contribute to platelet dysfunction and possibly other manifestations of uremic syndrome, including hemodialysis hypotension and administration of an NO synthesis inhibitor normalizes the bleeding time in uremic rats. Nonetheless, up to date controversial results on platelet function in dialyzed patients: impaired or enhanced, have been a matter of debate.

Endothelium in uremia

In renal failure endothelial dysfunction and atherosclerosis are almost universal, as well as cardiovascular complications. Endothelial cell injury is the probable cause due to uremic toxins retention, dyslipidemia, hypertension and secondary hyperparathyroidism as well as increased levels of IL-1 and TNFα. Signs of endothelial dysfunction have been reported in dialyzed patients [18,19-21]. The assessment of endothelial cell injury *in vivo* is complex due to multifunctional nature of these cells. Endothelial damage is an injury response mechanism, which includes impaired endothelium-dependent vasodilation, increased adhesion of platelets and leukocytes. This is a putative first step in atherogenesis. Moreover, exposure of endothelial cells to oxidized LDL *in vitro* releases various adhesion molecules including VCAM (vascular cell adhesion molecule), ICAM (intercellular cell adhesion molecule), selectins and vWF [22], which are considered as markers of endothelial cell injury. On the other hand, vascular endothelium provides effective anticoagulant properties by expressing surface bound proteoglycans, such as thrombomodulin and heparan sulfate, and by releasing coagulation factors inhibitors, such as protein S and tissue factor pathway inhibitor-TFPI [23]. Thus, endothelial dysfunction may be responsible for accelerated atherosclerosis in patients with chronic renal failure. So far, many reports devoted to disturbances in hemostasis and endothelium in hemodialyzed patients [24,25] did not focus on hemostasis and endothelial function in patients on CAPD.

P-selectin, released from activated platelets and endothelial cells may play a very important role in the development of atherosclerosis. However, it has been controversial whether plasma P-selectin concentration reflects activation of platelets or endothelial cells [26]. In our previous study [27], P-selectin did not differ between patients on CAPD and healthy volunteers. Platelet glycoprotein V–GPV shed to blood is considered as a new marker of platelet function. In our previous study we found a similar concentration of GPV in CAPD patients and the healthy volunteers [28].

E-selectin has only been described on endothelial cells and may therefore represent a circulating surrogate for evaluation of endothelial cell activation or damage [29]. In our previous study [27], E-selectin did not differ significantly between all three groups studied in contrast to the study of Bonomini et al. [30], who found elevated E-selectin in undialyzed CRF patients, HD and CAPD subjects. They also showed a strong linear correlation between serum creatinine and serum levels of adhesion molecules: ICAM, VCAM, E-selectin and P-selectin. In our study, we were unable to show such correlations between kidney function and concentration of adhesion molecules [28]. However, concentrations of ICAM, VCAM, TFPI (total, full length and truncated) and thrombomodulin were significantly

higher in CAPD patients when compared to the healthy volunteers. It may be due to the inadequate clearance as well as their enhanced synthesis/release. Jacobson et al. [21] found elevated markers of endothelial dysfunction: vWF, thrombomodulin, and soluble adhesion molecules: ICAM and VCAM, as well as strong correlations between them in dialyzed and nondialyzed patients with chronic renal failure. However, correlations were found in the whole group (10 HD patients, 20 CAPD, 25 with chronic renal failure).

Recent studies indicate that vascular endothelial growth factor (VEGF), the major stimulus of angiogenesis, prompts activated endothelial cells to become prothrombotic. On VEGF stimulation, endothelial cells increase TF expression on their membranes and thereby generate thrombin activity from prothrombin [31]. Moreover, recently Blann et al. [32] suggested that increased VEGF might be evidence of the early stages of atherosclerosis, i.e. increased angiogenesis in response to early injury of the arterial wall. On the other hand, elevated VEGF may just reflect increased turnover of endothelial cells, which are damaged by the disease process [33]. In our previous study, we found elevated VEGF in CAPD patients [28].

Vascular endothelial cells express CD40 and ligation of CD40 on endothelial cell is known to upregulate expression of the inflammatory adhesion molecules: E-selectin, VCAM-1 and ICAM-1 [34]. Slupsky et al. [35] demonstrated that ligation of CD40 on endothelial cells initiated a procoagulant phenotype which included upregulation of tissue factor and down regulation of thrombomodulin. In our previous study [27], we observed a significant rise in CD40 ligand in CAPD patients. Moreover, local ligation of CD40 on endothelial cell in the presence of increased TF concentration, observed in CAPD patients [18] might play a role in the thrombotic complications in these patients.

A novel cell adhesion molecule localized at the endothelial junction is CD146. It is constitutively expressed in all human endothelial cells irrespective of anatomical site or vessel calibers [36,37]. Moreover, an increase of CD146 expression is detectable on HUVEC treated with inflammatory cytokines [37], suggesting that endothelial activation modulates its expression. Recently, Bardin et al. [38] reported an increased plasma CD146 levels in several pathophysiological settings, linked to endothelial junctional alteration, i.e. chronic renal failure. This increase was corroborated by increased expression of CD146 on kidney biopsies from 5 patients with renal failure. Bardin et al. [38] suggested that elevation of CD146 in patients with CRF could be due to an increased release or to its reduced elimination. However, they did not study CD146 correlation with renal function.

Coagulation in uremia

Classically, the intrinsic pathway is initiated by the exposure of blood to a negatively charged surface (such as glass in the aPTT clotting time) and the extrinsic pathway is activated by tissue factor-TF exposed at the site of injury or TF-like material. Both pathways converge on the activation of factor X which then activates prothrombin to thrombin, the final enzyme of the clotting cascade. Thrombin converts fibrinogen from a soluble plasma protein into an insoluble fibrin clot. It is now established that the generation or exposure of TF at the wound site is the primary physiologic event in initiating clotting [39]. TF-induced coagulation plays an important role in the pathophysiology of many diseases including thrombosis, atherosclerosis, ischemia-reperfusion injury, sepsis or glomerulonephritis [40]. Factor VII participates in the initiation of TF pathway-induced coagulation, and an increase in factor VII activity has been recognized as a risk factor for cardiovascular disease, a common finding and a potent cause of mortality in renal patients [41]. The interactions of activated platelets and the clotting cascade, with their subsequent amplification, give rise to a hemostatic response that is rapid and localized to the injury site. It is also potentially explosive, and if unchecked, could lead to thrombosis, vascular inflammation, and tissue damage. Fortunately, antithrombotic pathways are mostly anchored on vascular endothelial cells, which play an active role in maintaining the fluidity of blood. The termination phase involves two circulating enzyme inhibitors, antithrombin (formerly called antithrombin III) and tissue factor pathway inhibitor-TFPI; and, a clotting-initiated inhibitory process, the protein C pathway. Expressed primarily by the microvascular endothelium-TFPI, appears to be the major physiologic inhibitor of TF-induced coagulation [40].

Significant alterations in the plasma levels of coagulation factors and natural anticoagulants have been observed in uremics. In comparison with hemodialyzed patients there are still a limited data concerning hemostasis in CAPD subjects. Indirect evidence of hypercoagulation in HD provide the following laboratory alterations: hyperfibrinogenemia, enhanced: factor VII activity, factor VIII and von Willebrand factor concentration, low: antithrombin III, protein C and S activities, activities of factor II, IX, X and XII despite their normal or elevated plasma concentrations [42,43]. In CAPD a peculiar coagulation profile is observed: hyperfibrinogenemia, elevated activities of factors II, VII, VIII, IX, X, XII, high concentrations of protein S, normal antithrombin III and protein C [44,45]. In our previous study [18] elevated plasma markers of ongoing coagulation – prothrombin fragments 1+2 (F1+2) and thrombin-antithrombin complexes were found in HD and CAPD patients relative to healthy volunteers. Thus, a conversion of prothrombin into thrombin by factor X appears to be more accelerated in CAPD patients, leading to increased fibrin formation. Sagripanti et al. [46] found that elevated prothrombin fragments 1+2 in hemodialyzed patients reflected increased *in vivo* conversion of prothrombin into thrombin rather than impaired renal catabolism or excretion of this polypeptide. Moreover, Kario et al. [47] shown that high plasma prothrombin fragments 1+2 were accompanied by factor VII hyperactivity in hemodialyzed patients, suggesting that increase in F1+2 actually reflected hypercoagulation. Opposite results presented Tomura et al. [48]. According to Kobayashi et al. [44] hypercoagulability and secondary hyperfibrinolysis occur in CAPD patients when compared to healthy volunteers. However, among 21 patients studied by them 19 were treated with rHuEPO (3 were diabetic), therefore, their results are difficult to interprete since erythropoietin affects coagulation and fibrinolysis. As the interactions between TF and factor VII can

trigger coagulation cascade, it is conceivable that the eventual result is increased thrombin generation.

In our previous study we found that concentrations of TF were significantly higher in dialyzed patients (HD, CAPD) when compared to the healthy volunteers as well as TFPI activity [49]. Cella et al. [50] did not observe any differences in TFPI activity between chronically hemodialyzed patients and healthy subjects, whereas Kario et al. [51] reported an increased plasma TFPI activity before dialysis. It could be due to a reduced kidney catabolism or to endothelial cell damage. High TFPI activity in uremia may also reflect endothelial cell injury due to hemodialysis treatment. The increased concentrations of other markers of endothelial cell damage such as vWF and thrombomodulin are in keeping with this concept.

However, in our study [18] vWF concentrations in CAPD subjects were lower than in HD patients. On the other hand, in CAPD patients there are no systemic anticoagulation but TFPI activity is also enhanced. Thus, increased TFPI activity before dialysis session in HD patients seems unlikely to be due to the effects of residual heparin from the previous dialysis session. TFPI is a potent inhibitor of the factor VIIa/TF complex in the presence of factor Xa, as well as being a direct inhibitor of factor Xa [40]. This high level of TFPI might thus counterbalance the increased activity of factor VII in uremia and may be considered as a defence mechanism against hypercoagulable state.

Fibrinolysis in uremia

To restore vessel patency following hemostasis, the clot must be organized and removed by plasmin in conjunction with wound healing and tissue remodeling. Fibrin binds plasminogen, the precursor molecule to plasmin, and tissue plasminogen activator (tPA). It leads to formation of active, proteolytic plasmin [52,53], which cleaves the polymerized fibrin strand at multiple sites, releasing fibrin degradation products (FDPs), i.e. D-dimers. The plasminogen/plasminogen-activator system is complex, paralleling the coagulation cascade [54]. Plasmin activity is regulated by vascular endothelial cells that secrete both plasminogen activators (tissue-type plasminogen activator and urokinase-type plasminogen activator) and plasminogen activator inhibitors (PAI-1 and PAI-2). Balance between tPA and PAI is the major determinant of the overall fibrinolytic activity. When fibrin is degraded by plasmin, new carboxy-terminal lysines are exposed in the partially digested clot. These residues provide additional sites for plasminogen binding to the clot, creating a positive feedback loop in the clot lysis. The carboxy-terminal lysines are susceptible to removal by carboxypeptidases [55,56]. Thrombin Activatable Fibrinolysis Inhibitor–TAFI, a proenzyme form of carboxypeptidase-B is a newly recognized physiologic substrate for the thrombin-thrombomodulin (TTM) complex [57]. Therefore, it couples two distinct in function systems: coagulation and fibrinolysis. Activated TAFI delays clot lysis.

In dialyzed patients both impaired overall fibrinolytic activity and hyperfibrinolysis have been reported [18,44,58]. Therefore, the question arises, whether activation of fibrinolysis is primary or secondary. Tomura et al. [48] found increased tissue plasminogen activator-tPA and decreased its inhibitor-PAI-1 in 17 HD patients when compared to 17 CAPD subjects. In CAPD patients overall fibrinolytic activity as reflected by prolonged ECLT is depressed when compared to HD subjects. Moreover, plasmin-antiplasmin complexes have been found to be elevated or normal in dialyzed patients [58,59]. It may suggest only local activation of fibrinolysis. According to Lane at al. [60] and others [43-45,59,61] in hemodialyzed and peritoneally dialyzed patients, hyperfibrinolysis is secondary to activation of coagulation cascade. At the same time, overall fibrinolytic activity is impaired [5,62,63]. In our previous study [18] we found that in CAPD patients overall fibrinolytic activity as reflected by prolonged ECLT was depressed when compared to HD subjects. Moreover, plasmin-antiplasmin complexes are lower in CAPD than in HD. However, FAI (fibrinolytic activity index = fibrinogen/ECLT) was significantly higher in non-diabetic CAPD patients when compared to non-diabetic HD subjects. Nakamura et al. [64] reported that HD patients exhibited a high PAP levels but a low plasmin activity. Moreover, Tomura et al. [48] showed lack of correlation between PAP and tPA or PAI in HD. It may be due to the fact that PAP complexes are not sensitive markers of plasmin generation in dialyzed subjects. Opatrny et al. [62] reported a fibrinolysis defect manifesting after standard fibrinolytic stimulus (DDAVP-1-deamino-8-D-arginine vasopressin) by an insufficient decrease in PAI-1 concentration in patients with type 2 diabetes mellitus maintained on chronic hemodialysis. On the other hand, Babazono et al. [63] compared coagulation and fibrinolysis in 23 diabetic patients on long-term CAPD with hemodialyzed diabetic patients. They found that CAPD patients had higher fibrinogen and von Willebrand factor as well as serum lipids relative to HD patients. They concluded that CAPD was associated with more atherogenic lipid profile than were on hemodialyses and with hypercoagulable state but not with decreased fibrinolysis state. We have reported for the first time that TAFI concentration and activity in dialyzed patients with diabetic nephropathy was significantly higher that in the relevant groups of dialyzed patients without diabetic nephropathy [65]. Previously, we found that TAFI concentrations were significantly higher in CAPD [66] as well as in kidney transplant recipients [67], two populations of kidney patients with decreased fibrinolytic activity and a hypercoagulable state. Differences in TAFI concentration and activity between HD and CAPD patients were at the level of statistical significance ($p=0.09$ and $p=0.07$, respectively).

Conclusions

Disturbances in hemostasis are common complications of kidney diseases. Their occurrence and severity correlate quite well with the progressive loss of renal function to end-stage renal disease. Both bleeding diathesis and thromboembolism have been identified [14]. The principal cause of these abnormalities is the uremic state and as a rule, it is at least partially reversible with the institution of adequate renal replacement therapy. The pathogenesis of uremic bleeding is multifactorial. It has been attributed to: platelet dysfunction, abnormal platelet-vessel wall interactions and altered rheological properties of the blood flow [4,68,69]. The most important determinants

Table 1. **Some hemostatic parameters in HD and CAPD patients**

	HD	CAPD
Fibrinogen	↑	↑↑
F II activity	↓	↑
F VII activity	↑	↑
FVIII activity	↓	↑
F IX activity	↓	↑
F X activity	↓	↑
F XII activity	↓	↑
Protein C activity	↓	↔
Protein S activity	↓	↑
antithrombin	↓	↔
vWF	↑	↑
thrombomodulin	↑	↑
TF	↑	↑
TFPI	↑	↑
F1+2	↑	↑
TAT	↑	↑
PAP	↑	↑
t-PA	↑	↓
PAI-1	↓	↑
TAFI	↔	↑

of the pathogenesis of the prothrombotic state in uremia are: increased levels of clotting factors and decreased levels of clotting inhibitors, hyperfibrinogenemia, diminished fibrinolytic activity, and platelet hyperaggregability (*Tab. 1*). At present, the incidence of bleeding is apparently declining, whereas thrombotic complications have become the predominant causes of mortality [41]. The intensity of hypercoagulability is thought to be related to the degree of hypoalbuminemia, being more evident at serum albumin levels of <2g/dL, with an implicated participatory role of the associated hypertriglyceridemia and changes in arachidonic acid metabolism that accompany the metabolic response to hypoalbuminemia [70].

References

1. Rabelink, TJ, Zwaginga, JJ, Koomans, HA, Sixma, JJ. Thrombosis and hemostasis in renal disease. Kidney Int, 1994; 46: 287-96.
2. Steiner, RW, Coggins, C, Carvalho, ACA. Bleeding time in uremia: A useful test to assess clinical bleeding. Am J Hematol, 1979; 7: 107-17.
3. Gawaz MP, Dobos G, Spath M, Schollmeyer P, Gurland HJ, Mujais SK. Impaired function of platelet membrane glycoprotein IIb-IIIa in end-stage renal disease. J Am Soc Nephrol, 1994; 5: 36-46.
4. di Minno G, Martinez J, McKean M, de la Rosa J, Burke JF, Murphy S. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. Am J Med, 1985; 79: 552-9.
5. Panicucci F, Sagripanti A, Pinori E, Vispi M, Lecchini L, Barsotti G, Giovanetti S. Comprehensive study of hemostasis in chronic uremia. Nephron, 1983; 33: 5-8.
6. Viener A, Aviram M, Better OS, Brook JG. Enhanced in vitro platelet aggregation in hemodialysis patients. Nephron, 1986; 43: 139-43.
7. Remuzzi G, Benigni A, Dodesini P, Schieppati A, Gotti E, Livio M, Mecca G, Donati B, de Gaetano G. Platelet function in patients on maintenance hemodialysis: Depressed or enhanced? Clin Nephrol, 1992; 17: 60-3.
8. Nakamura Y, Masui N, Nakagawa S. Evaluation of the platelet function of chronically uremic patients on regular dialysis treatment by platelet sensitivity test. J Jpn Soc Dial Ther, 1989; 22: 1341-5.
9. Arends JP, Krediet RT, Boeschoten EW, van der Lelie J, Veenhof CH, von dem Borne AE. Improvement of bleeding time, platelet aggregation and platelet count during CAPD treatment. Proc Eur Dial Transplant Assoc, 1981; 18: 280-3.
10. Kim SB, Chi HS, Park JS, Hong CD, Yang WS. Effect of increasing serum albumin on plasma D-Dimer, von Willebrand factor, and platelet aggregation in CAPD patients. Am J Kidney Dis, 1999; 33: 312-7.
11. Sloand EM, Bern MM, Kaldany A. Effect on platelet function of hypoalbuminemia in peritoneal dialysis. Thromb Res, 1986; 44: 419-25.
12. Kozek-Langenecker SA, Masaki T, Mohammad H, Green W, Mohammad SF, Cheung AK. Fibrinogen fragments and platelet dysfunction in uremia. Kidney Int, 1999; 56: 299-305.
13. Himmelfarb J, Holbrook D, McMonagle E, Ault K. Increased reticulated platelets in dialysis patients. Kidney Int, 1997; 51: 834-9.
14. Eberst E, Berkowitz LR. Hemostasis in renal disease: Pathophysiology and management. Am J Med, 1994; 96: 168-79.
15. Remuzzi G, Perico N, Zoja C, Corna D, Macconi D, Vigano G. Role of endothelium-derived nitric oxide in the bleeding tendency of uremia. J Clin Invest, 1990; 86: 1768-71.
16. Noris, M, Remuzzi, G. Uremic bleeding: Closing the circle after 30 years of controversies? Blood, 1999; 94: 2569-74.
17. Noris M, Benigni A, Boccardo P, Aiello S, Gaspari F, Todeschini M, Figliuzzi M, Remuzzi G. Enhanced nitric oxide synthesis in uremia: Implications for platelet dysfunction and dialysis hypotension. Kidney Int, 1993; 44: 445-50.
18. Małyszko J, Małyszko JS, Myśliwiec M. Comparison of hemostasis between CAPD and HD patients. Perit Dial Int, 2001; 21: 158-65.
19. Kawaguchi Y, Kubo H, Yamamoto H, Nakayama K, Shigematsu T, Sakai O. Is atherosclerosis accelerated by CAPD? Perit Dial Int, 1996; 16 (Suppl 1): S23-S30.
20. Kuriyama S, Tomonari H, Yoshida H, Hikita M, Sakai O. Endothelial cell dysfunction in patients with impaired renal function. Nippon Jinzo Gakkai Shi, 1996; 38: 372-8.
21. Jacobson SH, Egberg N, Hylander B, Lundahl J. Correlation between soluble markers of endothelial dysfunction in patients with renal failure. Am J Nephrol, 2002; 22: 42-7.
22. Bolton CH, Downs LG, Victory JG, Dwight JF, Tomson CR, Mackness MI, Pinkney JH. Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and proinflammatory cytokines. Nephrol Dial Transplant, 2001; 16: 1189-97.
23. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med, 1998; 340: 115-26.
24. Bombeli T, Mueller M, Haeberli A. Anticoagulant properties of the vascular endothelium. Thromb Haemost, 1997; 77: 408-23.
25. Gris JC, Branger B, Vecina F, Sabadani B, Fourcade J, Schved JF. Increased cardiovascular risk factors and features of endothelial activation and dysfunction in dialyzed uremic patients. Kidney Int, 1994; 46: 807-13.
26. Małyszko JS, Małyszko J, Pawlak D, Pawlak K, Buczko W, Myśliwiec M. Serotonergic mechanism are involed in the pathogenesis of thrombotic complication in rHuEPO-treated hemodialyzed patients. Nephron, 2000; 75: 612-8.
27. Ishiwata N, Takio K, Katayama M, Watanabe K, Titani K, Ikeda Y, Handa M. Alternatively spliced isoform of P-selectin is present in vivo as soluble molecule. J Biol Chem, 1994; 38: 23708-15.
28. Małyszko J, Małyszko JS, Myśliwiec M. Endothelial cell injury markers in chronic renal failure on conservative treatment and continuous ambulatory peritoneal dialysis (CAPD). Kidney Blood Press Res, 2004, 27: 71-7.
29. Gearing AJH, Hemingway I, Piggott R, Hughes J, Rees AJ, Cashman SJ. Soluble forms of vascular adhesion molecules. E-selectin, ICAM-1 and VCAM-1: Pathological significance. Ann NY Acad Sci, 1992; 667: 324-31.
30. Bonomini M, Reale M, Santarelli P, Stuard S, Settefrati N, Albertazzi A. Serum levels of soluble adhesion molecules in chronic renal failure and dialysis patients. Nephron, 1998; 79: 399-407.
31. Zucker S, Mirza H, Conner CE. Vascular endothelial growth factor induces tissue factor and matrix metalloproteinase production in endothelial cells: conversion of prothrombin to thrombin results in progelatinase-A activation and cell proliferation. Int J Cancer, 1998; 75: 780-5.
32. Blann AD, Belgore FM, Constans J, Conri C, Lip GYH. Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and atherosclerosis and the effects of fluvastatin and fenofibrate. Am J Cardiol, 2001; 87: 1160-3.
33. Blann AD, Lip GYH. The endothelium in atherothrombotic disease: assessment of function, mechanisms and clinical implications. Blood Coagul Fibrinol, 1998; 9: 297-306.

34. Karmann K, Min W, Fanslow WC, Pober JS. Activation and homologous desensitization of human endothelial cells by CD 40 ligand, tumor necrosis factor, and interleukin 1. J Exp Med, 1996; 184: 173-82.

35. Slupsky JR, Kalbas M, Willuweit A, Henn V, Kroczek RA, Muller-Berghaus G. Activated platelets induce tissue factor expression on human umbilical vein endothelial cells by ligation of CD 40. Thromb Haemost, 1998; 80: 1008-14.

36. Bardin N, Frances V, Lesaule G, Horschowski N, George F, Sampol J. Identification of the S-Endo 1 endothelial-associated antigen. Biochem Biophys Res Commun, 1996; 218: 210-6.

37. Bardin N, George F, Mutin M, Brisson C, Horschowski N, Frances V, Lesaule G, Sampol J. S-Endo 1, a pan-endothelial monoclonal antibody recognizing a novel human endothelial antigen. Tissue Antigens, 1996; 548: 531-9.

38. Bardin N, Moal V, Anfosso F, Daniel L, Brunet P, Sampol J, Dignat George F. Soluble CD146, a novel endothelial marker, is increased in physiopathological settings linked to endothelial junctional alteration. Thromb Haemost, 2003; 90: 915-20.

39. Rapaport, SI, Rao, LV. The tissue factor pathway: How it has become a "prima ballerina". Thromb Haemost, 1995; 74: 7-17.

40. Broze GJ Jr. Tissue factor pathway inhibitor. Thromb Haemostas, 1995; 74: 90-3.

41. Locatelli F, Del Vecchio L, Manzoni C. Morbidity and mortality on maintenance hemodialysis. Nephron, 1998; 80: 380-400.

42. Małyszko J, Małyszko JS, Pawlak D, Pawlak K, Buczko W, Myśliwiec M. Platelet function, hemostasis and serotonin in acute and chronic renal failure. Thromb Res, 1996; 83: 351-61.

43. Vaziri ND, Gonzales ED, Wang J, Said S. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stge renal disease: Effect of hemodialysis. Am J Kidney Dis, 1994; 23: 828-35.

44. Kobayashi M, Yorioka N, Yamakido M. Hypercoagulability and secondary hyperfibrinolysis may be related to abnormal lipid metabolism in patients treated with continuous ambulatory peritoneal dialysis. Nephron, 1997; 76: 56-61

45. Vaziri ND, Shah GM, Winer RL, Gonzales E, Patel B, Alikhani S, Nguyen QX, Yamamoto J. Coagulation cascade, fibrinolytic system, antithrombin III, protein C and protein S in patients maintained on continuous ambulatory peritoneal dialysis. Thromb Res, 1989; 53: 173-80.

46. Sagripanti A, Cozza V, Baicchi U, Camici A, Cupisti A, Barsotti G. Increased thrombin generation in patients with chronic renal failure. Int J Clin Lab Res, 1997; 27: 72-5.

47. Kario K, Matsuo T, Yamada T, Nakao K, Shimano C, Matsuo M. Factor VII hyperactivity in chronic dialysis patients. Thromb Res, 1992; 67: 105-9.

48. Tomura S, Nakamura Y, Doi M, Ando R, Ida T, Chida Y, Ootsuka S, Shinoda T, Yanagi H, Tsuchiya S, Marumo F. Fibrinogen, coagulation factor VII, tissue plasminogen activator, plasminogen activator inhibitor-1, and lipid as cardiovascular risk factors in chronic hemodialysis and continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis, 1996; 27, 848-54.

49. Małyszko J, Małyszko JS, Myśliwiec M. TF and TFPI in CAPD and HD. Nephrol Dial Transplant, 1998; 13, 2424-6.

50. Cella G, Vertolli U, Naso A, Vianello A, Rampin E, Sbarai A, Boeri G, Strauss WE. Tissue factor pathway inhibitor (TFPI) activity in uremic patients during hemodialysis. Thromb Res, 1996; 81: 671-7.

51. Kario K, Matsuo T, Yamada T, Matsuo M. Increased tissue factor pathway inhibitor levels in uremic patients on regular hemodialysis. Thromb Haemostas, 1994; 71: 275-9

52. Collen D. On the regulation and control of fibrinolysis. Edward Kowalski Memorial Lecture. Thromb Haemost, 1980; 43: 77-89.

53. Hoylaerts, M, Rijken, DC, Lijnen, HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. J Biol Chem, 1982; 257: 2912-9.

54. Kolev K, Machovich R. Molecular and cellular modulation of fibrinolysis. Thromb Haemost, 2003; 89: 610-21.

55. Nesheim M. Fibrinolysis and the plasma carboxypeptidase. Curr Opin Hematol, 1998; 5: 309-13.

56. Redlitz A, Tan AK, Eaton DL, Plow EF. Plasma carboxypeptidases as regulators of the plasminogen system J Clin Invest, 1995; 96: 2534-8.

57. Booth NA. TAFI meets the sticky ends. Thromb Haemost, 2001; 85: 1-2.

58. Haznedaroglu IC, Erdem Y, Dundar S, Caglar S, Kirazli S. TAT and PAP in hemodialysis patients: two cats in a bag? Thromb Res, 1995; 80: 447-9.

59. Ishii Y, Yano S, Kanai H, Maezawa A, Tsuchida A, Wakamatsu R, Naruse T. Evaluation of blood coagulation-fibrinolysis system in patients receiving chronic hemodialysis. Nephron, 1996; 73: 407-12.

60. Lane DA, Ireland H, Knight I, Wolff S, Kyle P, Curtis JR. The significance of fibrinogen derivates in plasma in human renal failure. Br J Haematol, 1984; 56: 251-60.

61. Alwakeel J, Gader AM, Hurieb S, al-Momen AK, Mitwalli A, Abu Aisha H. Coagulation inhibitors and fibrinolytic parameters in patients on peritoneal dialysis and haemodialysis. Int Urol Nephrol, 1996; 28: 255-61.

62. Opatrny K Jr, Zemanova P, Mares J, Vit L, Opatrna S, Sefrna F, Hejda V, Tomsu M, Eiselt J, Massry SG. Fibrinolysis defect in long-term hemodialysis patients with type 2 diabetes mellitus and its relation to metabolic disorder. Am J Nephrol, 2002; 22: 429-36.

63. Babazono T, Miyamae M, Tomonaga O, Omori Y.Cardiovascular risk factors in diabetic patients undergoing continuous ambulatory peritoneal dialysis. Adv Perit Dial, 1996; 12: 120-5.

64. Nakamura Y, Tomura S, Tachibana K, Chida Y, Marumo F. Enhanced fibrinolytic activity during the course of hemodialysis. Clin Nephrol, 1992; 38: 90-6.

65. Małyszko J, Małyszko JS, Hryszko T, Myśliwiec M. Thrombin Activatable Fibrinolysis Inhibitor (TAFI) and markers of endothelial cell injury in dialyzed patients with diabetic nephropathy. Thromb Haemost, 2004; 91: 480-6.

66. Hryszko T, Malyszko J., Małyszko JS, Brzósko S, Myśliwiec M. Patients on peritoneal dialysis but not on hemodialysis have elevated concentration and activity of Thrombin Activatable Fibrinolysis Inhibitor. Thromb Res, 2001; 104: 322-8.

67. Hryszko T, Małyszko J, Małyszko JS, Brzósko S, Pawlak K, Myśliwiec M. A possible role of thrombin activatable fibrinolysis inhibitor in disturbances of fibrinolytic system in renal transplant recipients. Nephrol Dial Transplant, 2001; 16: 1692-6.

68. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A. Defective platelet adhesion on vessel subendothelium in uremic patients. Blood, 1986; 68: 337-42.

69. Livio M, Marchesi E, Remuzzi G, Gotti E, Mecca G, de Gaetano G. Uremic bleeding: Role of anemia and beneficial effect of red cell transfusions. Lancet, 1982; 11: 1013-5.

70. Gandrille S, Aiach M. Albumin concentration influences fibrinolytic activity in plasma and purified systems. Fibrinolysis, 1990; 4: 225-32.