D-dimer, PT and APTT levels among Renal Transplant Patients in Sudan

A thesis submitted for partial fulfillment of requirements of M.Sc. degree in Hematology

Student
Zubaida Mohamed Ahmed Abdalbagi, B.S.c 2013

Department of Hematology – Faculty of Medical Laboratory Sciences - Khartoum University

Supervisor
Dr. Hiba Badreldin Khalil, PhD

Department of Hematology – Faculty of Medical Laboratory Sciences - Alneelain University

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اقرأ باسم ربك الذي خلق

صدق الله العظيم

سورة العلق

صدق الله العظيم
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List of Abbreviations

**ACEIs**: Angiotensin Converting Enzyme Inhibitors

**ACR**: Albumin-to-Creatinine Ratio

**AKI**: Acute Kidney Injury

**APC**: Activated Protein C

**APTT**: Activated Partial Thromboplastin Time

**ARB**: Angiotensin Receptor Blocker

**BD**: Brain-Dead

**BKPA**: British Kidney Patient Association

**CKD**: Chronic Kidney Disease

**CKD-MBD**: Chronic Kidney Disease-Mineral and Bone Disorder

**CT**: Computed Tomography

**DCD**: Donation after Cardiac Death

**D-D**: D-dimer

**DIC**: Disseminated Intravascular Coagulation

**DMSA**: Dimercaptosuccinic Acid

**dRVVT**: Dilute Russell's Viper Venom Time

**DVT**: Deep Venous Thrombosis
EDTA: European-Dialysis-and-Transplantation
ELT: EuglobulinLysis Time
ESKD: End-Stage Kidney Disease
ESRD: End Stage Renal Disease
FDP: Fibrin Degradation Product
FGF-23: Fibroblast Growth Factor-23
GFR: Glomerular Filtration Rate
GPIb: Glycoprotein Ib
HIT: Heparin-Induced Thrombocytopenia
HLA: Human Leukocyte Antigens
HMWK: High-Molecular-Weight Kininogen
HUS: Hemolytic-Uremic Syndrome
ICTH: International Committee on Thrombosis and Homeostasis
ITP: Immune Thrombocytopenic Purpura
IVIG: Intravenous Immunoglobulin
PAF: Platelet-Activating Factor
PAI1: Plasminogen Activator Inhibitor-1
PAI2: Plasminogen Activator Inhibitor-2
PE: Pulmonary Embolism
**PGI2**: Prostacycline

**PIVKAs**: Proteins Formed In Vitamin K Absence

**PLA2**: Phospholipase A2

**PNH**: Paroxysmal Nocturnal Hemoglobinuria

**PT**: Prothrombin Time

**PTH**: Parathyroid Hormone

**TCT**: Thrombin Clotting Time

**TEG**: Thromboelastography

**TF**: Tissue Factor

**TFPI**: Tissue Factor Pathway Inhibitor

**TM**: Thrombomodulin

**t-PA**: Tissue Plasminogen Activator

**tPA**: Tissue Plasminogen Activator

**TTP**: Thrombotic Thrombocytopenic Purpura

**TXA2**: Thromboxane A2

**VKORC**: Vitamin K epoxide Reductase

**VWF**: Von Willebrand Factor

**ZPI**: Protein Z-related Protease Inhibitor
Dedication

To all who gave my life meaning?

My parents

My husband

My family

My friends

To all who helped me even with words?
Acknowledgment

Thanks, praise to almighty God who gives me the strength and health to achieve this work and for every thing.

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Abstract

Background: Kidney Transplantation is acknowledged as a major advance of modern medicine which provides high-quality life years to patients with ESRD. Microvascular thrombosis and fibrinolytic disorders have been recognized as main cause of allograft rejection in renal transplanted patients, but the pathway through which it occurs has not been clarified yet. **Aim:** To determine D-dimer, PT and APTT levels among pre and post renal transplant patients in Sudan. **Materials and Methods:** A descriptive comparative cross sectional study obtained at Sudan University of Science and Technology in period from February to May 2017, the practical worked is performed in the Laboratory of Sharg Alnine Hospital in Khartoum state. Fifty patients of pre renal transplant on dialysis as control and 50 patients of post renal transplant from nephrology unit were enrolled in this study. Their age ranged between 18-70 years. Thirty nine (78%) of them were males and 11 (22%) were females. About 4.5 ml of citrated blood was collected from each patient for, D-dimer, PT and APTT performance and the data was analyzed by SPSS. **Results and Conclusions:** The study observed that, significant differences of D-dimer levels between control group and patients group (P .value< 0.05), while there were no significant differences between PT and APTT in control group and patients group (P. value> 0.05). The study concluded that, the renal transplantation can correct D-dimer elevation in patients of CKD.
ملخص الدراسة

مقدمة البحث: زراعة الكلى معترف بها أنها تطور رئيسي في الطب الحديث حيث تقدم جودة عالية منذ اعوام لمرضى الفشل الكلوي (المرحلة الأخيرة لمرضى الفشل الكلوي) في كل العالم و يصحح مشاكل تخثر الدم لمرضى الفشل الكلوي.

هدف البحث: قياس الدي دايمر، زمن البروثرومبين و زمن الثرمبوبلاستين الجزئي المنشط لدى مرضى زراعة الكلى (قبل وبعد الزراعة).

الطرق والوسائل: دراسة تحليلية وصفية اخذت من جامعة السودان للعلوم والتكنولوجيا في الفترة من فبراير إلى مايو 2017. الجزء العملي تم في مختبر مستشفى شرق النيل في ولاية الخرطوم. 50 من مرضى الكلى قبل الزراعة كمجموعة ضابطة و 50 بعد الزراعة في وحدة الكلى في مستشفى شرق النيل. اعمارهم تتراوح ما بين 18-70 سنة. 39% منهم ذكور و 11% منهم إناث. تم اخذ 4.1 مليلتر تقريبا من الدم الوريدي من كل مريض وتم وضعه في وعاء يحتوي على مانع تجلط ثلاثي سترات الصوديوم واستخلص المصل الدموي لقياس الدي دايمر، زمن البروثرومبين و زمن الثرمبوبلاستين الجزئي المنشط وتم تحليل النتائج بواسطة برنامج الحزم الإحصائية للعلوم الاجتماعية إصداره 20.

النتيجة والخلاصة: أظهرت النتيجة فروقات ذات دلالة إحصائية في مستوى الدي دايمر بين المرضى قبل زراعة الكلى وبعد الزراعة (القيمة المعنوية أقل من 0.05) بينما أظهرت النتائج عدم وجود فروقات ذات دلالة إحصائية بين المرضى قبل وبعد زراعة الكلى في زمن البروثرومبين و زمن الثرموبلاستين الجزئي المنشط (القيمة المعنوية أكبر من 0.05). اشارت المحصلة أن زراعة الكلى يمكن أن تصحح ارتفاع مستوى الدي دايمر في مرضى الفشل الكلوي.
Chapter One

1. Introduction and Literature Review

1.1 Chronic Kidney Disease

Chronic kidney disease (CKD), also known as chronic renal disease, is progressive loss in kidney function over a period of months or years. The symptoms of worsening kidney function are not specific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a bloodline relative with CKD. This disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, pericarditis or renal osteodystrophy (the latter included in the novel term CKD-MBD) (Liao, et al. 2012) (Ferri, et al. 2017). CKD is a long-term form of kidney disease; thus, it is differentiated from acute kidney disease (acute kidney injury) in that the reduction in kidney function must be present for over 3 months. CKD is an internationally recognized public health problem affecting 5–10% of the world population (Eknoyan, et al. 2004) (A Martínez, et al. 2014). Chronic kidney disease is identified by a blood test for creatinine, which is a breakdown product of muscle metabolism. Higher levels of creatinine indicate a lower glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. Creatinine levels may be normal in the early stages of CKD, and the condition is discovered if urinalysis (testing of a urine sample) shows the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests, and sometimes a kidney biopsy (removing a small sample of kidney tissue) are employed to find out if a
reversible cause for the kidney malfunction is present (Plantinga LC, et al. 2010). Previous professional guidelines classified the severity of CKD in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is often called end-stage kidney disease, end-stage renal disease, or end-stage kidney failure, and is largely synonymous with the now outdated terms chronic renal failure or chronic kidney failure; and usually means the patient requires renal replacement therapy, which may involve a form of dialysis, but ideally constitutes a kidney transplant. Urea accumulates, leading to azotemia and ultimately uremia (symptoms ranging from lethargy to pericarditis and encephalopathy). Due to its high systemic circulation, urea is excreted in eccrine sweat at high concentrations and crystallizes on skin as the sweat evaporates ("uremic frost"). Potassium accumulates in the blood (hyperkalemia with a range of symptoms including malaise and potentially fatal cardiac arrhythmias). Hyperkalemia usually does not develop until the glomerular filtration rate falls to less than 20-25 ml/min/1.73 m2, at which point the kidneys have decreased ability to excrete potassium. Hyperkalemia in CKD can be exacerbated by acidemia (which leads to extracellular shift of potassium) and from lack of insulin. Erythropoietin synthesis is decreased causing anemia. Fluid volume overload symptoms may range from mild edema to life-threatening pulmonary edema. Hyperphosphatemia, due to reduced phosphate excretion, follows the decrease in glomerular filtration (Chavkin LC, et al. 2011). Hyperphosphatemia is associated with increased cardiovascular risk, being a direct stimulus to vascular calcification (Hruska KA, et al. 2008). Moreover, circulating concentrations of fibroblast growth factor-23 (FGF-23) increase progressively as the renal capacity for phosphate excretion declines, but this adaptive response may also contribute to left ventricular hypertrophy and increased mortality in CKD patients (Faul C, et al. 2011)( Gutiérrez OM, et al. 2008). Hypocalcemia, due to 1, 25 dihydroxyvitamin
D3 deficiency (caused by stimulation of FGF-23 and reduction of renal mass) (Bacchetta J, et al. 2012) and resistance to the calcemic action of parathyroid hormone (Bover J, et al. 1994). Osteocytes are responsible for the increased production of FGF-23, which is a potent inhibitor of the enzyme 1-alpha-hydroxylase (responsible for the conversion of 25-hydroxycholecalciferol into 1, 25 dihydroxyvitamin D3) (Longo, et al, 2012). Later, this progresses to secondary hyperparathyroidism, renal osteodystrophy, and vascular calcification that further impair cardiac function. An extreme consequence is the occurrence of the rare condition named calciphylaxis (Brandenburg VM, et al. 2011). Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) represents one of the many complications of CKD. Notice the link between kidney, bone and heart in the CKD-MBD European-Dialysis-and-Transplantation (EDTA) Working Group logo. The concept of chronic kidney disease-mineral bone disorder (CKD-MBD) (Ferri, et al. 2017) (Moe S, et al. 2006) currently describes a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of: 1) abnormalities of calcium, phosphorus (phosphate), parathyroid hormone, or vitamin D metabolism; 2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength (renal osteodystrophy); and 3) vascular or other soft-tissue calcification. CKD-MBD has been associated to poor hard outcomes (Ferri, et al. 2017). Metabolic acidosis (due to accumulation of sulfates, phosphates, uric acid etc.) may cause altered enzyme activity by excess acid acting on enzymes; and also increased excitability of cardiac and neuronal membranes by the promotion of hyperkalemia due to excess acid (acidemia) (Adrogué H,J et al, 1981). Acidosis is also due to decreased capacity to generate enough ammonia from the cells of the proximal tubule (Damman, et al, 2014). Iron deficiency anemia, which increases in prevalence as kidney function decreases, is especially prevalent in those requiring hemodialysis. It is multifactorial
in cause, but includes increased inflammation, reduction in erythropoietin, and hyperuricemia leading to bone marrow suppression. People with CKD suffer from accelerated atherosclerosis and are more likely to develop cardiovascular disease than the general population. Patients afflicted with CKD and cardiovascular disease tend to have significantly worse prognoses than those suffering only from the latter (Damman, et al, 2014). Sexual dysfunction is very common in both men and women with CKD. A majority of men have a reduced sex drive, difficulty obtaining an erection, and reaching orgasm, and the problems get worse with age. A majority of women have trouble with sexual arousal, and painful menstruation and problems with performing and enjoying sex are common (Vecchio M, et al. 2010).

Complications of CKD contd…

Immune system
- Immunosuppression due to uraemia or drugs

Fluid and electrolyte homeostasis
- Hyperkalaemia
- Volume overload
- Dehydration

Neurological abnormalities
- GNS changes: mild personality change, asterixis, myoclonus, encephalopathy and convulsions
- Peripheral neuropathy, glove and stocking sensory loss, progressing to motor changes

Haemostasis and coagulation
- Uraemic thromboocytopenia
- Prothrombotic tendency/hypercoagulation and reduced fibrinolysis
- Vascular access thrombosis
1.1 Causes of Chronic Kidney Disease

The most common recognized cause of CKD is diabetes mellitus. High blood pressure is also a very common cause of chronic kidney disease. Other causes of CKD include idiopathic (i.e. unknown cause, often associated with small kidneys on renal ultrasound) and glomerulonephritis (Chavkin, et al. 2011). Together, these cause about 75% of all adult cases. Historically, kidney disease has been classified according to the part of the kidney anatomy involved (Rahman, e t al. 1998). Vascular disease includes large vessel disease such as bilateral renal artery stenosis and small vessel disease such as ischemic nephropathy, hemolytic-uremic syndrome, and vasculitis. Glomerular disease comprises a diverse group and is classified into: Primary glomerular disease such as focal segmental glomerulosclerosis and IgA
nephropathy (or nephritis). Secondary glomerular disease such as diabetic nephropathy and lupus nephritis. Congenital disease such as polycystic kidney disease. Tubulointerstitial disease includes drug- and toxin-induced chronic tubulointerstitial nephritis, and reflux nephropathy. Obstructive nephropathy is exemplified by bilateral kidney stones and diseases of the prostate such as benign prostatic hyperplasia. On rare cases, pinworms infecting the kidney can also cause nephropathy. Nontraditional causes of CKD (CKDu) are denoted if the common causes of CKD are not present: CKD of unknown cause is the subject of study by the Sri Lanka Ministry of Health and the World Health Organization 2009–2012 (Redmon JH, et al., 2014). Mesoamerican nephropathy, a form of CKDu, is "a new form of kidney disease that could be called agricultural nephropathy" (Orantes, et al. 2014).

1.1.2 Diagnosis

Diagnosis of CKD is largely based on the clinical picture combined with the measurement of the serum creatinine level. In many CKD patients, previous kidney disease or other underlying diseases are already known. A significant number present with CKD of unknown cause. In these patients, a cause is occasionally identified retrospectively (Qaseem A, et al. 2013).

1.2.2.1 Differential diagnosis

It is important to differentiate CKD from acute kidney injury (AKI) because AKI can be reversible. Abdominal ultrasound, in which the size of the kidneys is measured, is commonly performed. Kidneys with CKD are usually smaller (≤ 9 cm) than normal kidneys, with notable exceptions such as in early diabetic nephropathy and polycystic kidney disease. Another diagnostic clue that helps differentiate CKD from AKI is a gradual rise in serum creatinine (over several months or years) as
opposed to a sudden increase in the serum creatinine (several days to weeks). If these levels are unavailable (because the patient has been well and has had no blood tests), it is occasionally necessary to treat a patient briefly as having AKI until the kidney impairment has been established to be irreversible (Qaseem A, et al. 2013).

### 1.1.3 Severity-based Stages

All individuals with a glomerular filtration rate (GFR) < 60 ml/min/1.73 m2 for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage (Liao, et al. 2012).

The rationale for including these individuals is that reduction in kidney function to this level or lower represents loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications such as the development of cardiovascular disease. Protein in the urine is regarded as an independent marker for worsening of kidney function and cardiovascular disease (Johnson, et al. 2011).
Figure (1.2): Progression of Kidney Disease (D. Burkhard Aschhoff, 2017)

Table (1.1): Stages of Kidney Disease (Dr Eugene, 2012)
1.2.4 Treatment of Chronic Kidney Disease

The goal of therapy is to slow down or halt the progression of CKD to stage 5. Control of blood pressure and treatment of the original disease, whenever feasible, are the broad principles of management. Generally, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) are used, as they have been found to slow the progression of CKD to kidney failure. They have also been found to reduce the risk of major cardiovascular events such as myocardial infarction, stroke, heart failure, and death from cardiovascular disease when compared to placebo in individuals with CKD. Furthermore, ACEIs may be superior to ARBs for protection against progression to kidney failure and death from any cause in those with CKD (Xie, et al. 2015). Although the use of ACE inhibitors and ARBs represents the current standard of care for people with CKD, people progressively lose kidney function while on these medications, as seen in the IDNT (Lewis, et al. 2001) and RENAL [Brenner et al, 2001]. Replacement of erythropoietin and calcitriol, two hormones processed by the kidney, is often necessary in people with advanced disease. A target hemoglobin level of 9–12 g/dL
is recommended (Locatelli, et al. 2010) (Clement, et al. 2009). The normalization of hemoglobin has not been found to be of benefit (Levin, et al. 2008). It is unclear if androgens help with anemia (Yang, et al. 2014). Phosphate binders are also used to control the serum phosphate levels, which are usually elevated in advanced chronic kidney disease. Although the evidence for them is limited, phosphodiesterase-5 inhibitors and zinc show potential for helping men with sexual dysfunction. At stage 5 CKD, renal replacement therapy is usually required, in the form of either dialysis or a transplant (Vecchio, et al. 2010).

1.1.5 Prognosis of Chronic Kidney Disease

The prognosis of patients with chronic kidney disease is guarded as epidemiological data have shown that all-cause mortality (the overall death rate) increases as kidney function decreases (Perazella, et al. 2006) The leading cause of death in patients with chronic kidney disease is cardiovascular disease, regardless of whether there is progression to stage 5 (Perazella, et al. 2006) (Sarnak, et al. 2003) (Tonelli, et al. 2006). While renal replacement therapies can maintain patients indefinitely and prolong life, the quality of life is severely affected (Heidenheim, et al. 2004) (de Francisco, et al. 2006). Kidney transplantation increases the survival of patients with stage 5 CKD significantly when compared to other therapeutic options; however, it is associated with an increased short-term mortality due to complications of the surgery (Groothoff, et al. 2005) (Giri, 2004). Transplantation aside, high-intensity home hemodialysis appears to be associated with improved survival and a greater quality of life, when compared to the conventional three-times-a-week hemodialysis and peritoneal dialysis (Pierratos, et al. 2005).

1.2 Kidney Transplantation

Kidney transplantation or renal transplantation is the organ transplant of a kidney
into a patient with end-stage renal disease. Kidney transplantation is typically classified as deceased-donor (formerly known as cadaveric) or living-donor transplantation depending on the source of the donor organ. Living-donor renal transplants are further characterized as genetically related (living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient. Exchanges and chains are a novel approach to expand the living donor pool (Sack, et al. 2012).

1.2.1 History of Kidney Transplantation

One of the earliest mentions about the real possibility of a kidney transplant was by American medical researcher Simon Flexner, who declared in a reading of his paper on “Tendencies in Pathology” in the University of Chicago in 1907 that it would be possible in the then-future for diseased human organs substitution for healthy ones by surgery including arteries, stomach, kidneys and heart. In 1933 surgeon Yuriy Voroniy from Kherson in the Soviet Union attempted the first human kidney transplant, using a kidney removed 6 hours earlier from the deceased donor to be reimplanted into the thigh (de Francisco AL, Piñera C. 2006).

He measured kidney function using a connection between the kidney and the skin. His first patient died 2 days later as the graft was incompatible with the recipient's blood group so was rejected (Matevossian, et al. 2009). It was not until June 17, 1950, when a successful transplant could be performed on Ruth Tucker, a 44-year-old woman with polycystic kidney disease, at Little Company of Mary Hospital in Evergreen Park, Illinois. Although the donated kidney was rejected ten months later because no immunosuppressive therapy was available at the time—the development of effective antirejection drugs was years away—the intervening time gave Tucker's remaining kidney time to recover and she lived another five years (David, 2006). Dr.
John P. Merrill (left) explains the workings of a then-new machine called an artificial kidney to Richard Herrick (middle) and his brother Ronald (right). The Herrick twin brothers were the subjects of the world's first successful kidney transplant, Ronald being the donor. The first kidney transplants between living patients were undertaken in 1952 at the Necker hospital in Paris by Jean Hamburger although the kidney failed after 3 weeks of good function (Legendre, et al. 2010) and later in 1954 in Boston. The Boston transplantation, performed on December 23, 1954, at Brigham Hospital was performed by Joseph Murray, J. Hartwell Harrison, John P. Merrill and others. The procedure was done between identical twins Ronald and Richard Herrick to eliminate any problems of an immune reaction. For this and later work, Dr. Murray received the Nobel Prize for Medicine in 1990. The recipient, Richard Herrick, died eight years after the transplantation. In 1955, Charles Rob, William James 'Jim' Dempster (St Marys and Hammersmith, London) carried out the first deceased donor transplant in United Kingdom, which was unsuccessful (David, 2006).

In July 1959, 'Fred' Peter Raper (Leeds) performed first successful (8 months) deceased donor transplant in the UK. A year later, in 1960, the first successful living kidney transplant in the UK occurred, when Michael Woodruff performed one between identical twins in Edinburgh. Until the routine use of medications to prevent and treat acute rejection, introduced in 1964, deceased donor transplantation was not performed. The kidney was the easiest organ to transplant: tissue typing was simple, the organ was relatively easy to remove and implant, live donors could be used without difficulty, and in the event of failure, kidney dialysis was available from the 1940s. Tissue typing was essential to the success: early attempts in the 1950s on sufferers from Bright's disease had been very unsuccessful. The major barrier to organ transplantation between genetically non-identical patients lay in the recipient's
immune system, which would treat a transplanted kidney as a "non-self" and immediately or chronically reject it. Thus, having medications to suppress the immune system was essential. However, suppressing an individual's immune system places that individual at greater risk of infection and cancer (particularly skin cancer and lymphoma), in addition to the side effects of the medications. The basis for most immunosuppressive regimens is prednisolone, a corticosteroid. Prednisolone suppresses the immune system, but its long-term use at high doses causes a multitude of side effects, including glucose intolerance and diabetes, weight gain, osteoporosis, muscle weakness, hypercholesterolemia, and cataract formation. Prednisolone alone is usually inadequate to prevent rejection of a transplanted kidney. Thus other, non-steroid immunosuppressive agents are needed, which also allow lower doses of prednisolone (Hakim, Nadey. 2010).

1.2.2 Indications

The indication for kidney transplantation is end-stage renal disease (ESRD), regardless of the primary cause. This is defined as a glomerular filtration rate <15 ml/min/1.73 sq. m. Common diseases leading to ESRD include malignant hypertension, infections, diabetes mellitus, and focal segmental glomerulosclerosis; genetic causes include polycystic kidney disease, a number of inborn errors of metabolism, and autoimmune conditions such as lupus. Diabetes is the most common known cause of kidney transplantation, accounting for approximately 25% of those in the US. The majority of renal transplant recipients are on dialysis (peritoneal dialysis or hemodialysis) at the time of transplantation. However, individuals with chronic kidney disease who have a living donor available may undergo pre-emptive transplantation before dialysis is needed. If a patient is put on the waiting list for a deceased donor transplant early enough, they may also be transplanted pre-dialysis (Jarvik, et al. 2003).
1.2.3 Living donors

Potential donors are carefully evaluated on medical and psychological grounds. This ensures that the donor is fit for surgery and has no disease which brings undue risk or likelihood of a poor outcome for either the donor or recipient. The psychological assessment is to ensure the donor gives informed consent and is not coerced. In countries where paying for organs is illegal, the authorities may also seek to ensure that a donation has not resulted from a financial transaction. The relationship the donor has to the recipient has evolved over the years. In the 1950s, the first successful living donor transplants were between identical twins (Kiser, Kim. 2010).

In the 1960s–1970s, live donors were genetically related to the recipient. However, during the 1980s–1990s, the donor pool was expanded further to emotionally related individuals (spouses, friends). Now the elasticity of the donor relationship has been stretched to include acquaintances and even strangers ('altruistic donors'). In 2009, Minneapolis transplant recipient Chris Strouth received a kidney from a donor who connected with him on Twitter, which is believed to be the first such transplant arranged entirely through social networking (Kiser, Kim. 2010) (Pitts, Byron. 2015).

The acceptance of altruistic donors has enabled chains of transplants to form. Kidney chains are initiated when an altruistic donor donates a kidney to a patient who has a willing but incompatible donor. This incompatible donor then 'pays it forward' and passes on the generosity to another recipient who also had a willing but incompatible donor. Michael Rees from the University of Toledo developed the concept of open-ended chains (Rees, et al. 2009). This was a variation of a concept developed at Johns Hopkins University (Montgomery, et al. 2006). On July 30, 2008, an altruistic donor kidney was shipped via commercial airline from Cornell to the University of California, Los Angeles, thus triggering a chain of transplants (Butt, et al. 2009). The shipment of living donor kidneys, computer-matching software algorithms, and
cooperation between transplant centers has enabled long-elaborate chains to be formed (Sack, et al. 2012). In carefully screened kidney donors, survival and the risk of end-stage renal disease appear to be similar to those in the general population (Ibrahim, et al. 2009). However, women who have donated a kidney have a higher risk of gestational hypertension and preeclampsia than matched nondonors with similar indicators of baseline health (Garg, et al. 2014).

Traditionally, the donor procedure has been through a single incision of 4–7 inches (10–18 cm), but live donation is being increasingly performed by laparoscopic surgery. This reduces pain and accelerates recovery for the donor. Operative time and complications decreased significantly after a surgeon performed 150 cases. Live donor kidney grafts have higher long-term success rates than those from deceased donors (Garg, et al. 2014). Since the increase in the use of laparoscopic surgery, the number of live donors has increased. Any advance which leads to a decrease in pain and scarring and swifter recovery has the potential to boost donor numbers (Martinez, Edecio. 2009).

1.2.4 Deceased Donors

Deceased donors can be divided in two groups:

- **Brain-dead (BD) donors**

- **Donation after Cardiac Death (DCD) donors**

Although brain-dead (or 'heart beating') donors are considered dead, the donor's heart continues to pump and maintain the circulation. This makes it possible for surgeons to start operating while the organs are still being perfused (supplied blood). During the operation, the aorta will be cannulated, after which the donor's blood will be replaced by an ice-cold storage solution, such as UW (Viaspan), HTK, or
Perfadex. Depending on which organs are transplanted, more than one solution may be used simultaneously. Due to the temperature of the solution, and since large amounts of cold NaCl-solution are poured over the organs for a rapid cooling, the heart will stop pumping (Bland B, 2008).

'Donation after Cardiac Death' donors are patients who do not meet the brain-dead criteria but, due to the unlikely chance of recovery, have elected via a living will or through family to have support withdrawn. In this procedure, treatment is discontinued (mechanical ventilation is shut off). After a time of death has been pronounced, the patient is rushed to the operating room where the organs are recovered. Storage solution is flushed through the organs. Since the blood is no longer being circulated, coagulation must be prevented with large amounts of anti-coagulation agents such as heparin. Several ethical and procedural guidelines must be followed; most importantly, the organ recovery team should not participate in the patient's care in any manner until after death has been declared (Bland B, 2008).
1.2.5 Compatibility

In general, the donor and recipient should be ABO and crossmatch (HLA antigen) compatible. If a living donor is incompatible with their recipient, the donor could be exchange for a compatible kidney. In an effort to reduce the risk of rejection during incompatible transplantation, ABO-incompatible and desensitization protocols utilizing intravenous immunoglobulin (IVIG) have been developed, with the aim to reduce ABO and HLA antibodies that the recipient may have to the donor. In the 1980s, experimental protocols were developed for ABO-incompatible transplants using increased immunosuppression and plasmapheresis. The level of sensitization to donor HLA antigens is determined by performing a panel reactive antibody test on the potential recipient. However, HLA matching is a relatively minor predictor of transplant outcomes. In fact, living non-related donors are now almost as common
as living (genetically)-related donors (Bland B, 2008).

Laboratory Tests

- ABO Blood typing
- Tissue typing (HLA Matching)
- (Lymphocytotoxicity test)
- (Mixed leukocyte reaction)
- Screening for Presence of Preformed Antibodies to allogeneic HLA
- Crossmatching

Dr. T.V. Rao MD

Figure (1.4) Laboratory test of Compatibility (Freelance, 2012)

1.2.6 Procedure

In most cases the barely functioning existing kidneys are not removed, as removal has been shown to increase the rates of surgical morbidity. Therefore, the kidney is usually placed in a location different from the original kidney, often in the iliac fossa, so it is often necessary to use a different blood supply: The renal artery of the new kidney, previously branching from the abdominal aorta in the donor, is often connected to the external iliac artery in the recipient. The renal vein of the new kidney, previously draining to the inferior vena cava in the donor, is often connected to the external iliac vein in the recipient. There is disagreement in surgical textbooks regarding which side of the recipient’s pelvis to use in receiving the transplant. Campbell's Urology (2002) recommends placing the donor kidney in the recipient’s contralateral side (i.e. a left sided kidney would be transplanted in the recipient's right side) to ensure the renal pelvis and ureter are anterior in the event that future
surgeries are required. In an instance where there is doubt over whether there is enough space in the recipient’s pelvis for the donor's kidney, the textbook recommends using the right side because the right side has a wider choice of arteries and veins for reconstruction. Smith's Urology (2004) states that either side of the recipient's pelvis is acceptable; however the right vessels are 'more horizontal' with respect to each other and therefore easier to use in the anastomoses (Schall, John A. 2008).

Figure (1.5): Procedure of Kidney Transplantation [Mayo clinic staff, 2018]

1.2.7 Post Operation

The transplant surgery takes about three hours (Schall, John A. 2008). The donor kidney will be placed in the lower abdomen and its blood vessels connected to arteries and veins in the recipient's body. When this is complete, blood will be allowed to flow through the kidney again. The final step is connecting the ureter from the donor kidney to the bladder. In most cases, the kidney will soon start producing urine. Depending on its quality, the new kidney usually begins functioning immediately. Living donor kidneys normally require 3–5 days to reach normal functioning levels, while cadaveric donations stretch that interval to 7–15 days (Haller, et al. 2016). Hospital stay is typically for 4–10 days. If complications arise, additional medications (diuretics) may be administered to help the kidney
produce urine. Immunosuppressant drugs are used to suppress the immune system from rejecting the donor kidney. These medicines must be taken for the rest of the recipient's life. The most common medication regimen today is a mixture of tacrolimus, mycophenolate, and prednisolone. Some recipients may instead take cyclosporine, sirolimus, or azathioprine. The risk of early rejection of the transplanted kidney is increased if corticosteroids are avoided or withdrawn after the transplantation (Haller, et al. 2016). Cyclosporine, considered a breakthrough immunosuppressive when first discovered in the 1980s, ironically causes nephrotoxicity and can result in iatrogenic damage to the newly transplanted kidney. Tacrolimus, which is a similar drug, also causes nephrotoxicity. Blood levels of both must be monitored closely and if the recipient seems to have declining renal function or proteinuria, a biopsy may be necessary to determine whether this is due to rejection or cyclosporine or tacrolimus intoxication (Nankivell, 2011) (Naesens, 2015). Postoperative diet; kidney transplant recipients are discouraged from consuming grapefruit, pomegranate and green tea products. These food products are known to interact with the transplant medications, specifically tacrolimus, cyclosporine and sirolimus; the blood levels of these drugs may be increased, potentially leading to an overdose. Acute rejection occurs in 10–25% of people after transplant during the first 60 days. Rejection does not necessarily mean loss of the organ, but it may necessitate additional treatment and medication adjustments (Mert, et al. 2008).

1.2.8 Complications

Presence of lymphocytes within the tubular epithelium, attesting to acute cellular rejection of a renal graft, biopsy sample. Problems after a transplant may include: Post-operative complication, bleeding, infection, vascular thrombosis and urinary complications Transplant rejection (hyper acute, acute or chronic) Infections and
sepsis due to the immunosuppressant drugs that are required to decrease risk of rejection Post-transplant lymphoproliferative disorder (a form of lymphoma due to the immune suppressants) Imbalances in electrolytes including calcium and phosphate which can lead to bone problems Proteinuria. Other side effects of medications including gastrointestinal inflammation and ulceration of the stomach and esophagus, hirsutism (excessive hair growth in a male-pattern distribution) with cyclosporine, hair loss with tacrolimus, obesity, acne, diabetes mellitus type 2, hypercholesterolemia, and osteoporosis. A patient's age and health condition before transplantation affect the risk of complications (Naesens, 2015). Different transplant centers have different success at managing complications and therefore, complication rates are different from center to center. The average lifetime for a donated kidney is ten to fifteen years. When a transplant fails, a patient may opt for a second transplant, and may have to return to dialysis for some intermediary time. Infections due to the immunosuppressant drugs used in people with kidney transplants most commonly occur in mucocutaneous areas (41%), the urinary tract (17%) and the respiratory tract (14%). The most common infective agents are bacterial (46%), viral (41%), fungal (13%), and protozoan (1%). Of the viral illnesses, the most common agents are human cytomegalovirus (31.5%), herpes simplex (23.4%), and herpes zoster (23.4%). BK virus is now being increasingly recognized. Infection is the cause of death in about one third of people with renal transplants, and pneumonias account for 50% of the patient deaths from infection (Mert, et al. 2008).

1.2.9 Prognosis

Kidney transplantation is a life-extending procedure (McDonald SP, Russ GR. 2002).
The typical patient will live 10 to 15 years longer with a kidney transplant than if kept on dialysis. The increase in longevity is greater for younger patients, but even 75-year-old recipients (the oldest group for which there is data) gain an average four more years of life (Wolfe, et al. 1999). People generally have more energy, a less restricted diet, and fewer complications with a kidney transplant than if they stay on conventional dialysis. Some studies seem to suggest that the longer a patient is on dialysis before the transplant, the less time the kidney will last. It is not clear why this occurs, but it underscores the need for rapid referral to a transplant program. Ideally, a kidney transplant should be pre-emptive, i.e., take place before the patient begins dialysis. The reason why kidneys fail over time after transplantation has been elucidated in recent years. Apart from recurrence of the original kidney disease, also rejection (mainly antibody-mediated rejection) and progressive scarring (multifactorial) play a decisive role. Avoiding rejection by strict medication adherence is of utmost importance to avoid failure of the kidney transplant (Naesens M, 2014).

1.3 Hemostasis and Coagulation

This article is about blood clotting. Blood coagulation pathways in vivo showing the central role played by thrombin Coagulation. Is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Disorders of coagulation are disease states which can result in bleeding (hemorrhage or bruising) or obstructive clotting (thrombosis) (David, et al. 2009). Coagulation is highly conserved throughout biology; in all mammals, coagulation involves both a cellular (platelet) and a protein (coagulation factor) component (Alan D, Michelson. 2006). The system in humans
Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the vessel. Leaking of blood through the endothelium initiates two processes: changes in platelets, and the exposure of subendothelial tissue factor to plasma Factor VII, which ultimately leads to fibrin formation (Alvin, et al. 2001). Platelets immediately form a plug at the site of injury; this is called primary hemostasis. Secondary hemostasis occurs simultaneously: Additional coagulation factors or clotting factors beyond Factor VII respond in a complex cascade to form fibrin strands, which strengthen the platelet plug (Furie B, Furie BC. 2005).

1.3.1 Nomenclature

The usage of Roman numerals rather than eponyms or systematic names was agreed upon during annual conferences (starting in 1955) of hemostasis experts. In 1962, consensus was achieved on the numbering of factors I-XII. This committee evolved into the present-day International Committee on Thrombosis and Hemostasis (ICTH). Assignment of numerals ceased in 1963 after the naming of Factor XIII. The names Fletcher Factor and Fitzgerald Factor were given to further coagulation-related proteins, namely prekallikrein and high-molecular-weight kininogen, respectively. Factors III and VI are unassigned, as thromboplastin was never identified, and actually turned out to consist of ten further factors, and accelerin was found to be activated Factor V (Giangrande PL, 2003).

1.3.2 Physiology

1.3.2.1. Platelet Activation

When the endothelium is damaged, the normally isolated, underlying collagen is exposed to circulating platelets, which bind directly to collagen with collagen-
specific glycoprotein Ia/IIa surface receptors. This adhesion is strengthened further by von Willebrand factor (vWF), which is released from the endothelium and from platelets; vWF forms additional links between the platelets' glycoprotein Ib/IX/V and the collagen fibrils. This localization of platelets to the extracellular matrix promotes collagen interaction with platelet glycoprotein VI. Binding of collagen to glycoprotein VI triggers a signaling cascade that results in activation of platelet integrins. Activated integrins mediate tight binding of platelets to the extracellular matrix. This process adheres platelets to the site of injury. Activated platelets will release the contents of stored granules into the blood plasma [Nigel et al., 2009]. The granules include ADP, serotonin, platelet-activating factor (PAF), vWF, platelet factor 4, and thromboxane A2 (TXA2), which, in turn, activate additional platelets. The granules' contents activate a Gq-linked protein receptor cascade, resulting in increased calcium concentration in the platelets' cytosol. The calcium activates protein kinase C, which, in turn, activates phospholipase A2 (PLA2). PLA2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen. The activated platelets change shape from spherical to stellate, and the fibrinogen cross-links with glycoprotein IIb/IIIa aid in aggregation of adjacent platelets (primary hemostasis) (Pallister CJ, Watson MS, 2010).
With in 1-2 sec after injury to blood vessel, hemostatic process begins & proceed as out line bellow:

1. platelet adhesion
2. platelets activation
3. platelets release reaction
4. platelets aggregation

Figure (1.6): Role of Platelets in Hemostasis (Gaurav kumar, 2015)

1.3.2.2 Coagulation Factors

Table (1.2) Coagulation Factors and related substances number, name and function (Sanjeev, et al. 2014)

<table>
<thead>
<tr>
<th>Clotting factor number</th>
<th>Clotting factor name</th>
<th>Function</th>
<th>Plasma half-life (h)</th>
<th>Plasma concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>Clot formation</td>
<td>90</td>
<td>3000</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>Activation of I, V, VII, VIII, XI, XIII, protein C, platelets</td>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td>III</td>
<td>TF</td>
<td>Co-factor of VIIa</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium</td>
<td>Facilitates coagulation factor binding to phospholipids</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>Proaccelerin, labile factor</td>
<td>Co-factor of X-prothrombinase complex</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>VI</td>
<td>Unassigned</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VII</td>
<td>Stable factor, proconvertin</td>
<td>Activates factors IX, X</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>VIII</td>
<td>Antithrombinic factor A</td>
<td>Co-factor of IXa-tense complex</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>IX</td>
<td>Antithrombinic factor B or Christmas factor</td>
<td>Activates X: Forms tenase complex with factor VIII</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Prower factor</td>
<td>Prothrombinase complex with factor V: Activates factor II</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma thromboplatin antecedent</td>
<td>Activates factor IX</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor</td>
<td>Activates factor XI, VII and prekallikrein</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin-stabilising factor</td>
<td>Crosslinks fibrin</td>
<td>200</td>
<td>30</td>
</tr>
<tr>
<td>XIV</td>
<td>Prekallikrein (F. Fletcher)</td>
<td>Serine protease zymogen</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>XV</td>
<td>HMWK- (F. Fitzgerald)</td>
<td>Co factor</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>XVI</td>
<td>vWf</td>
<td>Binds to VIII, mediates platelet adhesion</td>
<td>12</td>
<td>10 µg/mL</td>
</tr>
<tr>
<td>XVII</td>
<td>Antithrombin III</td>
<td>Inhibits IIa, Xa, and other proteases</td>
<td>72</td>
<td>0.15-0.2 mg/mL</td>
</tr>
<tr>
<td>XVIII</td>
<td>Heparin cofactor II</td>
<td>Inhibits IIa</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>XIX</td>
<td>Protein C</td>
<td>Inactivates Va and Villia</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>XX</td>
<td>Protein S</td>
<td>Cofactor for activated protein C</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HMWK – High molecular weight kinnogen; vWf – Von Willebrand factor; TF – Tissue factor
1.3.2.3 Coagulation Cascade

The coagulation cascade of secondary hemostasis has two initial pathways which lead to fibrin formation. These are the contact activation pathway (also known as the intrinsic pathway), and the tissue factor pathway (also known as the extrinsic pathway) which both lead to the same fundamental reactions that produce fibrin. It was previously thought that the two pathways of coagulation cascade were of equal importance, but it is now known that the primary pathway for the initiation of blood coagulation is the tissue factor (extrinsic) pathway. The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin. Coagulation factors are generally indicated by Roman numerals, with a lowercase an appended to indicate an active form. The coagulation factors are generally serine proteases (enzymes), which act by cleaving downstream proteins. The exceptions are FIII, FV, FVIII, FXIII. FIII, FV and FVIII are glycoproteins, and Factor XIII is a transglutaminase (Pallister CJ, Watson MS. 2010). The coagulation factors circulate as inactive zymogens. The coagulation cascade is therefore classically divided into three pathways. The tissue factor and contact activation pathways both activate the "final common pathway" of factor X, thrombin and fibrin (Hoffbrand, 2002).
1.3.2.3.1. Tissue Factor Pathway (extrinsic)

The main role of the tissue factor pathway is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles, is released very rapidly. FVIIa circulates in a higher amount than any other activated coagulation factor. The process includes the following steps: Following damage to the blood vessel, FVII leaves the circulation and comes into contact with tissue factor (TF) expressed on tissue-factor-bearing cells (stromal fibroblasts and leukocytes), forming an activated complex (TF-FVIIa). TF-FVIIa activates FIX and FX. FVII is itself activated by thrombin, FXIa, FXII and Fxa (Pallister CJ, Watson MS, 2010).

The activation of FX (to form FXa) by TF-FVIIa is almost immediately inhibited by
tissue factor pathway inhibitor (TFPI). FXa and its co-factor FVa form the prothrombinase complex, which activates prothrombin to thrombin. Thrombin then activates other components of the coagulation cascade, including FV and FVIII (which forms a complex with FIX), and activates and releases FVIII from being bound to vWF. FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX; and so the cycle continues. ("Tenase" is a contraction of "ten" and the suffix "-ase" used for enzymes.) (Pallister CJ, Watson MS. 2010).

1.3.2.3.2 Contact Activation Pathway (intrinsic)

The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder. Instead, contact activation system seems to be more involved in inflammation, (Pallister CJ, Watson MS. 2010) and innate immunity. (Nigel etal, 2009) Despite this, interference with the pathway may confer protection against thrombosis without a significant bleeding risk (Long etal, 2015).

1.3.2.3.3 Final Common Pathway

The division of coagulation in two pathways is mainly artificial; it originates from laboratory tests in which clotting times were measured after the clotting was initiated by glass (intrinsic pathway) or by thromboplastin (extrinsic pathway). In fact
thrombin is present from the very beginning, already when platelets are making the plug. Thrombin has a large array of functions, not only the conversion of fibrinogen to fibrin, the building block of a hemostatic plug. In addition, it is the most important platelet activator and on top of that it activates Factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers. Following activation by the contact factor or tissue factor pathways, the coagulation cascade is maintained in a prothrombotic state by the continued activation of FVIII and FIX to form the tenase complex, until it is down-regulated by the anticoagulant pathways (Pallister CJ, Watson MS. 2010).

1.3.2.4. Fibrinolysis

Eventually, blood clots are reorganized and resorbed by a process termed fibrinolysis. The main enzyme responsible for this process (plasmin) is regulated by various activators and inhibitors (Hoffbrand A. V, 2002).

Figure (1.8): Fibrinolysis Process (Payel Bhattacharjee¹ and Debasish Bhattacharyy¹ 2014)

1.3.3 D-dimer
D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two D fragments of the fibrin protein joined by a cross-link [Adam et al., 2009]. D-dimer concentration may be determined by a blood test to help diagnose thrombosis. Since its introduction in the 1990s, it has become an important test performed in patients with suspected thrombotic disorders. While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential causes. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. In addition, it is used in the diagnosis of the blood disorder disseminated intravascular coagulation (Adam, et al. 2009).

1.3.3.1 History

D-dimer was originally described in the 1970s, and found its diagnostic application in the 1990s (Adam, et al. 2009).

1.3.3.2 Principles

D-dimer formation, shown are fibrinogen, with its one E domain and two D domains,
acted upon in cascade, by the following enzymes: Thrombin, to create a mesh of fibrin protofibrils; Factor XIII to crosslink the fibrin mesh (linking protofibril D domains), the scaffold for clot formation; Plasmin, whose action in fibrinolysis produces fibrin degradation products (FDPs), the smallest of which are D-dimers, protein fragments with one E and two crosslinked D domains from an original fibrinogen. Coagulation, the formation of a blood clot or thrombus, occurs when the proteins of the coagulation cascade are activated, either by contact with damaged blood vessel wall and exposure to collagen in the tissue space (intrinsic pathway) or by activation of factor VII by tissue factors (extrinsic pathway). Both pathways lead to the generation of thrombin, an enzyme that turns the soluble blood protein fibrinogen into fibrin, which aggregates into proteofibrils. Another thrombin-generated enzyme, factor XIII, then crosslinks the fibrin proteofibrils at the D fragment site, leading to the formation of an insoluble gel which serves as a scaffold for blood clot formation. The circulating enzyme plasmin, the main enzyme of fibrinolysis, cleaves the fibrin gel in a number of places. The resultant fragments, "high molecular weight polymers", are digested several times more by plasmin to lead to intermediate and then to small polymers (fibrin degradation products or FDPs). The cross-link between two D fragments remains intact, however, and these are exposed on the surface when the fibrin fragments are sufficiently digested. The typical D-dimer containing fragment contains two D domains and one E domain of the original fibrinogen molecule. D-dimers are not normally present in human blood plasma, except when the coagulation system has been activated, for instance because of the presence of thrombosis or disseminated intravascular coagulation. The D-dimer assay depends on the binding of a monoclonal antibody to a particular epitope on the D-dimer fragment. Several detection kits are commercially available; all of them rely on a different monoclonal antibody against D-dimer. For some of these, the area of the D-dimer to which the antibody binds is known. The binding of the
antibody is then measured quantitatively by one of various laboratory methods (Adam, et al. 2009).

### 1.3.3.3 Indications

D-dimer testing is of clinical use when there is a suspicion of deep venous thrombosis (DVT), pulmonary embolism (PE) or disseminated intravascular coagulation (DIC) (Suzuki, et al. 2010).

It is under investigation in the diagnosis of aortic dissection (Suzuki, et al. 2010) (Ranasinghe AM, Bonser RS. 2010). For DVT and PE, there are possible various scoring systems that are used to determine the a priori clinical probability of these diseases; the best-known is the Wells score (Wells, et al. 2003). For a very high score, or pretest probability, a D-dimer will make little difference and anticoagulant therapy will be initiated regardless of test results, and additional testing for DVT or pulmonary embolism may be performed. For a moderate or low score, or pretest probability: A negative D-dimer test will virtually rule out thromboembolism: the degree to which the D-dimer reduces the probability of thrombotic disease is dependent on the test properties of the specific test used in the clinical setting: most available D-dimer tests with a negative result will reduce the probability of thromboembolic disease to less than 1% if the pretest probability is less than 15-20%. If the D-dimer reads high, then further testing (ultrasound of the leg veins or lung scintigraphy or CT scanning) is required to confirm the presence of thrombus. Anticoagulant therapy may be started at this point or withheld until further tests confirm the diagnosis, depending on the clinical situation. In some hospitals, they are measured by laboratories after a form is completed showing the probability score and only if the probability score is low or intermediate. This reduces the need for unnecessary tests in those who are high-probability (Rathbun, et al. 2004).
Performing the D-dimer test first can avoid a significant proportion of imaging tests and is less invasive. Since the D-dimer can exclude the need for imaging, specialty professional organizations recommend that physicians use D-dimer testing as an initial diagnostic (Fesmire, et al. 2011)( Torbicki, et al. 2008)( Qaseem, et al. 2007).

![Clinical Probability Score of D-dimer](Suzanne Ekelund, 2015)

### 1.3.3.4 Interpretation

Various kits have 93-95% sensitivity (true positive rate). For hospitalized patients, one study found the specificity to be about 50% (true negative rate) in the diagnosis of thrombotic disease (Schrecengost, et al. 2003). False positive readings can be due to various causes: liver disease, high rheumatoid factor, inflammation, malignancy, trauma, pregnancy, recent surgery as well as advanced age (Kabrhel, et al. 2010). False negative readings can occur if the sample is taken either too early after thrombus formation or if testing is delayed for several days. Additionally, the presence of anti-coagulation can render the test negative because it prevents
thrombus extension. The anti-coagulation medications dabigatran and rivaroxaban decrease D-dimer levels but do not interfere with the D-dimer assay (Baglin, et al. 2012).

False values may be obtained if the specimen collection tube is not sufficiently filled (false low value if under filled and false high value if overfilled). This is due to the dilutional effect of the anticoagulant (the blood must be collected in a 9:1 blood to anticoagulant ratio). Likelihood ratios are derived from sensitivity and specificity to adjust pretest probability. In interpretation of the d-dimer, for patients over age 50 a value of (patient's age) x 10 μg/l may be abnormal (van Es, et al. 2012) (Douma, et al. 2010).

Table (1.3) Reference Ranges for D-dimer (Abbassi et al, 2009)

<table>
<thead>
<tr>
<th>Unit</th>
<th>Nonpregnant</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/L or µg/mL</td>
<td>&lt;0.5</td>
<td>0.05-0.95</td>
<td>0.32-1.29</td>
<td>0.13-1.7</td>
</tr>
<tr>
<td>µg/L or ng/mL</td>
<td>&lt;500</td>
<td>50-950</td>
<td>320-1290</td>
<td>130-1700</td>
</tr>
<tr>
<td>nmol/L</td>
<td>&lt;2.7</td>
<td>0.3-5.2</td>
<td>1.8-7.1</td>
<td>0.7-9.3</td>
</tr>
</tbody>
</table>

1.3.4 Role in Immune System

The coagulation system overlaps with the immune system. Coagulation can physically trap invading microbes in blood clots. Also, some products of the coagulation system can contribute to the innate immune system by their ability to increase vascular permeability and act as chemotactic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly antimicrobial. Many acute-phase proteins of inflammation are involved in the coagulation system.
In addition, pathogenic bacteria may secrete agents that alter the coagulation system, e.g. coagulase and streptokinase (David, et al. 2009).

### 1.1.5 Assessment of Hemostasis

Numerous tests are used to assess the function of the coagulation system: Common: aPTT, PT (also used to determine INR), fibrinogen testing (often by the Clauss method), platelet count, platelet function testing (often by PFA-100), thrombodynamics test. Other: TCT, bleeding time, mixing test (whether an abnormality corrects if the patient's plasma is mixed with normal plasma), coagulation factor assays, antiphospholipid antibodies, D-dimer, genetic tests (e.g. factor V Leiden, prothrombin mutation G20210A), dilute Russell's viper venom time (dRVVT), miscellaneous platelet function tests, thromboelastography (TEG or Sonoclot), euglobulin lysis time (ELT). The contact activation (intrinsic) pathway is initiated by activation of the "contact factors" of plasma, and can be measured by the activated partial thromboplastin time (aPTT) test. The tissue factor (extrinsic) pathway is initiated by release of tissue factor (a specific cellular lipoprotein), and can be measured by the prothrombin time (PT) test. PT results are often reported as ratio (INR value) to monitor dosing of oral anticoagulants such as warfarin. The quantitative and qualitative screening of fibrinogen is measured by the thrombin clotting time (TCT) [David et al, 2009]. Measurement of the exact amount of fibrinogen present in the blood is generally done using the Clauss method for fibrinogen testing. Many analyzers are capable of measuring a "derived fibrinogen" level from the graph of the Prothrombin time clot. If a coagulation factor is part of the contact activation or tissue factor pathway, a deficiency of that factor will affect only one of the tests: Thus hemophilia A, a deficiency of factor VIII, which is part of the contact activation pathway, results in an abnormally prolonged aPTT test but a normal PT test. The exceptions are prothrombin, fibrinogen, and some variants of
FX that can be detected only by either aPTT or PT. Deficiencies of fibrinogen (quantitative or qualitative) will affect all screening tests (David, et al. 2009).

1.3.6 Platelet Disorders

Platelet conditions may be congenital or acquired. Some inborn platelet pathologies are Glanzmann's thrombasthenia, Bernard-Soulier syndrome (abnormal glycoprotein Ib-IX-V complex), gray platelet syndrome (deficient alpha granules), and delta storage pool deficiency (deficient dense granules). Most are rare conditions. Most inborn platelet pathologies predispose to hemorrhage. Von Willebrand disease is due to deficiency or abnormal function of von Willebrand factor, and leads to a similar bleeding pattern; its milder forms are relatively common. Decreased platelet numbers may be due to various causes, including insufficient production (e.g., in myelodysplastic syndrome or other bone marrow disorders), destruction by the immune system (immune thrombocytopenic purpura/ITP), and consumption due to various causes (thrombotic thrombocytopenic purpura/TTP, hemolytic-uremic syndrome/HUS, paroxysmal nocturnal hemoglobinuria/PNH, disseminated intravascular coagulation/DIC, heparin-induced thrombocytopenia/HIT). Most consumptive conditions lead to platelet activation, and some are associated with thrombosis (Hatton, Chris. 2008).

1.4 Previous Studies

In 2016, Noha and Hiba measured D-dimer on CKD patients in Sudan which, their result showed higher level of D-dimer with no gender effect.

In 2015, D-dimer, TM, VWF, and ADAMTS13 plasma levels were assessed by ELISA by Ana et al in Brazilian renal transplanted patients. An increase of D-dimer
was observed in patients with higher levels of creatinine.

In 2010, PT, PTI, APTT, fibrinogen and D-dimer were measured by Minz *et al.* Their result showed that, a significant decrease in the D-dimer levels after transplantation, while PT, PTI, APTT, Fibrinogen levels in the pre and post-transplant period were within the normal range.

In 2007, PT, APTT, fibrinogen, AT, D-dimer and protein C and S were measured by Pawlick *et al* on CKD patients before and on postoperative days 1, 7, and 14, and showed there was no different in PT, APTT and fibrinogen in pre and post transplantation, while there was significant increasing in D-dimer, AT, protein C and S after surgery.

In 2007, AT III, total protein S, free protein S, protein C, F1+2, TAT and D-dimer were assessed by Ballow *et al* in patients with CRF before initiating dialysis and after starting regular HD or CAPD. The measurements were repeated in a group of patients who received a successful renal transplant. The HD group showed significant elevation in the plasma levels of AT III and total protein S, and a significant reduction in free protein S and protein C, when compared with healthy controls. In the transplant patients, there was significant elevation of AT III and total protein S, a reduction in free PS, and no significant changes in PC levels. A significant elevation in the levels of F1+2, TAT and D-dimer was founded in transplant patients.

1.5 **Rationale**

Kidney transplantation is the best way for patients with end-stage renal disease to preserving their life and get good prognosis. The end-stage renal disease (ESRD) is highly related with profound clinical effects on hemostasis ranging from thrombosis to bleeding complications. The pathogenesis of uremic bleeding is due to many
causes. The most important one is platelet dysfunction, mainly platelet-platelet and platelet-vessel wall interactions. Hemorrhagic feature observed in patients with chronic renal failure result from platelet defects, vessel wall damage, and deficiency of II, VII, IX, and X clotting factors. On the other hand, increased levels of fibrinogen and von Willebrand factor, as well as decreased plasma fibrinolytic activity, may lead to thrombotic complications in nephrotic syndrome. Fortunately this hemostatic complication of patients with CKD can be corrected by make successful kidney transplantation or kidney replacement therapy for those patients. CKD and renal transplant are associated with activation of coagulation that favors a hypercoagulable state. Microvascular thrombosis and fibrinolytic disorders have been recognized as main cause of allograft rejection in renal transplanted patients, but the pathway through which it occurs has not been clarified yet. Hemostatic biomarkers have been suggested to evaluate the thrombotic status and rejection risk in renal transplanted patients, mainly D-dimer levels, which inform about fibrin formation and degradation. The goal of this study was to determine D-dimer, PT, and APTT in Sudanese patients of renal transplantation, and to assess D-dimer as hemostatic biomarker to detect early allograft rejection.

1.6 Objectives

1.6.1 General Objective

To determine D-dimer, PT and APTT level among renal transplant patients in Sudan.

1.6.2 Specific Objectives

- To measure D. dimer in renal transplant patients using cobas C311.

- To measure Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in renal transplant patients using Biobas.
• To compare between patients and controls in the results of D-dimer, PT and APTT.

• To compare between patients and controls according to effect of age, gender, duration and INR on the result of D-dimer, PT and APTT.

Chapter Two

2. Materials and Methods

2.1 Materials

This is descriptive comparative cross-sectional study obtained at Sudan University of Science and Technology, Faculty of Medical Laboratory Sciences from February to May 2017. The study aimed to measure D-dimer, PT and APTT in patient’s pre and post renal transplantation. The practical was conducted in Sharg Alnile Hospital in hematology laboratory; sample size of 100 venous blood samples were collected from patients. Fifty samples were collected from pre as control and another 50 from transplant patients and each 50 samples were classified into groups according to
gender (males and females), age (above and below 35 years) and duration (more and less than 1 year). Approval was obtained from head of nephrology unit and informed consent was obtained individually from each patient before filling the questionnaire and pre designed questionnaire was recorded from each patient [Appendix1].

2.2 Inclusion Criteria

- Diagnosed Chronic renal failure patients on dialysis pre renal transplantation
- Renal transplant patients

2.3 Exclusion Criteria

- Patients on anti-coagulant therapy.
- Patient had auto immune diseases.
- Pregnant ladies.
- Patients had asthma.
- Patients had recent infection or inflammations that are known to affect the parameters we investigate.
- Smoker patients.
- Patient’s non consent for investigation also excludes.

2.4 Methods

2.4.1 D-dimer

The protocol of D-dimer was performed by full automated cobas C311 using latex particles of uniform size are coated with monoclonal antibodies (F (ab’) 2 fragments)
to the D-dimer epitope. The antigen/antibody complexes produced by the addition of samples containing D-dimer lead to an increase in the turbidity of the test reactants. The change in absorbance with time is dependent on the concentration of D-dimer epitopes in the sample [Appendix2].

**Reference value:**

<0.5 μg fibrinogen equivalent units/mL

**2.4.2 Prothrombin Time (PT)**

**2.4.2.1 Principle of Coagulometer**

The coagulometer (Automated Bio Bas) is an optical measurement system which detects a sudden variation in optical density when a clot is formed, which activate the chronometer and the stirring system, this permits the initiation of the time measurement when the reagent and plasma are in contact, a O.D variation is produced, that automatically activates the digital chronometer and the magnetic mixer. The time of clot appears on the display. The PT was performed by automated Bio Bas testing measure the clotting time of plasma in the presence of an optimal concentration of tissue extract (thromboplastin) with calcium chloride (cacl2) which indicates over all the efficiency of the extrinsic clotting system. Cuvettes were placed in incubation area for pre warming at 37c for at least 3 minutes. A magnetic was dispensed to each Cuvette, in the incubation area 100ul of PPP of patient (which were thawing in water bath at 37c) or control was dispensed in each Cuvette, after warming the Cuvette transferred to test column area 100ul of the mixture Ca+/thromboplastin was dispensed into Cuvette with the test in column area, the time was started immediately, then after clot produced the instrument automatically stopped the timer and the result of PT appear on the display of the instrument per seconds [Appendix3].
**Reference value**

11-17 seconds (depend on PT reagent)

**2.4.3 Activated Partial Thromboplastin time (APTT)**

The APTT was performed by automated Bio Bas Coagulometer testing in the batch or state mode. An aliquot of undiluted PPP was incubated at 37c with a particulate factor XII activator. A reagent containing phospholipid (partial thromboplastin) was added, followed by Cacl2. It measure over all activity of intrinsic pathway. Cuvettes were placed in incubation area for pre warming at 37 for at least 3 minutes. A magnetic was dispensed to each cuvette. In the incubation area 100 ul of PPP of patient (which were thawing in water bath at 37c) or control was dispensed in each cuvette. 100 ul of cephalin /kaolin mixture was added to each cuvette. After incubation for 3 minutes the cuvette transform to test column area, then 100 ul of CaCl2 were dispensed into cuvette in test column area. The timer was started immediately, after clot produce the instrument automatically stopped the timer and the result appears on the display per seconds [Appendix4].

**References value**

– 42 seconds (depend on APTT reagent).

**2.4.4 Statistical analysis:**

The data was analyzed using SPSS 20. Continuous data was expressed as means; ± Standard Deviation and Categorical data was expressed in frequencies and percentages. A two tailed t-test was used to compare every two means, while correlation test was used to detect a relation between variables. P ≤ 0.05 was considered to be statistically significant.
Chapter Three

3. Results

3.1 Descriptive Analysis

- A total of 100 Sudanese patients 50 (50%) pre renal transplantation as control and 50 (50%) post renal transplantation were enrolled in this study Table (3.1). Thirty nine (78%) were males, while 11 (22%) were females, no significant differences were found between groups (P.value>0.05) Figure (3.1).

- Twenty five of them their ages < 35 years (50%) and 25 (50%) > 35 years, no significant differences were found between groups (P.value>0.05). Nineteen (38%) of them had CKD for less than 1 year while 31 of them (62%) had the disease for more than 1 year Figure (3.3).

- The duration of transplantation was less than 1 year in 16 patients (32%) and more than 1 year in 34 (68%) patients Figure (3.4), no significant differences were found between groups (P.value>0.05).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
<th>Percent%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Transplant Patients</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td><strong>Age/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>&gt;35</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td><strong>Duration of Kidney disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 years</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>&gt;1 years</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td><strong>Duration of transplantation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 years</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>&gt;1 years</td>
<td>34</td>
<td>68</td>
</tr>
</tbody>
</table>
Figure (3.1): Gender distribution of control and post renal transplant patients
Figure (3.2) Duration of symptoms of control

Figure (3.3): Duration of Symptoms of transplant patients
The means of age, duration, PT, APTT, INR and D-dimer in control were (41.6 years, 1.6 years, 14.3 Sec, 32.7Sec, 1.1 and 0.9µgm/ml) respectively.

Table (3.2) Descriptive analysis of control

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.6</td>
<td>17.4</td>
</tr>
<tr>
<td>Duration</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>PT</td>
<td>14.3</td>
<td>1.2</td>
</tr>
<tr>
<td>PTT</td>
<td>32.7</td>
<td>4.6</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

On the other hand, the means of age, duration, PT, APTT, INR and D-dimer in transplant patients were (35.4 years, 1.7 years, 15.0 Sec, 30.8 Sec, 1.1 and 0.49 µgm/ml) respectively.

Table (3.3): Descriptive analysis of transplant patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Duration</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>PT</td>
<td>15.0</td>
<td>1.6</td>
</tr>
<tr>
<td>PTT</td>
<td>30.8</td>
<td>3.8</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Statistical significant is set at P.value < 0.05
3.2 D-dimer

The mean of D-dimer in control is 0.96 µgm/ml while in transplant patients is 0.46 so there was significance decrease in post transplantation. Table (3.4). Using two tailed test there was significance difference between means of D-dimer in control and transplant patients (P.value: 0.000).

Table (3.4): Comparison the D-dimer between control and transplant patients

<table>
<thead>
<tr>
<th>Coagulation parameter</th>
<th>Sample</th>
<th>Number</th>
<th>Mean</th>
<th>SD</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer</td>
<td>Control</td>
<td>50</td>
<td>0.9</td>
<td>0.6</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Transplant patients</td>
<td>50</td>
<td>0.4</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

3.2.1 Correlation test

Using correlation test there was no relation between control and transplant patient’s levels of D-dimer and duration, age, gender and INR in control and transplant patients. (P. values >0.05). Table (3.5) (3.6) respectively.

Table (3.5): Correlation test between D-dimer and duration, age, gender and INR in control
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>1.6</td>
<td>0.708</td>
</tr>
<tr>
<td>Age</td>
<td>41.6</td>
<td>0.664</td>
</tr>
<tr>
<td>Gender</td>
<td>1.3</td>
<td>0.659</td>
</tr>
</tbody>
</table>

Table (3.6): Correlation test between D-dimer and duration, age, gender and INR in transplant patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>1.7</td>
<td>0.558</td>
</tr>
<tr>
<td>Age</td>
<td>35.5</td>
<td>0.193</td>
</tr>
<tr>
<td>Gender</td>
<td>1.2</td>
<td>0.612</td>
</tr>
</tbody>
</table>

Chapter Four
4. Discussion, Conclusions and Recommendations

4.1 Discussion

Regular follow up of transplanted kidney is critical to assess graft function, which permits getting total medical management to the organ. Unfortunately serum creatinine levels and renal biopsy follow up cannot detect early changes in new kidney, because serum creatinine assessment fail to detect acute renal function alteration, and the renal biopsy is so slow. So we must use new biomarkers for rapid detection for alteration in graft function. In this regard, it is well known that the activation of blood coagulation or suppression of fibrinolysis plays a role in the progression of atherosclerosis in renal transplanted patients and it seems to be the major cause of mortality after transplant and these hemostatic abnormalities with unknown cause. The hemostasis/fibrinolysis evaluation in renal transplanted patients in this study included the determination of three biomarkers: D-dimer, PT and PTT levels. In fact, other studies also reported an increase in D-dimer plasma levels in a short-term after transplantation. After surgery, in the immediate post-transplant which already high before transplantation and this agreed with Mohammed. N and Khalil. H in 2016 on Sudanese renal failure patients, it is really expected to increase D-dimer plasma levels, but it decreases with regression of creatinine plasma levels sometime after transplantation and stable graft function. There are few studies associating renal function, creatinine, and D-dimer plasma levels, as well as other hemostatic biomarkers, in long-term post-transplant. Moreover, D-dimer is a classic marker of fibrin degradation and further studies are needed to clarify its role in renal transplanted patients. The present study showed that the mean of D-dimer level in patient with renal transplantation was significantly decrease when compared with D-dimer of the CKD patients (p. value < 0.05) with no effect of duration, age and gender and there was no significant different in PT and APTT which is agreed with
M. Minz et al in 2010. A similar study has been carried on patients of CKD, and post transplantation showed significantly decrease levels of D-dimer, but disagreed with Pawlicki et al in 2007, Mladen et al in 2011, Ballow et al in 2007 and study in Brazilian Renal Transplanted Patients in 2015 by Ana et al which they founded increasing in D-dimer and this is due to they were conducted their studies in early period after transplantation, but this study in long period and this justify the different. The increasing of D-dimer in early period after transplantation can be due to post operation according to Daniel Dindo et al in 2009 which they founded that, the D-dimers may be elevated after surgery. However, the kinetics of postoperative D-dimers remains unknown hampering the use of D-dimer testing in surgical patients with suspected venous thromboembolism. Changes in coagulation after renal transplantation, both in the short and long term, have been studied only to a very limited extent. One would assume that with restoration of normal renal function following a successful renal transplant, these hemostatic mechanisms would return to normal. However, there are several factors relevant in the pre - and post-transplant periods known to influence the coagulation process, such as the function of the kidney, the immune response, and the immunosuppressive agents used post-transplantation.

4.2 Conclusions

- D-dimer is high in control.
- PT and APTT are normal in control.
• D-dimer, Prothrombin time and Activated partial thromboplastin time were normal in patient with chronic renal failure post renal transplantation in early five years.
• D-dimer could be benefit for post transplantation monitoring as biomarker after healing from the operation.

4.3 Recommendations

• More recent studies must be made on kidney transplantation to get more benefits and with increase sample size.
• D-dimer should be considered for patients’ pre and post renal transplantation to follow up and management to avoid risk of thrombosis.
• Further studies on D-dimer to clarify its role in renal transplanted patients are needed.
• New hemostatic biomarkers must be measure in patients after kidney transplantation to maximize management of organ recovery.
• More recent studies must be made on rejected group to assess D-dimer.

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