Hematologic Complications of Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is a global public health problem with both high prevalence and mortality. Subjects with CKD are fragile patients with highest number of comorbidities and prescribed medications as well as the highest rate of death and placement in long-term facilities. CKD is defined based on the presence of kidney damage or reduced glomerular filtration rate (GFR), which is considered the best overall index of kidney function. CKD staging is based on its cause, the GFR level, and degree of albuminuria. The past 20 years have seen significant improvement in recognition of the incidence, prevalence, and complications of CKD due to the standardized definition and staging of CKD in 2002. The two most common causes of mortality in the CKD population are cardiovascular disease (CVD) and Infection. Disturbances in immune homeostasis, chronic inflammation and anemia play a major role in both.

Keywords: Chronic Kidney Disease, Hematologic Complications.

Background

Definition and Staging of Chronic Kidney Disease
CKD is a general term for a number of heterogeneous disorders that result in sustained kidney damage with implications for the health of the individual. The initial decline of kidney function is asymptomatic and clinical manifestations of kidney failure occur late in the course of the disease. Definitions of kidney disease therefore include measures of function (e.g., GFR) and measures of damage (e.g., proteinuria, anatomical abnormalities).

Definition of CKD:
CKD is defined according to the KDOQI and KDIGO guidelines by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause (Definition and classification of CKD. Kidney Int Suppl (1)). The persistence of the damage or decreased function for at least three months is necessary to distinguish CKD from acute kidney disease. Kidney damage refers to pathologic abnormalities, whether established via renal biopsy or imaging studies, or inferred from markers such as urinary sediment abnormalities or increased rates of urinary albumin excretion. Decreased kidney function refers to a decreased glomerular filtration rate (GFR), which is usually estimated (eGFR) using serum creatinine and one of several available equations.

Kidney damage: Kidney damage includes pathologic abnormalities in the native or transplanted kidney. Kidney damage is identified in most cases by the presence of one of the following clinical markers:

- Albuminuria: In clinical practice, Albuminuria is thought as the best marker for impaired kidney function. Albuminuria reflects increased glomerular permeability to macromolecules (2). Albuminuria may reflect primary kidney disease or kidney involvement in systemic disease. In particular, albuminuria...
may represent widespread endothelial dysfunction, such as can be seen with hypertension, diabetes, hypercholesterolemia, smoking, obesity, and other disorders.

Although a number of different measurement methods have been used to assess and define albuminuria, the albumin-to-creatinine ratio (ACR) in an untimed "spot" urine has many advantages (3). The generally accepted threshold for an abnormally elevated ACR is 30 mg/g (3.4 mg/mmol) or greater. The KDIGO recommended that albuminuria above this threshold, regardless of cause, should be considered part of the definition of CKD (4). Individuals with a urine ACR >30 mg/g (or equivalent) have a significantly increased risk for all-cause and cardiovascular mortality (5), ESRD (6), AKI, and CKD progression compared with those who have a lower ACR (7), even when eGFR is normal. As an example, individuals with an ACR of 30 to 299 mg/g and an eGFR of 90 to 105 mL/min per 1.73 m2 had an 11-fold higher relative risk for ESRD than those whose eGFR was similar but whose ACR was below 30 mg/g.

- **Urinary sediment abnormalities**: Urinary sediment abnormalities such as red or white blood cell casts may indicate the presence of glomerular injury or tubular inflammation.

- **Imaging abnormalities**: Kidney damage may be detected by the presence of imaging abnormalities such as polycystic kidneys, hydronephrosis, and small and echogenic kidneys.

- **Pathologic abnormalities**: A kidney biopsy may reveal evidence for glomerular, vascular, or tubulointerstitial disease.

- **Kidney transplantation**: Patients with a history of kidney transplantation are assumed to have kidney damage whether or not they have documented abnormalities on kidney biopsy or markers of kidney damage.

- **Decreased GFR**: Glomerular filtration rate (GFR) is the best marker for kidney function (8). Measured GFR varies in normal individuals by age and sex (9), dietary protein intake, and possibly by race-ethnicity, although the magnitude of racial variations is not well known. Based upon clearance measurements in healthy people and in people with kidney disease, the widely accepted threshold defining a decreased GFR is less than 60 mL/min per 1.73 m2; kidney failure is defined as a GFR <15 mL/min per 1.73 m2 or treatment by dialysis.

According to KDIGO guidelines a measured GFR below this threshold should be considered part of the definition of CKD. GFR can be measured directly using the clearance of exogenous filtration markers such as inulin, iothalamate, or iohexol (9). However, these measurement methods are complex to implement. Thus, in clinical practice, GFR is typically estimated (estimated GFR, or eGFR) from the serum concentration of creatinine, an endogenous filtration marker.

In routine practice, therefore, individuals who have an eGFR below 60 mL/min per 1.73 m2 are defined as having CKD. These individuals have a significantly increased risk for all-cause and cardiovascular mortality, ESRD, AKI and CKD progression in compared with those whose eGFR is 60 mL/min per 1.73 m2 or higher, even if the ACR is normal (4). As an example, individuals with an eGFR of 45 to 59 mL/min per 1.73 m2 and a urine ACR less than 10 mg/g had a fivefold higher relative risk of ESRD compared than those with a similarly normal ACR but with an eGFR of 60 mL/min per 1.73 m2 or greater.
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Red Blood Cells

- Anemia in CKD:

Introduction:

Anemia is a common complication of CKD and associated with increased mortality and morbidity. A retrospective analysis of combined data from non-Medicare patients aged 18-63 years and from Medicare patients aged 66-85 years estimated the prevalence of anemia at 28% in patients with stage 3-5 NDDCKD with a prevalence of 22.4% in stage 3 CKD, 41.3% in stage 4 CKD, and 53.9% stage 5 CKD. In the older Medicare population, the prevalence of anemia in CKD (ACKD) was 50.1%, with a prevalence of 43.9% in stage 3 CKD, 64.0% in stage 4 CKD, and 72.8% stage 5 CKD. In patients with ESRD treated with hemodialysis (HD) for a period of 90 or more days, 80-83% had ACKD, which required erythropoiesis-stimulating agent (ESA) therapy. A study conducted in 2020 had found the mean hemoglobin concentration in DD-CKD patients was 8.6 g/dl in a predialysis collected samples (10).

Pathophysiology:

Erythropoietin (EPO), produced mainly by interstitial fibroblasts in kidney, is decreased in CKD. Patients with CKD are also experiencing EPO resistance. Both factors inhibit erythropoiesis. Epo production is stimulated mainly by hypoxia. Hypoxia inhibits prolyl hydroxylase domain (PHD) leading to increasing levels of hypoxia-inducible factor (HIF). Elevated levels of HIF stimulate EPO production (11). EPO levels do not elevate in CKD in spite of renal tissue hypoxia, which may be due to loss of fibroblast capacity for EPO expression. This leads to relatively decreased EPO levels, which becomes more evident as CKD progresses.

Iron homeostasis is also affected in CKD leading to potentiation of the pathophysiologic pathways of ACKD. Iron metabolism dysfunction can also produce ESA resistance (12), especially in DDCKD patients. Iron-restricted erythropoiesis is also common in CKD patients. Iron-restricted erythropoiesis may come in different pictures: iron deficiency, iron deficiency anemia, or functional iron deficiency (FID). Iron deficiency means decreased iron stores without anemia. Iron deficiency anemia means low RBCs mass due to decreased iron stores. FID denotes iron-restricted erythropoiesis due to inability to transfer iron to active bone marrow even with normal iron stores (13).

Oxygen is transported by hemoglobin (Hb), a tetramer with two globin chains (α and β). Each chain binds to a heme group made of a porphyrin ring and an iron atom, which carries the oxygen. Iron homeostasis is under strict regulation. Most iron in the body is restored from dead cells (old RBCs phagocytized by macrophages or hepatocytes). Few amounts of iron are absorbed to replace losses. Gastrointestinal dietary iron (Fe3+) is reduced by duodenal cytochrome B, ferric reductase enzyme, to (Fe2+) to be absorbed by duodenal enterocyte apical divalent metal transporter 1 (DMT1). then intracellular iron is stored as ferritin. Then transferred to the blood via basolateral transporter Ferroportin. In the blood, iron is oxidized (Fe3) and attached to transferrin (apotransferrin before attaching to iron). Transferrin transfers iron to tissues using it (especially, bone marrow) or for storage (mainly by the liver), where it binds to transferrin receptor (TfR). Then transferrin is taken up by cells and binds to intracellular ferritin. Transferrin has two forms: monoferric one in normal state, and diferric one during iron overload state (12).

Ferroportin is also responsible for cellular efflux of iron from its stores like macrophages and hepatocytes (14). hepcidin, produced in the liver, downregulates ferroportin. In states of iron overload or inflammation,
hepcidin binds to ferroportin and the complex is endocytosed and lysed by lysosomes (15). Elevated hepcidin leads to iron sequestration and failure of iron efflux from storage cells. Hepcidin is involved in FID and hypo-response to ESA therapy. CKD is associated with high hepcidin level as a result of chronic inflammation and decreased renal excretion. Ferroportin is also diminished in CKD. Both, high hepcidin and low ferroportin, decrease iron absorption from GIT (16) and decrease iron transfer from stores to bone marrow. Dysregulated bone and mineral metabolism play a role in Epo resistance and iron-restricted erythropoiesis. Vitamin D is a potent inhibitor of hepcidin (17). Decreased vitamin D level in CKD is associated with elevated hepcidin level and FID. Also, iron is thought to be involved in regulation of fibroblast growth factor 23 (FGF-23) (18). Iron deficiency increases FGF-23 production by osteocytes. CKD patients have higher FGF-23, leading to enhanced phosphate excretion. Patients with CKD, particularly those receiving dialysis (19), have decreased iron absorption and chronic blood loss because of platelet dysfunction, and blood loss in the dialysis membrane and tubing. Other cause for ACKD includes diminished erythropoiesis by uremic toxins, Epo resistance by (chronic inflammation or secondary hyperparathyroidism, hemolysis, vitamin B12 [cobalamin], or folate deficiency) or erythrocyte short life span (20). Renin-angiotensin system is also involved in EPO secretion. Angiotensin-converting-enzyme inhibitor (ACEI) therapy may play a role in ESAs resistance (21).

**Diagnosis:**

Anemia in CKD is associated with reduction in eGFR (in mL/min/1.73 m2 body surface area) (22). Anemia may become clinically evident when the eGFR decreases below 60 mL/min/1.73 m2 but is most common in individuals with eGFR <30 mL/min/1.73 m2. Hemoglobin concentration is considered better than hematocrit in evaluation of ACKD, as the latter is affected extra cellular fluid volume. The 2012 KDIGO Guideline for Anemia in CKD adopted the definition of WHO for anemia as a hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men (8). KDIGO anemia guideline recommends, without anemia, hemoglobin should be evaluated at least every three months in DD-CKD, every six months in stage 4-5 CKD, and yearly in stage 3 CKD (8). In anemic CKD patients, without ESA, it should be evaluated at least every month in patients with DD-CKD, and every three months in NDD-CKD. In patients with ACKD treated with ESA, Hb should be monitored at least every month during the initiation phase. In maintenance phase, Hb evaluation should be every three months in NDD-CKD patients, and every month in DD-CKD. Diagnostic workup for anemia in CKD should aim at exclusion of other causes of anemia in those patients. screening for occult GI blood loss is advised. RBCs are typically normochromic, with a normal MCH, normocytic with a normal MCV, and have a normal RDW. Echinocytes or burr cells may be found. reticulocyte count confirms decreased erythropoiesis. Evaluation of iron, transferrin saturation (TSat), and ferritin is important to exclude iron deficiency. many guidelines accept transferrin saturation at 30% or less and ferritin at 500 ng/mL or less as indicator for iron deficiency and iron therapy. clinical challenge occurs with FID, when lab results are conflicting, with low transferrin saturation and high ferritin, here safety of iron therapy is doubtful. At least, iron parameters are tested every three months in anemic CKD patients receiving ESA therapy. This should be more frequent when ESA is started or adjusted, or to evaluate iron therapy (8), both ferritin and transferrin saturation should be used together to diagnose iron deficiency or to evaluate response to iron therapy.
Ferritin, as an acute phase reactant, may be increased in patients with chronic inflammation (12). Serum levels less than 100 mcg/L in NDD-CKD or less than 200 mcg/L in DD-CKD are needed to confirm the diagnosis of iron deficiency. No evidence is available to support a certain ferritin upper limit above which FID is excluded.

Hypochromic RBCS and the reticulocyte Hb content are used less frequently to evaluate iron deficiency (13). Hepcidin level evaluation is not currently advised to assess iron status. Evaluation of vitamin B12 and RBC folic acid levels should be performed (8). Assessment of Epo level is difficult due to technical restrictions and doesn’t affect the management, as a result, it isn’t part of diagnostic workup. Absolute Epo level is usually normal or minimally elevated. But compared with the severity of anemia, relative EPO level is decreased (23).

**Prognosis:**
Mortality and Morbidity rates are increased with increased levels of anemia in CKD. Repeated hospitalizations are also reported to be increased as ACKD progresses. Left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH), independent risk factors for increased mortality risk, are also increased with ACKD. ACKD is an important risk factor for heart failure, new-onset atrial fibrillation increased CVD and mortality, impaired cognitive function, decreased functional status and exercise tolerance, decreased quality of life, and increased RBC transfusion requirements. (24).

Treatment of ACKD is not associated with reversal of mortality risk. Also, literature shows discrepancy about the effect of treating ACKD on comorbidities such as health related quality of life (HRQOL) (25). But blood transfusion rates found to be significantly decreased (26).

**Anemia in CKD:**

- **Treatment:**
  Management ACKD aims to minimize blood loss, iron replacement, and ESAs administration. Replenishing iron stores first decreases required ESA dose and minimizes ESA resistance. (27).
  Iron replacement is considered a cornerstone in the pharmacological therapy in ACKD. Oral iron is administered between meals not co-administered with calcium-based phosphate-binders. Absorption could be increased by coadministration of vitamin C. Increased hepcidin and decreased ferroportin in CKD especially ESRD leads to diminished duodenal iron absorption resulting in iron deficiency. Therefore, guidelines (8), in patients with ESRD recommend IV rather than oral iron therapy. Clinical trials and meta-analyses comparing the efficacy of oral vs. IV iron in the treatment of ACKD in patients with stage 3-5 CKD reached a similar conclusion (28).
  In patients on RRT, who are commonly having iron deficiency anemia, there is no consensus on the IV iron dose that could be taken safely every month. Some evidence indicates that a safe monthly dose is 100-200 mg per month does not exceed 300 mg per month. Doses above 400 mg per month are associated with high mortality rate in DD-CKD patients (29). However, a meta-analysis of data from seven randomized controlled trials showed that higher dose iron (defined as >400 mg/month) was not associated with a higher risk of infection or all-cause mortality. Similarly, the same meta-analysis analyzed data from fifteen observational trials and again higher dose iron (defined as >200 mg/month) was not associated with an increased risk of all-cause mortality, infection, cardiovascular events, or hospitalizations (30).
  Oral iron formulations (e.g., ferrous sulfate, ferrous gluconate, ferrous fumarate) are relatively safe. Side effects of oral iron are commonly gastrointestinal including dark stool, dyspepsia, and constipation. Sacroferric oxyhydroxide and ferric citrate, new drugs, are acting as phosphate-binders and iron supplements.
IV iron formulations (e.g., iron sucrose, ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron dextran) can lead to hypersensitivity, including anaphylactic and anaphylactoid reactions. Anaphylaxis on initial administration is most common with iron dextran, and least common with iron sucrose (31). Evidence regarding safety of IV iron compared to oral iron is not uniform. Some studies reported a similar risk for infectious or cardiovascular events with oral and IV iron in patients with NDD-CKD and ESRD. Other studies found that compared to oral iron, IV iron is associated with a higher risk of infectious or cardiovascular events in NDD-CKD (32).

Iron replacement therapy may result in iron overload leading to formation of circulating free iron, which enhances bacterial growth in vitro. Free iron leads also to impaired immune effector cell function, endothelial dysfunction, and increased oxidative stress (33).

MRI showed hepatic iron overload in HD patients receiving IV iron. However, the clinical significance of this sign is not established. In calcific uremic arteriolopathy, iron was found deposited in microvasculature. More studies are needed to assess the role of iron in the pathophysiology of this disease. FDA approved the first recombinant human Epo (rHuEPO) in 1989 for treatment of ACKD in DD-CKD and in 1993 for NDD-CKD patients (34).

Pharmacological therapy of anemia decreases the need for RBC transfusions, may cause partial regression of LVH, may reverse clinical manifestations and symptomatology, may improve functional status, and some even report improved survival. The benefits of treatment of anemia remain a topic of debate. For example, a systematic review of the effect of ESA therapy on HRQOL in CKD patients did not reveal any significant improvement (25).

**ESAs approved by FDA include:**

B- Darbepoetin alpha was approved for use in DD and NDD-CKD patients on September 17, 2001.
C- Methoxy polyethylene glycol-epoetin beta, a continuous erythropoiesis receptor activator (CERA), was approved for use in all CKD patients on November 14, 2007.
D- On May 15, 2018, the first epoetin alpha biosimilar, epoetin alfa-epbx, was approved by the FDA for treatment ACKD.

ESA therapy is initiated on clinical symptoms of anemia, or when Hb levels decreases below 9 g/dL. Target Hb should be 10-11 g/dL. Levels above 12 g/dL must be avoided as they lead to poor blood pressure control, increased risk of stroke and mortality (34).

Most starting ESA doses are weight based. For example, epoetin alpha is usually started at 50-100 units/kg three times a week. Darbepoetin alpha is usually started at a dose of 0.45 mcg/kg once a week or 0.75 mcg/kg once every 2 weeks in dialysis patients or at a dose of 0.45 mcg/kg every 4 weeks in NDDCKD (usually 60-200 mcg every 2-4 weeks). Methoxy polyethylene glycol-epoetin beta is usually started at a dose of 0.6 mcg/kg once every 2 weeks (usually 25-75 mcg every 2-4 weeks). All ESA doses are titrated to achieve a goal Hb level of 10-11 g/dL in patients with ESRD. ESAs should be stopped if Hb level exceeds 11-11.5 g/dL, and the dose reduced before resumption of therapy.

Higher or normal hemoglobin goals must be avoided (35). ESA and iron therapy have a survival benefit in patients with decreased Hb. However, benefit disappears, and mortality risk is elevated when therapy is used in patients with high hemoglobin levels (36).

In patients with ACKD and cancer, ESAs are relatively contraindicated due to evidence pointing to enhancement of tumor growth and increased mortality in the cancer patient population (37).
Inhibitors of HIFPHDs, (38), currently under clinical trials, increase HIF concentration by decreasing degradation of the alpha subunit of HIF. Higher levels of HIF upregulate expression of hypoxia-induced genes, such as Epo and DMT1. Trials found that HIFPHDs are effective in management of anemia in CKD by increasing endogenous EPO and improving iron homoeostasis (e.g., improved intestinal iron absorption and decreased circulating hepcidin levels). Induction of tumor growth and pulmonary hypertension are theoretic side effects of these novel drugs, but no serious effects were reported.

**Erythrocytosis/Polycythemia:**

Erythrocytosis can occur with CKD in two scenarios: cystic kidney disease (mostly autosomal dominant polycystic kidney disease [ADPKD]), and after kidney transplantation. In ADPKD, erythrocytosis is thought to be due to pericystic local tissue hypoxia and dysregulated HIF proteins, with a secondary increase in Epo production. In ESRD patients treated with HD and not on Epo therapy, an elevated Hb concentration was not associated with increased risk of mortality (39). Erythrocytosis in this patient population may be associated with cystic kidney disease, chronic hypoxia due to pulmonary or CVD, and tobacco use.

Erythrocytosis after transplantation complicates around 8-15% of kidney transplants and occurs 8-24 months after transplantation with a spontaneous remission rate of 25% at 2 years (40). This is clinically relevant because 10-30% of polycythemic patients develop arterial or venous thrombotic complications (including cerebrovascular accident and pulmonary embolism) with a 1-2% mortality rate. Treatment with an ACEI or an angiotensin receptor blocker (ARB) is preferred (40). Angiotensin II (AII) is a direct stimulus to Epo production. Increased (AII) production may be encountered in patients with renal hypoperfusion and tissue hypoxia, such as those with transplant renal artery stenosis or native renovascular disease, who develop erythrocytosis, which improves with ACEI or ARB therapy (41).

**Platelets:**

- **Platelet Dysfunction:**

  **Introduction**

Patients with CKD are at increased risk of hemorrhage as well as thrombosis. Both risks increase progressively with worsening CKD. Abnormalities in either eGFR or UAER have been associated with increased risk of hemorrhage. A patient with an eGFR of <15 mL/min/1.73 m2, and an UACR >300 mg/g has an adjusted relative risk of all-cause major hemorrhage of 5.5 compared to one with an eGFR >90 mL/min/1.73 m2, and an UACR <30 mg/g. It is estimated that 14.3% of patients will develop a major hemorrhagic event for ESRD patients within three years after initiating dialysis. These results were also noted in more specific CKD subpopulations. Patients with CKD and high CVD risk have a 1.5-fold increased risk of bleeding compared to matched subjects with no CKD (42). This risk is increased with albuminuria as well as decreased eGFR, but the risk association is stronger with albuminuria. For example, the risk is 3.5-fold in a patient with an eGFR <45 mL/min/1.73 m2 and albuminuria compared to a patient with eGFR above 45 mL/min/1.73 m2 and no albuminuria. Similarly, in patients with non-ST-elevation myocardial infarction or unstable angina who had percutaneous coronary intervention and received anticoagulant therapy, CKD was associated with a higher risk of major and minor bleeding as well as restenosis at 30 days and 180 days.

The risk increased progressively with the severity of CKD (43). NDD-CKD adult patients aged 66 years or more who were treated with warfarin for atrial fibrillation had an increased risk of major hemorrhage. The risk is also higher in dialysis patients. Finally, the risk of gastrointestinal hemorrhage was significantly higher in NDD-CKD patients depending on the eGFR. In a patient with eGFR <30 mL/min/1.73 m2, the
The hazard ratio was 7.06 compared to a patient with eGFR >90 mL/min/1.73 m² (44). The risk of hemorrhage is also approximately five times higher in dialysis patients compared to patients without CKD (45).

**Pathophysiology:**

Platelets come from bone marrow megakaryocytes and migrate to the circulation, where a major role in primary hemostasis. Platelets have heterogeneous components (46):

1. A peripheral zone consisted of a plasma membrane glycocalyx. A zone that contains the surface glycoproteins (GP), integral for platelet activation and adhesion and aggregation; a lipid bilayer, which contains tissue factor (coagulation factor III) that plays a key role in binding coagulation factors after platelet activation; and a submembrane area with a membrane contractile cytoskeleton made of actin filaments that determine platelet morphology and mediate receptor translocation to the surface and regulate platelet activation signal systems.

2. A sol-gel zone which has a matrix of circumferential microtubules and microfilaments. This is important for the cytoplasmic contractile cytoskeleton. This plays a major role in the platelet morphology and keeps secretery organelles apart from each other and from other structures. Also, on platelet activation, it contracts to place organelles in the platelet center, where they release their contents.

3. An Organelle Zone contains alpha-granules where von Willebrand factor (VWF) can be found, dense granules that contain serotonin (5-hydroxytryptamine, 5HT) and adenosine diphosphate (ADP), and lysosomes.

After endothelial injury, platelets move to the site of injury, where platelet adhesion occurs. Adhesion is mediated by the binding of exposed subendothelial extracellular matrix collagen to platelet surface GPVI and integrin α2b1, and in conditions of high shear, the binding of GPIbα-IX-V complex to VWF (47). Platelet activation occurs when platelet thrombin receptors, protease-activated receptors PAR1 and PAR4, interact with thrombin (byproduct of prothrombin, coagulation factor II) (48). An activation signal may be amplified via a positive feedback loop generated by the interaction of ADP and 5HT (released by platelet dense granules) with platelet receptors P2Y1, P2Y12, and 5HT2A, or by the interaction of thromboxane A2 (the product of arachidonic acid metabolism via the cyclooxygenase 1 pathway) with its thromboxane prostanoid receptor on the platelet surface.

Platelet aggregation is mediated by fibrinogen (coagulation factor I) and by the binding of VWF to activated platelet surface GP integrin αIibβ3 (previously known as GPIIb/IIIa) (49). The aggregation can be increased by other mediators. Platelet adhesion, activation, and aggregation result in the formation of a platelet plug. This plug is transformed to a thrombus by secondary hemostasis and formation of a fibrin clot.

**References.**


