Chapter 5

Thromboembolism in Renal Diseases

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Additional information is available at the end of the chapter

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Abstract

Patients with renal diseases are prone to both thrombosis and bleeding, as they have profound changes in all three classic components of coagulation, defined approximately 150 years ago by Virchow: blood flow, vessel wall (endothelial injury), and coagulation properties of the blood (e.g., coagulation and fibrinolytic systems and platelets). The prothrombotic state in chronic kidney disease (CKD), glomerular diseases (including systemic lupus and vasculitis), and some less frequent conditions (idiopathic retroperitoneal fibrosis, antiphospholipid syndrome, hemolytic-uremic syndrome, etc.) is associated with vascular endothelial damage, increase in certain coagulation and antifibrinolytic factors, decrease in anticoagulation proteins, dyslipidemia, hypoalbuminemia, changes in platelet membranes, hemo- and peritoneal dialysis and heparin treatment, increased microRNAs and circulating microparticles, antiphospholipid antibodies, nephrotic syndrome, anemia with high platelet count, and so on. Nevertheless, the same patients have substantially increased risk of bleeding due to platelet dysfunction and intake of certain medications (antiaggregants, heparin and low-molecular weight heparins, and anemia). The aim of this review is to present the main thrombo-embolic risk factors in a wide variety of patients with renal diseases, including chronic glomerulonephritis (primary and secondary), chronic renal disease, and idiopathic retroperitoneal fibrosis. We have evaluated the risk factors for arterial and venous thromboses in a wide variety of renal patients with both glomerular and non-glomerular diseases, including the presence of nephrotic syndrome, inborn and acquired coagulation defects (i.e., factor V Leiden, MTHFR gene mutation, 20210 prothrombin gene mutation, and antiphospholipid antibodies), corticosteroid treatment, and dyslipidemia. We are describing the results of these investigations and suggesting prophylactic anticoagulant strategies in such patients. Multiple risk factors influence the coagulation system in renal disease leading to both hypercoagulation and hemorrhagic diathesis. Therefore, renal patients should be thoroughly investigated for coagulation abnormalities, especially if pathogenic (i.e., corticosteroid and immunosuppressive) and anticoagulation treatment is to be initiated. Moreover, the doses of anticoagulant/antiaggregant and hemostatic medications should be considered carefully, having in mind the underlying diseases and risk factors, renal function, and concomitant treatment.

Keywords: thromboembolism, glomerulonephritis, retroperitoneal fibrosis, coagulation, anticoagulation

1. Introduction

Patients with renal diseases are prone to both thrombosis and bleeding, as they have profound changes in all three classic components of coagulation, defined approximately 150 years ago by Virchow: blood flow, vessel wall (endothelial injury), and coagulation properties of the blood (e.g., coagulation and fibrinolytic systems, platelets). In this aspect, chronic kidney disease (CKD) is a unique state with the simultaneous presentation of both thrombophilia and hemorrhagic diathesis.

The *prothrombotic state* in CKD, glomerular diseases (including systemic lupus and vasculitis), and some less frequent conditions (idiopathic retroperitoneal fibrosis (RPF), antiphospholipid syndrome (APS), hemolytic-uremic syndrome, etc.) is associated with [1–10]:

- vascular endothelial damage,
- increase in certain coagulation and antifibrinolytic factors,
- decrease in anticoagulation proteins,
- dyslipidemia,
- nephrotic syndrome and hypoalbuminemia,
- changes in platelet membranes,
- hemo- and peritoneal dialysis (PD) and heparin treatment,
- increased microRNAs and circulating microparticles (MPs),
- antiphospholipid antibodies,
- anemia with high platelet count, and so on.

Nevertheless, the same patients have *substantially increased risk of bleeding* due to [6–8]:

- platelet dysfunction,
- impaired platelet-vessel wall interactions,
- intake of certain medications (antiaggregants, heparin and low-molecular weight heparins (LMWHs), and anemia),
- vascular wall abnormalities,
- accompanying disease and conditions (i.e., anemia, myeloma, amyloidosis, etc.), and
- dialysis treatment.

2. Overview of coagulation abnormalities in renal diseases

Renal diseases have high prevalence among the population worldwide. On the other hand, thrombo-embolic complications, including large vascular thromboses (stroke and myocardial infarction and peripheral arterial disease), deep vein thrombosis (DVT) and pulmonary embolism (PE), venous access thromboses, placental thromboses, thromboses of retinal vein and/or arteries, and so on, are also very prevalent in adults, especially in the groups > 65 years of age. Due to the specific metabolic, vascular, plasma, and platelet changes and at the background of inborn hemostasis and bleeding disorders, renal diseases can be associated with both hypercoagulation (thrombophilia) and bleeding (hemorrhagic diathesis) [3–7]. Moreover, CKD itself, irrespective of its underlying cause, is a major risk factor for thromboembolic complications [4–8, 10].

2.1. Hypercoagulation

The underlying mechanism of *thrombophilia* in renal disease, including CKD and chronic renal failure (CRF), is associated with platelet abnormalities, coagulation cascade changes, anemia, endothelial dysfunction and damage, circulating microparticles and miRNAs, atherosclerosis, inborn (protein S and C and anti-thrombin III deficiency, 20210 prothrombin gene mutation, methylene tetrahydrofolate reductase (MTHFR) gene mutation, factor V Leiden, etc.) and acquired thrombophilia (antiphospholipid syndrome and nephrotic syndrome), intake of certain medications and illicit drugs (including corticosteroids, cocaine, heparin, etc.), and dialysis [6–8, 10]. All these changes could be summarized as: increased platelet activation/aggregation, activated coagulation and decreased endogenous anticoagulation, and decreased fibrinolysis.

2.1.1. Platelet abnormalities/dysfunction

In catabolic patients, especially on peritoneal dialysis, it has been shown that decreased plasma levels of nitric oxide (NO) and L-arginine are associated with increased platelet aggregation. Moreover, the increase of phosphatidylserine on platelet surface in CKD/CRF leads to activation of caspase-3 and binding of factor V with subsequent thrombin formation. Besides, CKD/CRF patients have increased PAC-1 fibrinogen receptor and circulating P-selectin that lead to formation of platelet-leukocyte aggregates and formation of free oxygen radicals leading to increased tendency toward thrombosis.

In dialysis, especially in peritoneal dialysis (PD), hypoalbuminemia is thought to lead to platelet activation.

It should be mentioned that in CKD/CRF, there are other functional platelet abnormalities associated with increased bleeding tendency, including decreased GPIb on platelet surface, suppressed function of GPIIb/IIIa, inhibited platelet aggregation changes in platelet alpha-granules, changes in calcium levels, abnormalities in prostaglandin and arachidonic acid metabolism, increased circulating fibrinogen fragments, uremic toxins that inhibit both thrombopoiesis in

the bone marrow and platelet aggregation, amyloid deposition in the vessel walls and bone marrow inhibits platelet-vessel wall interactions and thrombopoiesis, and so on.

Paradoxically, in patients with CRF, the described platelet adhesion defects are accompanied by hypercoagulation due to endothelial damage and increased coagulation factor levels and activity plus decreased fibrinolytic activity.

2.1.2. Coagulation cascade abnormalities

CKD/CRF is a well-known pro-inflammatory state with increased acute-phase proteins (including C-reactive protein [CRP] and coagulation factors, i.e., fibrinogen) and interleukin 6 (IL-6), increased plasma tissue factor (TF) levels, increased nuclear factor kappa-B (NF-kB) and PAR-1 receptor, decreased levels and activity of anti-thrombin III. On the other hand, in CKD and CRF, marked activation of rennin-angiotensin-aldosterone system (RAAS) is described with increase in plasma fibrinogen levels and plasminogen activator inhibitor 1 (PAI-1). The latter mechanism is associated with both prothrombotic state and progression of CKD itself and closes a vicious circle of CKD—hypertension and prothrombotic state—CKD progression and thrombosis, leading to further worsening of CKD and thromboses.

In (auto)immune renal diseases, hypercoagulability state is due to increased acute-phase proteins and coagulation cascade factors plasma levels and vascular wall/endothelial abnormalities with or without concomitant platelet count and/or activation changes.

2.1.3. Anemia

Anemia in CKD is due to erythropoietin deficiency, iron deficiency due to malabsorption of iron + chronic gastrointestinal tract (GIT) bleeding + intake of medications + folic acid and B12 deficiency + chronic inflammation and hypercatabolic state. Anemia is associated with both thrombophilia (especially in cases with chronic bleeding and compensatory increase in platelet count) and bleeding tendency (due to affection of platelet-vessel wall interaction, decreased release of adenosine diphosphate (ADP) and decreased scavenging of NO, inactivation of prostaglandin I2 [PGI2]). The correction of anemia with erythropoiesis-stimulating agents is also a double-edged sword; it can lead to the correction of bleeding tendency but it could also increase blood viscosity and arterial pressure and lead to increased incidence of stroke and myocardial infarction.

2.1.4. Endothelial dysfunction and damage

Endothelial dysfunction and damage in CKD/CRF is associated with changes in tissue plasminogen activator (tPA), PAI-1 and von Willebrand factor (vWF) secretion and in NO synthesis and secretion. These alterations, as it has been mentioned above, can lead to both hyper- and hypocoagulation due to impaired platelet-vessel wall interaction and changes in vascular tone and inflammatory response (including oxygen radical generation and scavenging).

Another suspected culprit for the development of hypercoagulation in CKD/CRF is hyperhomocysteinemia leading to endothelial damage, changes in fibrin formation tPA secretion, increase in PAI1, and metalloproteinase-9 activity.

In renal transplantation (RT) patients, the calcineurin inhibitor and/or azathioprine-induced endothelial damage + corticosteroid treatment could lead to hypercoagulation and venous thromboembolism (VTE).

In illicit drug users, the intake of heroin, cocaine, and amphetamines has been associated with both renal damage (marked vasoconstriction, rhabdomyolysis, and glomerulosclerosis) and thrombosis (thrombotic microangiopathy due to endothelial damage) [11]. Moreover, in heroin-dependent subjects, drug-induced antiphospholipid antibodies with thrombo-embolic complications have been described [11, 12].

2.1.5. Microparticles

Microparticles (MPs) are cell-membrane residues containing phospholipids (phosphatidylserine) and proteins (tissue factor, residues of cell receptors, etc.). MPs are formed during different processes, such as cell development, differentiation and aging, inflammation, and cell death. MPs are known to have pro-coagulant effects due to phosphatidylserine and TF. Sometimes MPs are associated with small and presumed non-coding single-stranded RNA molecules, called microRNAs (miRNAs). These miRNAs are known to participate in post-transcriptional gene modulation. It has been discovered that they can modulate platelet function via the P2Y12 receptor and/or the VAMP8 or via influencing the platelet mRNA regulation.

2.1.6. Atherosclerosis and vascular injury

Atherosclerosis is a well-known and independent risk factor for the development of large vascular incidents (including stroke and myocardial infarction). All CKD/CRF patients, especially in the presence of nephrotic syndrome, chronic inflammation, and corticosteroid treatment, have accelerated atherosclerosis development. Moreover, the co-morbidities in atherosclerosis and CKD/CRF patients (diabetes, hypertension, obesity, and dyslipidemia) also predispose to both arterial and venous thromboses, probably via following mechanisms: endothelial/vessel wall injury and platelet dysfunction. Microalbuminuria, a marker of endothelial injury, is associated with the risk for the development of both arterial and venous thromboses.

2.1.7. Hypercoagulation in glomerulonephritis

In patients with glomerular diseases, hypercoagulation is associated with four major factors: nephrotic syndrome, vasculitis and vascular wall inflammation, and medications (corticosteroids and cyclosporine A).

The nephrotic syndrome leads to hypercoagulation due to imbalance between pro-and anticoagulation factors: decreased protein C and S and anti-thrombin III, decreased fibrinolysis, and increased coagulation factor plasma levels. The development of DVT and/or PE is one of the major complications of the nephrotic syndrome. The latter substantially increases the risk for venous thromboembolism.

Vasculitis/vascular wall inflammation in systemic and renal vasculitis, including antineutrophil cytoplasmic antibody (ANCA)-positive cases, leads to hypercoagulation due to structural

changes in the vessel wall, endothelial damage, and dysfunction and activation of coagulation cascade. Moreover, high platelet count is observed in acute and chronic inflammation.

Rarely, in patients with systemic vasculitis, parenchymal organ bleeding has been described, associated with microvascular damage and development of small cracks filled with blood (peliosis).

The intake of corticosteroids is associated with increased platelet count and aggregability, increase in coagulation factors plasma levels, and in acute-phase proteins. On the other hand, corticosteroid treatment is associated with the development of GIT hemorrhages due to the inhibition of prostaglandin synthesis. Cyclosporine A treatment can lead to endothelial cell damage with the subsequent development of hypercoagulation and thrombotic microangiopathy. Cocaine, amphetamines, and heroin also affect endothelial cells and can lead to the development of thrombotic microangiopathy.

2.1.8. Antiphospholipid antibodies (APLs)

These autoantibodies are directed against negatively charged plasma or membrane phospholipids and/or phospholipid binding proteins and/or phospholipid-protein complexes. They are the major laboratory criterion for the classification of the antiphospholipid syndrome. APLs affect not only the coagulation system but also endothelial function and platelets. They are known to cause both arterial and venous thromboses, low platelet count, reproductive failure, and accelerated atherosclerosis.

Their determination in renal diseases is crucial because the results can affect both the diagnosis (particularly in chronic glomerulonephritis patients in whom systemic lupus erythematosus (SLE) is suspected) and the treatment, especially at the background of other thrombophilic factors, such as nephrotic syndrome, corticosteroid treatment, vasculitis, dyslipidemia, and diabetes.

The suspected pathogenic mechanism of the pro-coagulant action of APL and the development of vascular injury are [13–18]:

- inhibition of the activated protein C,
- activation of the tissue factor,
- inhibition of anti-thrombin III,
- damage of the membrane annexin V,
- inhibition of the anticoagulant activity of beta-2-glycoprotein-I (b2GPI),
- inhibition of fibrinolysis,
- endothelial cell activation,
- increased expression of adhesion molecules on endothelial cells and leukocyte adhesion to the vascular endothelium,
- neutrophil leukocyte activation and degranulation,
- increased platelet activation and aggregation,

- increased adhesion of b2GPI and prothrombin to the cell membranes,
- effect on endothelial cell apoptosis,
- inhibition of the prostacyclin secretion from endothelial cells, and
- accelerated atherosclerosis.

On the other hand, APLs have several anticoagulant effects, associated with inhibition of factor IX and X activation and of the conversion of prothrombin to thrombin [14]. The factors that modulate the pro- and anticoagulant effects of ALA probably are the phospholipids that bind APL and the antigenic specificity of the latter.

The development of thrombosis in APL-positive patients has been explained by the so-called *second-hit theory*: the presence of APL (first hit) itself is not sufficient for the generation of thrombus but when a second abnormality develops (i.e., endothelial damage, platelet dysfunction, etc.), thrombus may be formed [14]. Moreover, APL could represent the second hit—at the background of inborn or acquired thrombophilia: factor V Leiden or prothrombin gene mutation, MTHFR, protein C/S or anti-thrombin deficiency, nephritic syndrome, chronic renal failure, chronic endothelial damage or dysfunction in chronic inflammation, corticosteroid treatment, and so on. In APS patients, we showed increased platelet activation markers' expression [16]. Some of the APS patients have other underlying inborn coagulation deficiency [18]: protein S/C or anti-thrombin III deficiency, factor V Leiden, 20210 prothrombin gene mutation. This fact supports the described second-hit theory.

2.1.9. Heparin-induced thrombocytopenia type II (HIT II)

HIT II is associated with the heparin-induced synthesis of platelet-activating antibodies against the complex heparin-platelet factor 4. It is observed in 0.5–5% of all heparin-treated patients. In such patients, platelet levels are low but thrombo-embolic complications (usually venous thromboses) appear due to platelet activation.

2.2. Bleeding tendency (hemorrhagic diathesis)

The underlying mechanisms of *hemorrhagic diathesis* in renal diseases, CKD and CRF, are associated with platelet dysfunction, uremic toxins, dialysis membranes, impaired platelet-vessel wall interaction, anemia, and intake of certain medications (including aspirin and non-steroid anti-inflammatory drugs [NSAIDs], anticoagulants, antiaggregants, and antibiotics) [6–8].

2.2.1. Platelet dysfunction

The main cause of hemorrhagic diathesis in chronic renal diseases, CKD and CRF, are platelet abnormalities, including low platelet count in CKD/CRF due to bone marrow suppression and/or immune thrombocytopenia, changes in alpha-granules with increased adenosine triphosphate (ATP)/ADP ratio, and reduced serotonin content, dysregulation of arachidonate and prostaglandin synthesis and degradation (mainly decreased thromboxane A2), increased plasma levels of fibrinogen fragments.

The changes in alpha-granules are associated with decreased platelet factor 4, fibronectin B, platelet-derived growth factor, vWF, fibrinogen, serotonin, factors V and XIII, transforming growth factor B, and so on.

2.2.2. Uremic toxins

In CKD and CRF, several uremic toxins affect platelet degranulation and adhesion: phenol and phenolic acid, guanidinosuccinic acid, middle molecules (molecular weight of 500–3000 Da). Moreover, uremic toxins inhibit thrombopoiesis in the bone marrow. Low calcium levels in CKD/CRF can also contribute to hypocoagulation. Hemodialysis (HD) and peritoneal dialysis have dual and controversial effect on bleeding and coagulation. Both methods are associated with hypercatabolism, pro-inflammatory state, malabsorption, anemia, and low calcium that could cause both bleeding and hypercoagulation. Moreover, the administration of heparin could cause both bleeding and thromboses (HIT II).

Parathyroid hormone (PTH) has been shown to inhibit platelet aggregation (at least *in vitro*). In hemodialysis, the dialysis membrane can lead to platelet activation and aggregation, but the removal of uremic toxins can (at least partially) correct coagulation abnormalities.

And, finally, circulating fibrinogen fragments that are elevated in CKD/CRF can competitively bind to GPIIb/IIIa platelet receptors and decrease platelet adhesion and aggregation.

2.2.3. Dialysis membranes

Dialysis membranes lead to persistent platelet activation (including increased number and percentage of P-selectin/CD63-positive circulating platelets), formation of platelet-leukocyte (with the generation of free oxygen radicals), and platelet-erythrocyte aggregates [9]. The process of platelet activation is dependent on the type of dialyzer membranes used (more pronounced in cellulose diacetate and polysulfone membranes and less severe in EVAL membranes). The persistent chronic inflammation and hypercatabolism in CRF/CKD also contribute to hypercoagulation. Yet, some patients on dialysis develop thrombocytopenia with bleeding diathesis.

The dialysis (HD and continuous ambulatory peritoneal dialysis [CAPD]) is known to correct, at least partially, the coagulation abnormalities in CKD/CRF.

2.2.4. Platelet-vessel wall interaction

Platelet-vessel wall interactions are associated with the binding of platelets to vWF and fibrinogen on endothelial surface and the activation of platelet receptors (GPIb and GPIIa/IIIb). In the hypercatabolic environment of CKD/CRF, significant decrease of platelet GPIb has been reported, along with decreased platelet binding to fibrinogen and vWF (plus decreased vWF levels), decreased activation of GPIIa/IIIb [6]. The impaired platelet adhesion is thought to be caused by dialyzable uremic toxins, as dialysis corrects the described abnormalities. Moreover, the administration of vWF-containing cryoprecipitates and of desmopressin (known

to stimulate endothelial release of vWF) has been shown to ameliorate platelet-vessel wall interactions. And finally, the changes in vascular tone in response to vasoactive substances (nitric oxide and prostacyclin) associated with the accumulation of uremic toxins also contribute to the impairment of platelet-endothelial interactions.

2.2.5. Anemia

Anemia is known to directly influence bleeding because red blood cells lead to platelet aggregation and stimulate ADP release and PGI2 inactivation. Moreover, in patients with CKD/CRF, the infusion of red blood cells and/or the correction of erythrocyte levels with erythropoiesis-stimulating agents and iron lead to reduction of bleeding time. On the other hand, one should not forget that the correction of anemia increases the risk for major vascular incidents (myocardial infarction and stroke).

2.2.6. Drugs and medications

In patients with renal diseases, many drugs may cause severe bleeding episodes, even life-threatening, due to changes in the drug clearance and drug accumulation anticoagulants: direct thrombin inhibitors, aspirin and non-steroid anti-inflammatory drugs [NSAIDs], interaction with platelet membranes (beta-lactam antibiotics, inhibition of cyclooxygenase (aspirin and NSAIDs).

In patients with opioid dependence, Savona et al. [19] describe heroin-induced autoimmune thrombocytopenia. Moreover, in heroin and cocaine/amphetamine dependency, the development of endothelial drug injury may lead to thrombotic microangiopathy with both thromboses and bleeding [11].

The underlying mechanisms for the development of hypercoagulation and bleeding tendency in CKD are summarized in **Table 1**.

The main clinical presentations of thromboses in renal diseases are summarized in **Table 2**.

Hypercoagulation	**Bleeding**
Platelet activation	Platelet defects
Vascular endothelial damage	Impaired platelet-vessel wall activations
Microparticles and micro RNA	Vascular damage
Oxidative stress	Oxidative stress
Increased von Willebrand factor (vWF)	Defective binding of vWF to GPIIb/IIIa
Increased	Defective prostacyclin and NO synthesis
Increased factor XIIa and VIIa and thrombin formation	Anemia
Decreased protein C and protein S and anti-thrombin III	
Increased tissue factor and acute-phase proteins: fibrinogen, CRP	

Hypercoagulation	Bleeding
Decreased tissue plasminogen activator (tPA)	Increased tPA
Increased plasminogen activator inhibitor 1 (PAI1)	Decreased PAI1
Uremic toxins	Uremic toxins
Increased rennin-angiotensin-aldosterone (RAAS) activity	
Antiphospholipid antibodies	
- Pro-thrombotic gene mutations	Medications
- Factor V Leiden	- Beta-lactam antibiotics
- MTHFR	- Aspirin and NSAIDs
- 20210 prothrombin gene mutation	- Anticoagulants
- Protein C, S, and anti-thrombin deficiency	- Antiaggregants
Nephrotic syndrome	Amyloidosis, myeloma
Anemia	Anemia
Atherosclerosis: dyslipidemia, diabetes, arterial hypertension, peripheral vascular disease	Vasculitis
Corticosteroid treatment, cyclosporine A, cocaine	Corticosteroid treatment
Heparin-induced thrombocytopenia type II	
Hemodialysis and peritoneal dialysis	Hemodialysis and peritoneal dialysis

Table 1. Factors leading to coagulation abnormalities in renal diseases.

Hypercoagulation
- Venous thromboembolism (deep venous thrombosis [DVT] and/or pulmonary embolism [PE]).
- Major vascular incidents (myocardial infarction and/or stroke, peripheral arterial disease).
- Hemodialysis vascular access and/or central venous access thrombosis.
- Peripheral vascular access thrombosis.
- Thrombotic microangiopathy.
Bleeding
- Skin and linings: ecchymoses, epistaxis, gingival bleeding, gastrointestinal bleeding, subungual hematoma, genital bleeding, hematuria, hemoptysis, and skin hemorrhages (petechiae, purpura, and suffusions).
- Intracranial hemorrhage (epidural, subdural, subarachnoid, and intracranial).
- Vascular access bleeding.
- Parenchymal organ bleeding (including peliosis).

Table 2. Clinical presentation of coagulation abnormalities in renal diseases.

3. Coagulation abnormalities and their clinical presentation in different renal diseases

3.1. Glomerulonephritis, systemic lupus, and vasculitis

Christiansen et al. [2] examined the risk of VTE in 128,096 Danish patients hospitalized for VTE for the period 1980–2010 (78,623 with DVT and 54,473 with PE) and compared them with 642,426 age- and gender-matched control and found that kidney disease is associated with higher OR for VTE (range between 1.41 for hypertensive nephropathy and 2.89 for nephritic syndrome), with the association being stronger during the first 3 months after the diagnosis of CKD but remaining elevated for the following 5 years. Therefore, the authors concluded that patients with chronic nephropathies are at increased risk for VTE, especially in cases of nephritic syndrome and glomerulonephritis.

In 182 patients with idiopathic glomerulonephritis (125 male and 57 female, mean age 35.6 ± 13.4 years), hospitalized for the period 2000–2005, we observed thrombotic complications in 27: stroke in 6, myocardial infarction in 12, DVT in 15, PE in 7 (the sum is more than 27 because several patients had more than 1 thrombotic complications) [15 and unpublished data]. The main risk factors for the development of thrombotic incidents were nephrotic syndrome (OR 3.220), corticosteroid treatment (OR 2.617), and renal failure (OR 1.51). **Figure 1** shows the typical S1Q3T3 electrocardiography (ECG) changes in a male patient with membranous glomerulonephritis and pulmonary embolism.

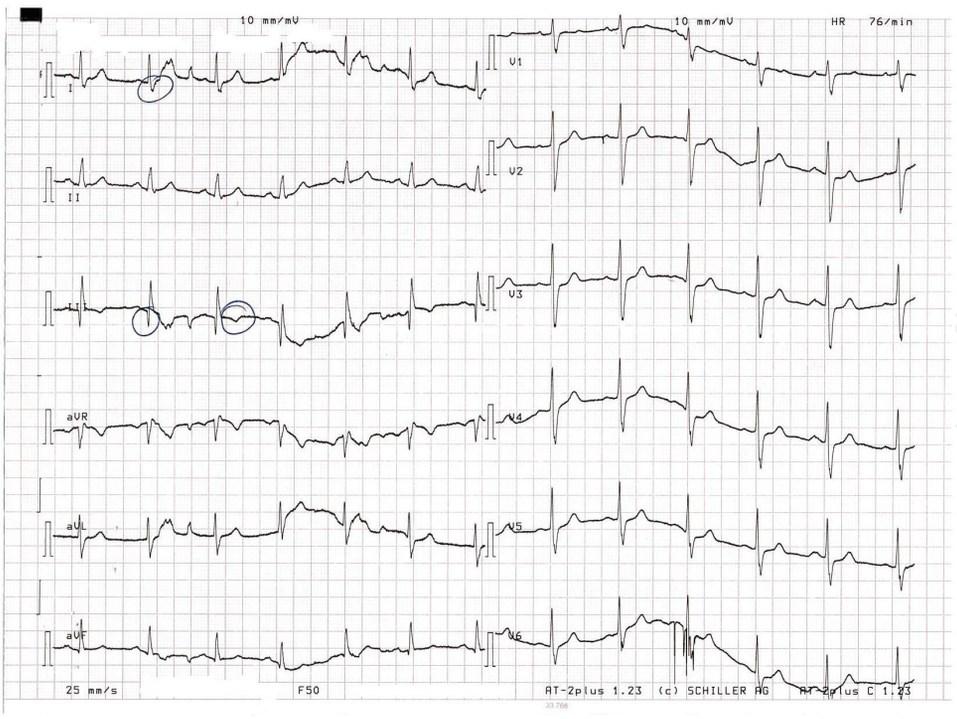

Figure 1. ECG of a patient with idiopathic membranous glomerulonephritis with nephrotic syndrome and pulmonary embolism (PE). Typical S1Q3T3 changes.

In 106 patients with SLE (63 with biopsy-proven lupus nephritis [LN]), 7 male and 56 female, mean age 37.4 ± 10.4 years; 43 without clinical/laboratory data for renal involvement, 7 male and 36 female, mean age 44.1 ± 17.8 years) for the period 2000–2005, we observed thrombotic complications in 34 patients (32.1%) (7/43 without LN and 27/63 with LN) [15]. Following thrombotic incidents were observed:

- Arterial thromboses: coronary incidents in 3, stroke/transient ischemic attack in 8.
- Venous thromboses: DVT in 13, PE in 6, vena axillaris/subclavia thrombosis in 1, vena cava inferior thrombosis in 1.
- Reproductive failure in 8.
- Disseminated intravascular coagulation in 3.
- Thrombotic microangiopathy in 1.

The sum of incidents is more than 34 because several patients had more than 1 thrombotic complication.

The development of thrombotic complications correlated with the presence of positive IgG and IgM anticardiolipin antibody (ACL) and IgG b2GPI (but not IgM b2GPI) and their levels, the presence of APS, the serum cryoglobulin levels and showed weak correlation with the presence of vasculitis (thrombosis+/vasculitis+ 11/106 patients vs. thrombosis−/vasculitis+ 6/106 patients, $r = 0.306$, $p = 0.01$).

For the total population of SLE patients (with and without LN), the development of thrombotic complications correlated with systemic lupus erythematosus disease activity index (SLEDAI) (mean SLEDAI in thrombotic patients 16.2 ± 8.7 vs. 7.6 ± 3.9 for non-thrombotic patients, $r = 0.566$, $p = 0.0001$) and systemic lupus collaborating clinics (SLICC) indices (mean SLICC 2.9 ± 2, vs. 0.7 ± 1.1, respectively, $r = 0.593$, $p = 0.0001$), with the presence of renal involvement (27/63 with LN vs. 7/43 without LN, $\chi^2 = 8.286$, $r = 0.380$, $p = 0.004$).

For the total SLE population (with and without LN), following markers for increased thrombotic risk were identified: arthritis/arthralgiae, serositis, central nervous system involvement, renal involvement, nephritic urinary sediment, nephrotic syndrome, positive IgG and IgM ACL and IgG (but not IgM) b2GPI antibodies, APS, corticosteroid treatment, and vasculitis (**Table 3**).

Marker	OR (95% CI)	*p*
Arthritis/arthralgiae	5.167 (1.433–18.627)	0.007
Serositis	2.537 (1.062–6.059)	0.034
Central nervous system involvement	9 (3.321–24.388)	0.0001
Renal involvement (LN, nephritic urinary sediment, proteinuria, nephrotic syndrome)	3.857 (1.49–9.984)	0.004
Positive IgG ACL	16.8 (6.083–46.398)	0.0001

Marker	OR (95% CI)	*p*
Positive IgM ACL	6.5 (2.305–18.326)	0.0001
Positive IgG b2GPI	5.672 (1.175–28.251)	0.025
APS	148.455 (18.171–1212.827)	<0.0001
Corticosteroid treatment	3.220 (1.576–6.49)	0.0001
Vasculitis	5.261 (1.747–15.838)	0.001

Table 3. Markers of thrombotic risk in 106 patients with SLE [15].

In the investigated LN patients, the development of thrombotic complications correlated with the presence of vasculitis, the duration and the number of SLE criteria, the central nervous system involvement, oral ulcerations, arthritis/arthralgiae, LN histological activity index, the amount of proteinuria, serum cryoglobulin levels, the levels and positivity of IgG and IgM ACL, the mean IgG b2GPI levels, SLEDAI and SLICC, APS, and inversely correlated with serum IgG levels (lower in more severe nephrotic syndrome).

In LN patients, the following markers of increased thrombotic risk were identified: oral ulcerations and vasculitis, positive ANCA, central nervous system involvement, nephrotic syndrome, positive IgG and IgM ACL and IgG b2GPI, hypocomplementemia C3, APS, and corticosteroid treatment (**Table 4**).

The results of our studies in APS patients with and without SLE [16] showed correlation between CD63 expression and activated partial thromboplastin time (aPTT), CD61 expression and IgG and IgM ACL, and b2GPI, CD42a, and b2GPI.

Marker	OR (95% CI)	*p*
Oral ulcerations	2.0 (1.97–3.79)	0.001
Central nervous system involvement	10.54 (3.094–35.905)	0.0001
Nephrotic syndrome	2.448 (0.869–6.895)	0.05
ANCA	3.008 (1.068–8.473)	0.035
Positive IgG ACL	18.229 (5.097–65.127)	<0.0001
Positive IgM ACL	7.563 (1.848–30.955)	0.002
Positive IgG b2GPI	5.238 (1.057–25.966)	0.036
Hypocomplementemia C3	2.020 (1.204–3.387)	0.015
APS	5.5 (2.939–10.294)	<0.0001
Corticosteroid treatment	3.077 (1.507–6.283)	0.01
Vasculitis	17.5 (2.053–149.153)	0.001

Table 4. Markers of increased thrombotic risk in 63 LN patients [15].

The results of our investigations on the platelet activation markers in female patients with complicated pregnancy [18], including edema-proteinuria-hypertension (EPH) gestosis, revealed that these patients have increased anticardiolipin and beta-2-glycoprotein I antibodies, and the levels of ACL correlate with CD63 expression (marker of platelet degranulation). Some of the APL-positive patients also had inborn coagulation defects (i.e., factor V Leiden 20210 prothrombin gene mutation and MTHFR gene mutation).

3.2. Retroperitoneal fibrosis

Idiopathic retroperitoneal fibrosis (RPF) is a rare autoimmune fibrosing disease associated with the development of fibrous tissue and/or chronic inflammatory infiltrates (**Figure 2**) in the retroperitoneal space that envelops the aorta, iliac vessels, and ureters (**Figure 3**) [20]. In approximately 15% of the patients, extra-abdominal fibrosis is observed. In some RPF patients with vascular involvement, thrombotic incidents have been described [20]. For the period 1998–2017, we followed 33 patients with idiopathic retroperitoneal fibrosis (25 male and 8 female). Overall 17 patients had thrombotic incidents: iliac/femoral vein thrombosis in 8, vena cava inferior thrombosis in 4, portal vein thrombosis in 2, infiltration (with or without thrombosis) of the inferior mesenteric artery and its branches (**Figure 4**) in 3, aortic aneurism with thrombosis (**Figure 5**) in 2, DVT with or without PE in 5 (the sum of events is more

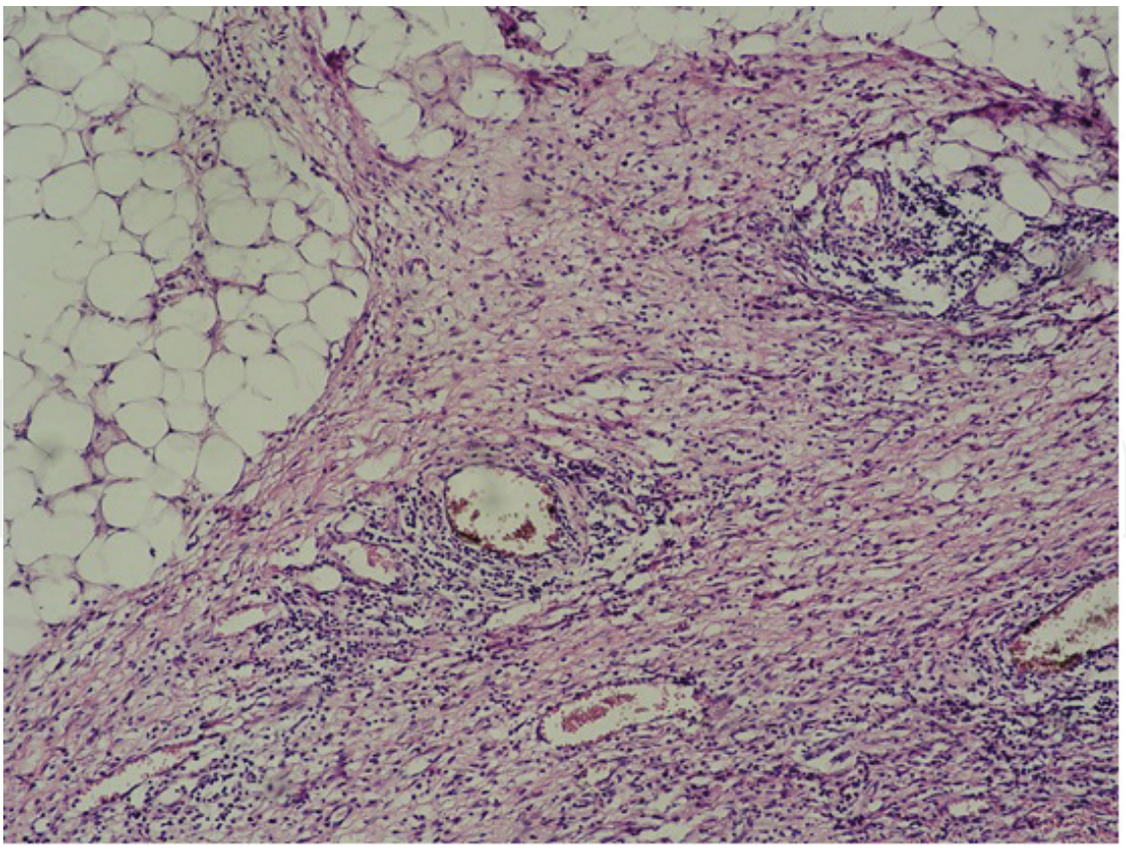

Figure 2. Biopsy specimen of retroperitoneal infiltrates in a patient with idiopathic retroperitoneal fibrosis (RPF)—inflammatory infiltrate with abundance of lymphocytes and fibrous tissue.

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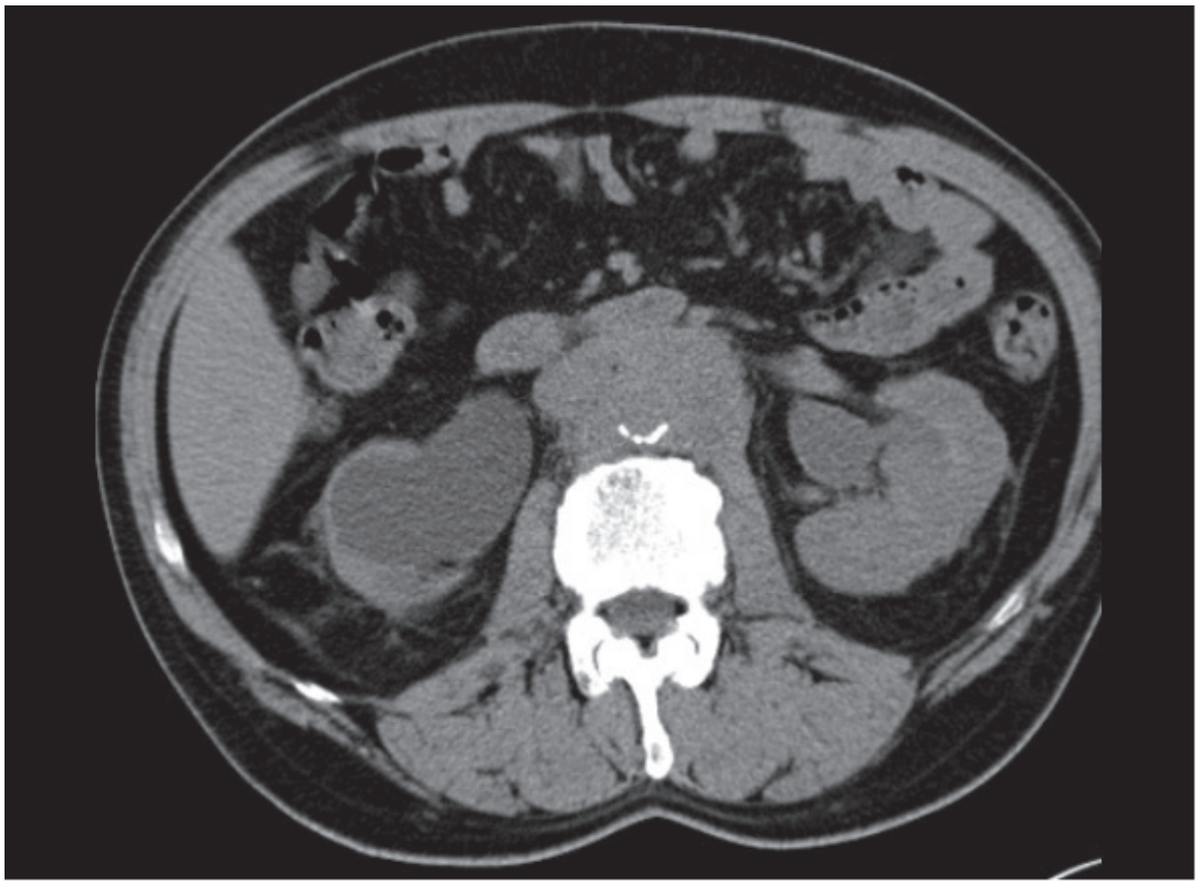

Figure 3. CT image of a patient with idiopathic RPF. Bilateral hydronephrosis and retroperitoneal infiltrates that envelop the aorta, iliac vessels, and ureters.

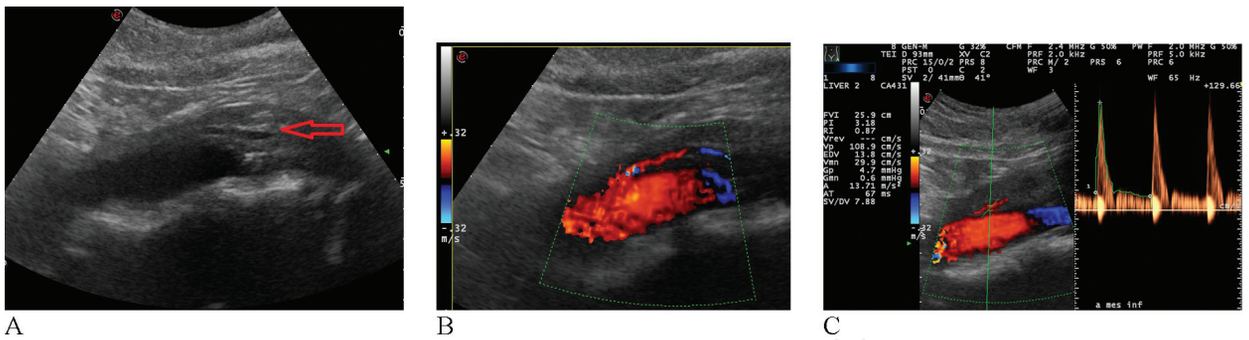

Figure 4. Abdominal ultrasound in a patient with idiopathic RPF (arrow) with involvement of the abdominal aorta and inferior mesenteric artery (A and B), no Doppler data for stenosis of the inferior mesenteric artery (C). *Courtesy of Dr. R. Krasteva-Lolova.*

than 17 because several patients had more than 1 thrombotic complication). In one patient, the DVT episodes with varico- and hyrdocele (**Figure 6**) were the first manifestation of RPF. The underlying mechanism of thrombosis in RPF is associated with vascular wall changes, endothelial dysfunction in chronic inflammation, corticosteroid/azathioprine treatment, and immune phenomena (including APL).

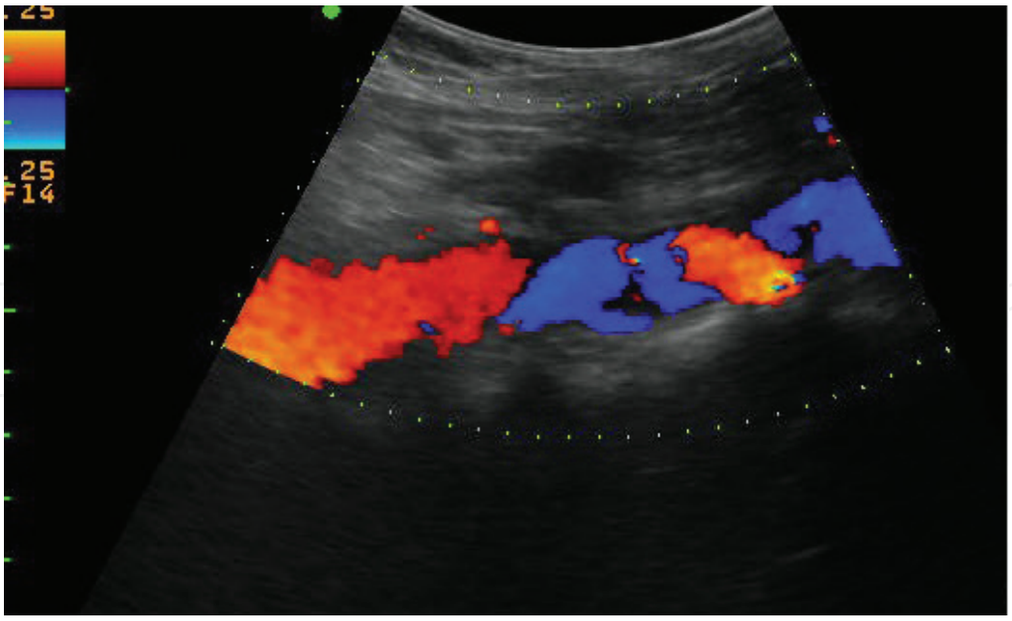

Figure 5. Abdominal Doppler ultrasound of a patient with idiopathic RPF with aortic aneurism.

3.3. Drug abuse

The intake of illicit drugs (including heroin, cocaine, and amphetamines) has been reported to be associated with thrombotic incidents. The possible underlying mechanisms of thrombosis are overdose with rhabdomyolysis with or without acute renal failure and vascular damage; drug-induced endothelial cell injury with thrombotic microangiopathy; platelet and coagulation

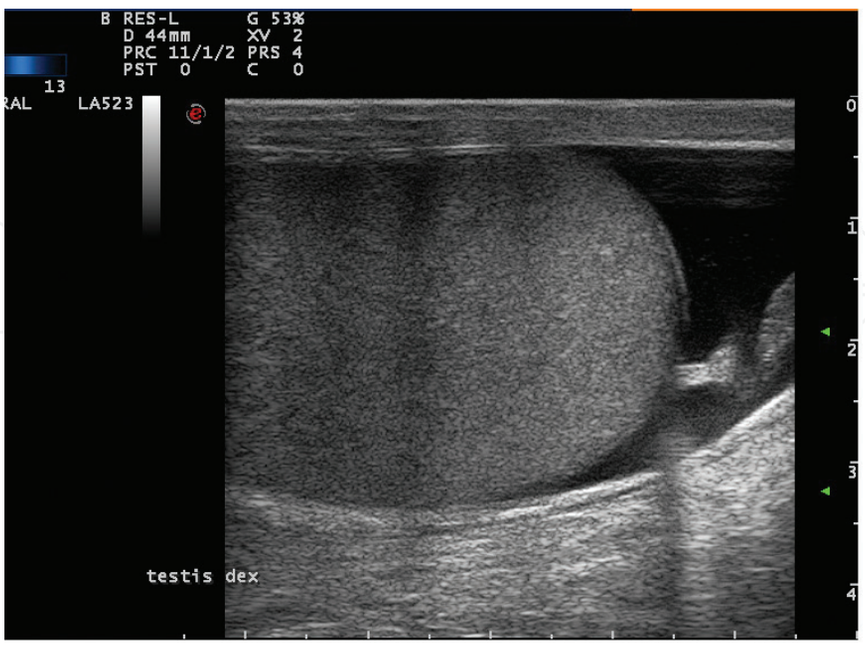

Figure 6. Ultrasound examination of the testicles (right testicle) of a male patient with idiopathic RPF manifesting with femoro-popliteal thrombosis and hydrocele.

abnormalities due to chronic inflammation, drug- and infection-induced APL [11, 12, 15, 19]. In a group of 15 heroin abusers (12 male and 3 female, mean age 23.9 ± 4.2 years), we observed renal involvement in 6 [15]. One of the patients with biopsy-proven renal involvement (chronic tubulo-interstitial nephritis) and negative hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) developed ilio-femoral vein thrombosis and acute renal failure at the background of positive IgG ACL. After the cessation of heroin abuse, ACL levels subsided back to the normal values that suggests heroin-induced autoantibodies. The results of our investigations suggest that in patients with illicit drug abuse, the clinician should be aware of the possible renal and thrombotic complications.

3.4. Chronic kidney disease and chronic renal failure

Chronic renal disease and chronic renal failure are associated with significantly elevated risk for the development of venous thromboembolism due to platelet and coagulation abnormalities, impaired fibrinolysis, and endothelial damage and dysfunction. CKD is classified in five stages according to the degree of glomerular filtration rate (GFR) decrease (**Table 5**). The prevalence of CKD/CRF in adults >20 years of age in the NHANES III study [21] is approximately 11%. This fact shows the social significance of CKD. Having in mind the increased thrombotic risk in mild to moderate CKD patients (1.3–2-fold increase compared to the general population) and end-stage renal disease (2.3-fold compared to the general population), the clinician should be aware of VTE as a possible complication of CKD/CRF and of the need of proper anticoagulation strategy [3, 10].

3.5. Hemodialysis and peritoneal dialysis

As it was mentioned above, dialysis treatment is associated with both thrombosis and increased risk for bleeding episodes [1, 4–7]. The coagulation abnormalities (including the changes in the coagulation pathway, anticoagulation, and fibrinolysis/antifibrinolysis) in hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) are summarized in **Table 6**. These changes are accompanied by platelet abnormalities and altered platelet-vascular wall interactions [7]. The

Stage	GFR (ml/min/1.72 m^2 body surface)	Prevalence (USA, NHANES III, adults >20 years of age) (%) [21]
0	>90, Normal GFR, no risk for CKD/CRF, no underlying renal disease or damage	89
1	>90, Persistent microalbuminuria and/or risk for CKD/CRF—underlying renal disease or damage	3.3
2	60–89	3.0
3	30–59	4.3
4	15–29	0.2
5	<15 (or dialysis treatment)	0.2

Table 5. Definition of chronic kidney disease and prevalence in the USA according to the NHANES III [21].

Marker	Hemodialysis	Peritoneal dialysis (CAPD)
Coagulation pathway		
Fibrinogen, factor VII, vWF, tissue factor	↑	↑
Factor II, VIII, IX, X, XII	↓	↑
Prothrombin fragments 1 + 2	↑	↑
Anticoagulation		
Thrombomodulin, tissue factor pathway inhibitor	↑	↑
Protein S	↓	↑
Protein C, anti-thrombin III	↓	-
Fibrinolysis		
Tissue plasminogen activator	↑	↓
Plasminogen activator inhibitor 1	↓	↑
Thrombin activable fibrinolysis inhibitor	-	↑

Table 6. Coagulation abnormalities in hemodialysis and in peritoneal dialysis.

in vitro and *in vivo* studies reveal somewhat contradictive results—patients on dialysis can have both increased and decreased platelet aggregation and the initiation of dialysis partially corrects the pre-existing abnormalities in platelet function, characteristic for CKD/CRF [7, 9]. The degree of anemia and hypoalbuminemia seem to correlate with prolonged bleeding time, and the chronic inflammation seems to increase the thrombotic risk [7]. Heparin treatment in HD can induce both bleeding and thromboses (HIT II). The alterations in NO synthesis also lead to decreased platelet aggregation [7].

A major problem in these patients represents the vascular access thrombosis, especially in diabetics and in patients with systemic connective tissue disease (with or without the APS). Anticoagulation strategies in dialysis treatment are discussed further in the text.

3.6. Renal transplantation

VTE is a frequent complication of renal transplantation (RT). According to the literature, 6–7% of RT patients develop VTE [5, 22], including DVT, PE, graft thrombosis, renal vein thrombosis, and thrombotic microangiopathy [8]. The underlying mechanisms, as discussed earlier, include impaired platelet function and platelet-vessel wall interactions, hypercoagulation at the background of chronic inflammation, corticosteroid treatment and CKD, the effect of calcineurin inhibitors and azathioprine on endothelial function, OKT3, and so on [8].

Luna et al. [5] retrospectively analyzed 577 cadaveric RTs performed for the period 1992–2009, excluding the cases with known hypercoagulability before RT. The incidence of VTE was 6%. The authors evaluated the type of thrombosis according to recipient variables, differences in dialysis within 24 h before transplantation (0 no dialysis, 13.8% dialysis out of hospital, and

4.2% dialysis in hospital; $p = 0.029$) and iliac vascular pathology (10% yes vs. 5% no; $p < 0.04$). The authors suggest that donor-related factors are age >60 years (11% vs. 5%; $p = 0.01$), stroke versus trauma as a cause of death (9.3% vs. 4.7%; $p = 0.049$), and graft atheroma (16.7% yes vs. 5.1% no; $p = 0.042$). The authors also investigated the treatment-associated risk factors tacrolimus versus cyclosporine (7.4% vs. 2.3%; $p = 0.001$) and sequential therapy (10.7% yes vs. 3.3% no; $p = 0.001$), basiliximab (adjusted for donor and recipient age, and graft atheroma). The multivariate analysis revealed that the predictive factors for VTE after RT (increasing the risk for VTE (16-fold)) are stroke donor death (OR 3.88), recipient iliac vascular pathology (OR 2.81), and graft atheroma (OR 3.63).

Poli et al. [22] studied 484 RT and found 7% prevalence of first episode of VTE. The authors investigated the importance of the cessation of oral anticoagulation and found that compared to VTE patients without renal disease the recurrence of VTE in RT patients is very high (50% or 14/28 compared to <10% or 8/84). In RT patients, the authors also find higher levels of homocysteine, circulating fibrinogen fragments 1 + 2 and D-dimer that are characteristic for CKD/CRF patients in general. The authors recommend prolonged oral anticoagulation in RT patients to prevent the risk of VTE recurrence, despite the elevated bleeding risk.

4. Anticoagulation strategies

Due to the high risk of VTE all patients with chronic renal diseases, including glomerulonephritis, systemic connective tissue diseases, and vasculitis with renal involvement, retroperitoneal fibrosis, hemodialysis, should be considered possible candidates for anticoagulation, especially in the presence of coagulation abnormalities (anticoagulation factor deficiency, vasculitis, nephrotic syndrome, and CKD/CRF) and/or predisposing factors (atrial fibrillation, various veins, cardiac and renal failure, etc.). Nevertheless, patients with renal diseases represent significant therapeutic challenge if anticoagulation is needed, because they are prone to both thromboses and hemorrhages and because the gastrointestinal absorption and the renal clearance of certain anticoagulants are altered in CKD/CRF [3].

4.1. Unfractioned heparin and low-molecular weight heparins (LMWHs)

Unfractionated heparin (UFH) is a 3–30 kDA sulphated polysaccharide that binds positively charged surfaces. Its anticoagulant response is mediated by binding to factor IIa and factor Xa. UFH anticoagulant effect is monitored using activated partial thromboplastin time (aPTT). UFH has reticulo-endothelial and, to a lesser extent, renal clearance. Therefore, its clearance in CKD/CRF is unpredictable. UFH doses should be reduced in moderate to severe CRF (creatinine clearance below 30 ml/min) with close monitoring of aPTT (1.5–2x prolongation) in order to prevent over-anticoagulation and severe bleeding episodes [6]. In VTE episodes at the background of CRF, Hughes et al. [3] recommend loading dose of 60 U/kg/h with maintenance dose of 12 U/kg/h. Significant side effects of UFH include bleeding, heparin-induced thrombocytopenia, osteopenia, and alopecia, especially in prolonged administration.

LWMHs are synthetic UFH derivatives with shorter heparin chains and stronger affinity to factor Xa with lower affinity to factor IIa. Their pharmacokinetic profile is more predictable than that of UFH. Moreover, self-administration of the medication is possible. LMWHs have lower affinity and binding to endothelial cells and platelets and no routine monitoring of coagulation parameters is required. The only suitable monitoring parameter is anti-Xa levels that is not routinely used in clinical practice. The most frequent side effects in prolonged administration are HIT, osteopenia, and alopecia, and their incidence is much lower compared to that on UFH.

The LMWHs dose should also be reduced in CRF [3]:

- In glomerular filtration rate (GFR) >40 ml/min, full dose once daily.
- In GFR 30–39 ml/min, 80–90% of the recommended dose once daily.
- In GFR <30 ml/min, 60% of the recommended daily dose twice a day.

To avoid sub- or supradosing, monitoring of anti-Xa levels is advisable in CRF patients with GFR <50 ml/min.

4.2. Warfarin and indirect anticoagulants

Indirect anticoagulants are vitamin K antagonists that inhibit the synthesis of vitamin K-dependent coagulation factors. The routine laboratory marker for the monitoring of their effect is prothrombin time (PT)/international normalized ration (INR). In CRF patients with GFR 30–59 ml/min, the maintenance dose required for stabile PT prolongation is 10% lower than that in non-CRF population and in GFR <30 ml/min, the dose is 20% lower [3]. Moreover, CKD/CRF patients tend to have labile PT/INR and the anticoagulant effect is quite unpredictable. In a review on mechanisms of vascular calcifications, El-Abbadi et al. [23] emphasize that indirect anticoagulants can increase vascular calcifications due to vitamin K inhibition-dependent increase of serum phosphate levels. Another major complication is the warfarin-related nephropathy—unexplained increase in serum creatinine with ≥0.3 mg% after the initiation of warfarin treatment probably due to intraglomerular bleeding and tubular obstruction by erythrocyte casts. This complication is associated with marked increase in mortality in CRF patients.

4.3. Newer oral anticoagulants

These medications are synthetic anti-Xa agents (apixaban and rivaroxaban) or anti-IIa agents (dabigatran and direct thrombin inhibitors). Rivaroxaban and apixaban have approximately 30% renal clearance and their effect in CRF patients is more predictable, whereas dabigatran has mainly renal clearance (85%) and in CRF patients tends to accumulate, and its effect in this population is unpredictable. Therefore, rivaroxaban and apixaban are approved for CRF patients with CFR<30 ml/min (with dose reduction of approximately 50%, the dose of rivaroxaban in CFR 15–49 ml/min is 15 mg/day, and <15 ml/min is contraindicated; the dose of apixaban in GFR 15–29 ml/min is 2.5 mg twice a day) and dabigatran is not approved

in patient with GFR<30 ml/min [3]. It should be noted that both rivaroxaban and apixaban (anti-Xa agents) have high protein binding and are metabolized via CYP3A4. Therefore, they should be used with caution in patients with nephrotic syndrome or hypoproteinemia/hypoalbuminemia of other origin and in combination with CYP3A4 inhibitors or inductors.

4.4. Antiaggregants

Aspirin, NSAIDs, and clopidogrel should be used with caution in patients with renal diseases because their anti-platelet effects are unpredictable in GFR <30 ml/min, because CRF patients have significant platelet function abnormalities and frequently are thrombocytopenic and anemic and because their clearance is significantly altered in severe renal impairment. Moreover, NSAIDs and aspirin tend to cause severe, even life-threatening gastrointestinal bleeding episodes, especially at the background of uremic gastro-enteropathy, low platelet count, or corticosteroid treatment.

5. Conclusion

Patients with renal diseases are prone to both thrombosis and bleeding. The prothrombotic state in chronic nephropathies is associated with [6–8] vascular endothelial damage, changes in certain coagulation and antifibrinolytic factors, decrease in anticoagulation proteins, dyslipidemia, hypoalbuminemia, changes in platelet membranes, hemo- and peritoneal dialysis and heparin treatment, increased microRNAs and circulating microparticles, antiphospholipid antibodies, nephrotic syndrome, anemia with high platelet count, and so on. Nevertheless, the same patients have substantially increased risk of bleeding due to platelet dysfunction, and intake of certain medications (antiaggregants, heparin and low-molecular weight heparins, and anemia) [6–8].

In this review, we have presented the main thrombo-embolic risk factors in a wide variety of patients with renal diseases, including chronic glomerulonephritis (primary and secondary), CKD/CRF, idiopathic retroperitoneal fibrosis, and dialysis treatment. We have presented our data on thrombotic incidents in patients with glomerular and non-glomerular diseases and the role of certain prothrombotic factors, such as nephrotic syndrome, inborn and acquired coagulation defects (i.e., factor V Leiden, MTHFR gene mutation, 20210 prothrombin gene mutation, and antiphospholipid antibodies), corticosteroid treatment, and so on. Therapeutic and prophylactic anticoagulation in these patients is influenced by many factors, including the underlying renal disease, renal, hepatic, and cardiac function, co-morbidities and accompanying treatment. Moreover, the doses of anticoagulant/antiaggregant and hemostatic medications should be considered carefully. The best and the safest anticoagulant medications in patients with chronic renal diseases (including glomerulonephritis, vasculitis, and CKD/CRF) at this point seem to be LMWHs followed by UFH in dose regimens in accordance with renal function because of their favorable safety profile, flexible dosing regimen, self-administration, short and predictable action, and the possibility to correct the dose according to GFR.

Abbreviations

ACL	Anticardiolipin antibody
ADP	Adenosine diphosphate
ANCA	Antineutrophil cytoplasmic antibody
APL	Antiphospholipid antibody
APS	Antiphospholipid syndrome
aPTT	Activated partial thromboplastin time
ATP	Adenosine triphosphate
b2GPI	Beta-2-glycoprotein I antibody
CAPD	Continuous ambulatory peritoneal dialysis
CKD	Chronic kidney disease
CRF	Chronic renal failure
CRP	C-reactive protein
CT	Computed tomography
DVT	Deep vein thrombosis
ECG	Electrocardiography
EPH	Edema-proteinuria-hypertension
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
GP	Glycoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
HIT II	Heparin-induced thrombocytopenia type II
HIV	Human immunodeficiency virus
IL-6	Interleukin 6
INR	International normalized ration
LMWH	Low-molecular weight heparin

LN	Lupus nephritis
MPs	Microparticles
MTHFR	Methylene tetrahydrofolate reductase
NF-kB	Nuclear factor kappa-B
NO	Nitric oxide
NSAIDs	Non-steroid anti-inflammatory drugs
PAI-1	Plasminogen activator inhibitor 1
PD	Peritoneal dialysis
PE	Pulmonary embolism
PGI2	Prostaglandin I2
PT	Prothrombin time
PTH	Parathyroid hormone
RAAS	Rennin-angiotensin-aldosterone system
RPF	Retroperitoneal fibrosis
RT	Renal transplantation
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SLICC	systemic lupus collaborating clinics
TF	Tissue factor
tPA	Tissue plasminogen activator
UFH	Unfractionated heparin
VTE	Venous thromboembolism
vWF	Von Willebrand factor

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