

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**

**DOCTORAL SCHOOL**

**PHD THESIS**

**ABSTRACT**

**HEMOSTASIS IN ACUTE KIDNEY INJURY  
AND CHRONIC KIDNEY DISEASE**

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**2018**

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**Keywords:** hemostasis, acute kidney injury, chronic kidney disease, hemorrhage, thrombosis.

## **Introduction**

Hemostasis disorders in uremic patients (acute kidney injury and chronic kidney disease) are a major concern in nephrology, in intensive care units and in other medical specialties (surgery, obstetrics and gynecology, etc.) because these disorders are extremely complex regarding their physiopathological generating mechanisms, as well as their clinical manifestations and the required therapeutic procedures.

## **Current State of Knowledge**

### **I. Acute Kidney Injury**

The term acute kidney injury refers to the acute worsening of the kidney function, involving an increase of urea and creatinine retention that can or cannot associate reduced diuresis. Combining the RIFLE and AKIN criteria is part of the KDIGO Guidelines, in which acute kidney injury is classified in three stages based on the serum creatinine level elevation and diuresis. Stage III includes patient treated by hemodialysis. (2)

The incidence of acute kidney injury in hospitals and intensive care units is continuously increasing. About 4-5% of all patients admitted in intensive care units require renal substitution therapy and up to two thirds of these admitted patients develop some degree of acute kidney injury that can be found in the RIFLE criteria. (3,4)

### **II. Chronic Kidney Disease**

Chronic kidney disease (CKD) is defined by structural or functional renal abnormalities, that persist more than 3 months, highlighted by a urinary albumin/creatinine ratio higher than 30mg/g and other abnormal laboratory tests or a decrease of the glomerular filtration rate (GFR) below 60 ml/min/1.73m<sup>2</sup>. (52)

According to the first detailed global report (Global Kidney Health Atlas) regarding healthcare providing for kidney disease one out of ten people worldwide suffers from chronic kidney

disease. (54) In Romania, the estimated prevalence of chronic kidney disease is 6.7% according to the 2013 PREDATORR trial. (55)

Hemostasis disorders, especially hemorrhage, are frequently found in chronic kidney disease patients, mostly in advanced stages. The hemorrhagic syndrome's pathogenesis is mostly related to platelet dysfunction, not only regarding the blood platelet count, but also regarding their function. Other factors related to the coagulation mechanism are also involved (vascular factors and coagulation factors). (102) Hypercoagulation is less found in stage 5 chronic kidney disease. The most frequently mentioned factors involved in hypercoagulation are: the nephrotic syndrome and proteinuria, dyslipidemia and hypercoagulation in the extracorporeal blood circuit (platelet aggregation, an increase of FI and FVIII coagulation factors, fibrinolysis inhibition etc.). (110)

### **III. Hemostasis Physiology and Physiopathology**

Hemostasis is a biological phenomenon offering protection against hemorrhagic and thrombotic accidents. (108) Both hemorrhagic and thrombotic complications are associated with renal pathology. In both these two cases immunologic factors, as well as other factors related to renal dysfunction (retention substances that affect the vascular endothelium and platelets) are involved. (102,185)

## **Personal Contribution**

### **IV. Working Hypothesis, Aims and Objectives**

The main aims of our research were:

1. To determine the effects of acute kidney injury (treated or not using hemodialysis) and those of end-stage chronic kidney disease on hemostasis;
2. To determine the effects of hemodialysis renal replacement therapy and other medication on hemodialysis;

The main objectives of our research were:

1. To individually analyze each type of kidney failure syndrome (acute kidney injury and chronic kidney disease) considering hemostasis disorders and to outline their common and differentiating clinical and physiopathological features;
2. To assess the kidney dysfunction's etiological factor's impact on hemostasis;
3. To assess the impact of hemostasis disorders on the outcome of kidney failure patients;
4. To analyze the evolution of acute kidney injury patients that required hemodialysis compared to those who did not;

## **V. Material and Method**

We performed two observational prospective trials. The first trial consisted in analyzing acute kidney injury patients divided in two groups: the first group included patients that underwent hemodialysis and the control group included patients that required medical treatment only and, therefore, less severe acute kidney injury cases. We also conducted a second trial in which we analyzed a group of stage 5 chronic kidney disease patients in a chronic hemodialysis program.

We recorded data regarding each patient (age, gender, blood tests results, hemorrhagic or thrombotic complications, comorbidities, acute kidney injury etiology, hemodialysis treatment). These data were stored in individual databases and tables for each group of patients. Later on, we recorded a series of complications caused by hemostasis alterations. In order to achieve correlations between different parameters, we used the “regression” (Microsoft Excel), the ANOVA test and Student's T-test, as these statistical tests are useful in comparing averages for two or more groups and generating values for p and R square parameters.

## **VI. Results**

The first trial included 81 cases of acute kidney injury treated by hemodialysis and 111 cases of acute kidney injury patients that did not require this procedure and the second trial followed 218 stage 5 chronic kidney disease patients included in a chronic hemodialysis program.

In the first trial patients were classified based of the etiological factor that had caused the acute kidney injury: severe sepsis and septic shock, posttraumatic, postoperative, pancreatitis, toxic, leptospirosis, aggravated chronic nephropathies. Therefore, in the first group of patients severe sepsis and septic shock represented the main cause of acute kidney injury (34.56%), while in the second group septic etiology represented only 17.11% of all cases. In contrast, in the second group, the main cause of acute kidney injury consisted in non-septic hydroelectrolytic balance disorders.

We noticed an important difference regarding the rate of hemorrhagic complications between the two groups of patients from the first trial. Therefore, in the first group of patients, hemorrhagic complications were found in 59.25% of all cases, while in the second group these complications were found in only 15.32% of all subjects. We also found a significant difference regarding hemorrhagic complications in septic acute kidney injury cases. The rate of these complications was 96.42% in the first group and only 5.26% in the second one.

Taking into consideration all clinical aspects of bleeding complications from both groups of the first trial, we noticed a highly significant difference ( $p = 0.00725$ ) in favor of patients undergoing hemodialysis.

Regarding thrombotic complications, we did not record any major thrombosis in patients with acute kidney injury (major vessel thrombus spotted at vascular echography, intracardiac thrombus identified by echocardiography or other thrombus revealed by contrast computer tomography) and so we can conclude that prophylactic anticoagulation was extremely effective. However, microthrombi (in the setting of disseminated intravascular coagulation) were found in histological examination of samples obtained from acute kidney injury deceased patients that had been treated using hemodialysis.

In the second trial, hemorrhagic disorders were found in 42.2% of all chronic kidney disease patients, but most of these complications were related to vascular access and severe hemorrhage was very rare. In this group of patients we also recorder thrombotic complications, as hemodialysis had to be stopped before the usual 4 hour duration in 14.22% of all cases. Considering the fact that most patients (98.62%) underwent 3 hemodialysis procedures per week

and that the total number of procedures recorder within a year was 31392, we can consider that the complication rate was low.

We classified hemorrhagic complications in two categories (mild/moderate and severe), based on criteria explained in the chapter regarding “Material and Method”. Severe hemorrhage were more frequent only in the first group of hemodialysis acute kidney injury patients in which these complications represented 56.25% of all hemorrhage, while in the second acute kidney injury group they represented 23.52% and in the second trial 34.78% of all hemorrhagic complications were severe.

Mortality was significant only in the case of acute kidney injury patients that required hemodialysis, as in this first group 43.2% off all patients were deceased. The highest mortality rate was found in postoperative acute kidney injury (60%) and in patients with severe acute pancreatitis (58.33%). We also found a significant correlation ( $p = 0.01$ ) between the rate of hemorrhagic complications and the mortality rate considering individual acute kidney injury etiology groups. In the other two groups mortality rates were lower than 10% and therefore we could not proceed towards a detailed statistical analysis of deceased patients.

## **VII. Discussion**

### **Trial 1: Hemostasis Disorders in Acute Kidney Injury**

The acute kidney injury’s etiological factor affects hemostasis through various mechanisms, as shown by our analyzed patients and literature data. Etiological factors are complex and have a different physiopathological background depending on the acute kidney injury’s etiology and also on its clinical aspect. Therefore, severe acute kidney injury cases (RIFLE stage III) required hemodialysis and had a much stronger impact on hemostasis (59.25% rate of hemorrhagic complications) compared to those who did not require renal substitution (15.31% rate of hemorrhagic complications). Other factors, such as various therapies, surgical procedures required to treat the cause of kidney injury, and hemodialysis, are also involved.

Septic shock and severe sepsis had the most obvious impact on the coagulation balance, as well as posttraumatic and postoperative shock. In these situations, hemostasis is affected from the

onset by intravascular disseminated coagulation. Coagulation factors are consumed, with an impact on the vascular endothelium, as well as a systemic impact. (211)

The evolution and prognosis of acute kidney injury patients requiring hemodialysis was influenced by hemorrhagic complications. All cause general mortality recorded in the RIFLE stage III acute kidney injury group was 43.2% during hospitalization, in correlation with the hemorrhage rate. Comparing our results with literature data, the mortality rate was higher than that published in a meta-analysis that included more than 49000 RIFLE criteria-classified patients (37% mortality rate in “Failure” stage), but it is below the highest literature-reported rate of 62%. (222, 223) In exchange, the mortality rate of RIFLE stages I and II acute kidney injury patients was at the lower limit of the previously published data. (1, 22)

### **Trial 2: Hemostasis Disorders in Stage 5 Chronic Kidney Disease**

Hemostasis affecting mechanisms in chronic kidney disease are mostly related to the uremic syndrome and they involve three aspects: one regarding the vascular endothelium, another regarding platelets (alterations in their number and function), and the last aspect refers to the coagulation factors.

Vascular alterations consist in increased vessel fragility vascular endothelial permeability. The vascular system is affected especially in advanced chronic kidney disease stages (stages 4 and 5) because of the retention of several metabolic factors due to reduced renal excretion. Platelets are affected in terms of reduced count, but this finding is not present in all cases. Alterations of platelet quality (so-called thrombasthenia) are more important than their reduced number. A reduced interaction between platelets and endothelium occurs, leading to altered adhesion and aggregation. (67)

In patients with chronic kidney disease, the frequently-associated comorbidities can also affect the coagulation balance. In our studied group, liver dysfunction was present in 15.12%, diabetes mellitus in 22.01%, and cardiovascular disease that required anticoagulant or antiplatelet treatment in 42.19% of all patients.

## VIII. General Conclusions

1. Hemostasis disorders (hemorrhagic and thrombotic) are found in both acute kidney injury and chronic kidney disease, but in different proportions and mostly caused by different physiopathological mechanisms;
2. In hemodialysis-treated acute kidney injury patients hemorrhagic complications occurred in over 50% of all cases, unlike in patients that did not require hemodialysis, in which the incidence of hemostasis disorders was much lower; therefore we consider that hemodialysis has an important role in altering hemostasis;
3. In end-stage chronic kidney disease patients, hemostasis disorders occurred in approximately 40% of all cases during one year follow-up, the actual number of complications being low compared to the total number of hemodialysis procedures;
4. In acute kidney injury patients the kidney failure's etiology had an important role in causing hemorrhagic complications;
5. Long-term anticoagulant and antiplatelet treatment, as well as existing comorbidities, had an important contribution in causing hemorrhagic complications in patients with chronic kidney disease;
6. The most hemorrhagic complications in the first group with acute kidney injury undergoing hemodialysis occurred in septic patients, while in the second group the most hemorrhages were found in pancreatitis patients and postoperative;
7. Mild and moderate hemorrhages were frequently found in chronic kidney disease patients and in those with medically treated acute kidney injury, while severe hemorrhage was more frequent in hemodialysis-treated acute kidney injury;
8. Thrombotic complications with a clinical or imagistic diagnosis occurred only in chronic kidney disease patients, outlining the efficacy of prophylactic anticoagulation in admitted patients;
9. Thrombotic complications in chronic kidney disease patients were very few compared to the total number of hemodialysis procedures;

10. In acute kidney injury patients only microthrombosis were found in histological examination of deceased patients, occurring in the context of disseminated intravascular coagulation, sometimes associated with hemorrhagic syndromes;

11. Mortality was high in patients with acute kidney injury undergoing hemodialysis, while it was less significant in the other two groups;

12. Mortality was correlated with hemorrhagic complications in acute kidney injury undergoing hemodialysis;

13. Hemorrhagic complications had a negative impact on the evolution of some admitted patients, worsening the renal failure syndrome;

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