Comparison between cardiovascular changes in adults and children pre and post renal transplantation

Thesis

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Introduction and aim of the work

Morbidities related to the cardiovascular system (CVS) are responsible for 90% of deaths in chronic kidney disease (CKD), even before reaching end-stage renal failure (ESRD).

Renal transplant recipients are also at much greater risk of deteriorating renal function than the general population . Renal transplant recipients have many conventional risk factors for acute cardiovascular disease, including hypertension, hyperlipidemia, and post transplant diabetes mellitus**.**

The long-term outcome of pediatric renal transplantation recipients has improved dramatically in the past 3 decades, as a result of the use of more potent immunosuppressive agents and a decline in mortality from infections.

Cardiovascular events are among the most frequent causes for long-term morbidity and mortality in children after renal transplantation.

Pediatric patients post-kidney transplant are at continuous risk for developing cardiovascular disease.

The aim of this work is evaluation of the impact of renal transplantation on the cardiac morphological and functional characteristics and its clinical correlation with renal graft function and comparing the effect of transplantation on cardiac morphological and functional characteristics in children and adults.

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Appreviations

- **Appreviation**

- ACC: American College of Cardiology
- ACEI: angiotensin-converting enzyme inhibitor
- AGE: advanced glycation end products
- ARB: angiotensin receptor blocker
- ATGAM: Antithymocyte Globulin
- BUN: blood urea nitrogen
- C-ANCA: cytoplasmic pattern antineutrophil cytoplasmic antibody
- CBC: complete blood count
- CCB: calcium channel blocker
- CHF:congestive heart failure
- CKD: chronic kidney disease
- CNI: calcineurin inhibitor
- CNI: calcineurin inhibitors
- COPD:chronic obstructive pulmonary disease
- Cr: creatinine
- CrCl: creatinine clearance
- CRF : chronic renal failure
- CRP: C-reactive protein
- CVD: cardiovascular disease
- DASH: Dietary Approaches to Stop Hypertension
- DE : dobutamine echocardiography
- DHP: dihydropyridine
- DM: diabetes mellitus
- DSS: dipyridamole thallium/ sestamibi scintigraphy
- ED: erectile dysfunction
- EF : Ejection Fraction
- ESRD: end stage renal disease
- FS : Fraction systolic
- FSGS: focal and segmental glomerulosclerosis
- GFR: glomerular filtration rate
- GI: gastrointestinal
- GTT: glucose tolerance test.
- HCTZ: hydrochlorothiazide
- HD: hemodialysis
- HDL: High density lipoprotein
- Hg: hemoglobin

- HMG-CoA: hepatic hydroxymethyl glutaryl–CoA
- HTN: hypertension
- HUS: hemolytic-uremic syndrome
- ICG : international consensus guidelines
- IgA: immunoglobulin A
- IHD: ischemic heartdisease
- JNC VII : Joint National Committee
- K/DOQI : Kidney Disease Outcomes Quality Initiative
- LDL: low density lipoprotein
- LFT: liver function tests.
- LVED: left ventricular end-diastolic
- LVES: : left ventricular end-systolic
- LVH: left ventricular hypertrophy
- LVH: Left ventricular hypertrophy
- LVMI **:** Left ventricular mass index
- NCEP III: the National Cholesterol Education Project Plan III
- NHANES III: The Third National Health and Examination Survey
- NODAT: new-onset diabetes after transplantation
- NRT : nicotine replacement therapy
- P-ANCA: positive antineutrophil cytoplasmic antibody
- RAS: renin-angiotensin system
- RATG: rabbit anti-human thymoglobulin
- RCIN: radiocontrastinduced nephropathy
- RTR: renal transplant recipients.
- TTP: thrombotic thrombocytopenic purpura
- USRDS: United States Renal Data System
- VLDL: very low density lipoprotein

Chapter One

Renal Failure in adults and children

The kidneys play key roles in body function, not only by filtering the blood and getting rid of waste products, but also by balancing levels of electrolytes in the body, controlling blood pressure, and stimulating the production of red blood cells.

The kidneys are located in the abdomen toward the back, normally one of each side of the spine. They get their blood supply through the renal arteries directly from the aorta and send blood back to the heart via the renal veins to the vena cava. (The term "renal" is derived from the Latin name for kidney.) ***(David; 1996*)**

The kidneys have the ability to monitor the amount of body fluid, the concentrations of electrolytes like sodium and potassium, and the acid-base balance of the body. They filter waste products of body metabolism, like urea from protein metabolism and uric acid from DNA breakdown. Two waste products in the blood can be measured: blood urea nitrogen (BUN) and creatinine (Cr).

When blood flows to the kidney, sensors within the kidney decide how much water to excrete as urine, along with what concentration of electrolytes. For example, if a person is dehydrated from exercise or from an illness, the kidneys will hold onto as much water as possible and the urine becomes very concentrated. When adequate water is present in the body, the urine is much more dilute, and the urine becomes clear. This system is controlled by renin, a hormone produced in the kidney that is part of the fluid and blood pressure regulation systems of the body. **(Bruce,2000 and Remuzzi et al, 1997)**

Kidneys are also the source of erythropoietin in the body, a hormone that stimulates the bone marrow to make red blood cells. Special cells in the kidney monitor the oxygen concentration in blood. If oxygen levels fall, erythropoietin levels rise and the body starts to manufacture more red blood cells.

After the kidneys filter blood, the urine is excreted through the ureter, a thin tube that connects it to the bladder. It is then stored in the bladder awaiting urination, when the bladder sends the urine out of the body through the urethra.**(Benjamin C. Wedro,2010)**

Definition

Chronic kidney disease (CKD) refers to the myriad problems that follow loss of kidney function. It results from a large number of diseases that either are systemic and damage the kidney or are intrinsic to the kidney. ***(David,1996*)**

CKD has two characteristics:

First, there is chronicity because the kidney damage of CKD is rarely repaired and loss of function persists, unlike the course of acute kidney failure.

Second, loss of kidney function generates even more kidney damage so that CKD progressively worsens even if the disorder that caused it becomes inactive. CKD is the preferred term because another widely used one, chronic renal failure or insufficiency, is not as easily identifiable by patients as a disorder that affects the kidney**. (Bommer,2002)**

In addition, chronic renal failure suggests that the kidneys have lost all of their function, whereas CKD covers the spectrum of clinical problems beginning with abnormalities detectable only by laboratory testing to a late stage, labeled uremia.

Uremia literally means “urine in the blood” and represents the toxic state principally resulting from accumulation of unexcreted waste products derived from metabolism of protein. **(Frei U et al, 2001)**

When the kidney fails to perform most of its function, the clinical state is labeled end-stage renal disease (ESRD), and dialysis or transplantation is required to sustain life. The progressive and chronic nature of CKD is emphasized because treatment can slow or even halt the loss of kidney function, and many symptoms of uremia can be ameliorated or eliminated**.(William E. Mitch,2007)**

Chronic kidney disease (CKD) is a worldwide public health problem and is now recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF).

The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months. **(Coresh et al, 2005).**

Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR. The different stages of chronic kidney disease form a continuum in time; prior to February 2002, no uniform classification of the stages of chronic kidney disease existed. At that time, K/DOQI published a classification of the stages of chronic kidney disease, as follows:

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
- Stage 5: Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis)

In stage 1 and stage 2 chronic kidney disease, GFR alone does not clinch the diagnosis.

Other markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests, should also be present in establishing a diagnosis of stage 1 and stage 2 chronic kidney disease.

The K/DOQI definition and the classification of chronic kidney disease allow better communication and intervention at the different stages. **(Pradeep Arora, 2010)**

Epidemiology

The increase in the number of patients with ESRD in the United States and other industrialized countries has features of an epidemic. For example, the number of patients with ESRD in the United States increased by an average of 5% between 1980 and 1990, and the incidence of ESRD was 219 per million population in 1991 but grew to 334 per million by 2000. **(Bommer , 2002)**

A recent assessment suggests that the rate of increase of patients with ESRD is falling to an annual increase of 1% or less, possibly because of the emphasis on earlier detection of CKD and aggressive treatment of hypertension and especially more widespread treatment with blockers of the renin-angiotensin-aldosterone system.

Population-based studies such as the National Health and Nutrition Survey, a cross-sectional survey of U.S. adults, have uncovered the magnitude of the CKD problem .

Approximately 8 million persons are afflicted with stage 3 or stage 4 CKD and hence are at high risk of progressive kidney failure. Two disorders account for almost 70% of all new ESRD patients; in 2003, 44.8% had diabetes mellitus and 27.1% had hypertension-induced kidney damage. **(Hakim, Lazarus 1999)**

The populations experiencing the highest incidence were the elderly (i.e., >65 years) and African Americans plus Native and Asian Americans.

The reasons for the racial susceptibility to CKD are unknown. Besides a racial susceptibility, groups that have been identified as being at high risk for progressing from CKD to ESRD are those with hypertension, diabetes mellitus, or cardiovascular disease and those with family members who have ESRD.

Other epidemiologic factors that have been identified as increasing the risk of progressive CKD include smoking, albuminuria, obesity, and hyperlipidemia. The presence of any of these factors should be sought and attempts made to correct them in treating a patient with CKD.**(William E. Mitch,2007)**

In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. Kidney disease is the ninth leading cause of death in the United States.

Data from the United States Renal Data System (USRDS) indicated that there has been an increase of 104% in the prevalence of chronic renal failure (CRF) between the years 1990-2001**. (Brown et al, 2003)**

There is an even higher prevalence of the earlier stages of chronic kidney disease.

According to the Third National Health and Nutrition Examination Survey, it was estimated that 6.2 million people (ie, 3% of total US population) older than 12 years had a serum creatinine value above 1.5 mg/dL; 8 million people had a glomerular filtration rate (GFR) of less than 60 mL/min, the majority of them being in the Medicare senior population (5.9 million people**). (Doolan et al, 1998).**

Therefore, for the first time, the US Surgeon General's mandate for America's citizenry, Healthy People 2010, contains a chapter focused on chronic kidney disease. The objectives of this chapter are to articulate goals and to provide strategies to reduce the incidence, morbidity, mortality, and health costs of chronic kidney disease in the United States.

The burden of chronic kidney disease can be assessed by multiple criteria, all of which underscore the need for improved detection, treatment, and monitoring of clinical and fiscal outcomes.

Reducing renal failure will require additional public health efforts, including effective preventive strategies and early detection and treatment of chronic kidney disease.

Because of the nonuniform definition of kidney disease prior to February 2002, among other factors, most patients with earlier stages of chronic kidney disease have not been recognized o r adequately treated**.(Drey N et al, 2003).**

The Third National Health and Examination Survey (NHANES III) estimated that the prevalence of chronic kidney disease in adults in the United States was 11% (19.2 million): 3.3% (5.9 million) had stage 1, 3% (5.3 million) had stage 2, 4.3% (7.6 million) had stage 3, 0.2% (400,000) had stage 4, and 0.2% (300,000) had stage 5.

Furthermore, the prevalence of chronic kidney disease stages 1-4 increased from 10% in 1988 -1994 to 13.1% in 1999-2004. This increase is partially explained by the increase in the prevalence of diabetes and hypertension, the two most common causes of chronic kidney disease**.(Levey et al, 2005).**

Race:

CKD affects all races, but, in the United States, a significantly higher incidence of ESRD exists in blacks as compared to whites; the incident rate for blacks is nearly 4 times that for whites**.(Nwankwo et al, 2005).**

Sex:

In NHANES III, the distribution of estimated GFRs for the CKD stages was similar in both sexes.

Nonetheless, the USRDS 2004 Annual Data Report reveals that the incident rate of ESRD cases is higher for males with 409 per million population in 2002 compared to 276 for females**.(Hsu et al, 2004).**

Age:

CKD is found in persons of all ages.

Nonetheless, in the United States, the highest incidence rate of ESRD occurs in patients older than 65 years.

Besides diabetes mellitus and hypertension, age is an independent major predictor of CKD. Of the US population older than 65 years without diabetes mellitus or hypertension, 11% had CKD stage 3 or worse according to the NHANES III**.**

(McClellan et al, 2005).

The geriatric population is the most rapidly growing kidney failure (CKD stage 5) population in the United States.

Note that after age 30 years progressive physiological glomerulosclerosis occurs, with GFR (and creatinine clearance [CrCl) falling linearly at a rate of approximately 8 cc/min/1.73 m^2/y from a maximal GFR of 140 cc/min/1.73 m^2.

Aging also results in concomitant progressive physiological decrease in muscle mass such that daily urinary creatinine excretion also decreases; this combination of factors results in constant serum creatinine values over time in a given individual, despite a decrease in CrCl (and GFR**).(Coresh et al, 2003).**

Pathophysiology:

Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR. Regardless of the etiology of renal injury, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. ***(Thomas et al.; 2003)***

This nephron adaptability allows for continued normal clearance of plasma solutes such that substances such as urea and creatinine start to show significant increases in plasma levels only after total GFR has decreased to 50**%.(Hakim,Lazarus, 1999).**

When the renal reserve has been exhausted, the plasma creatinine value will double with a 50% reduction in GFR.

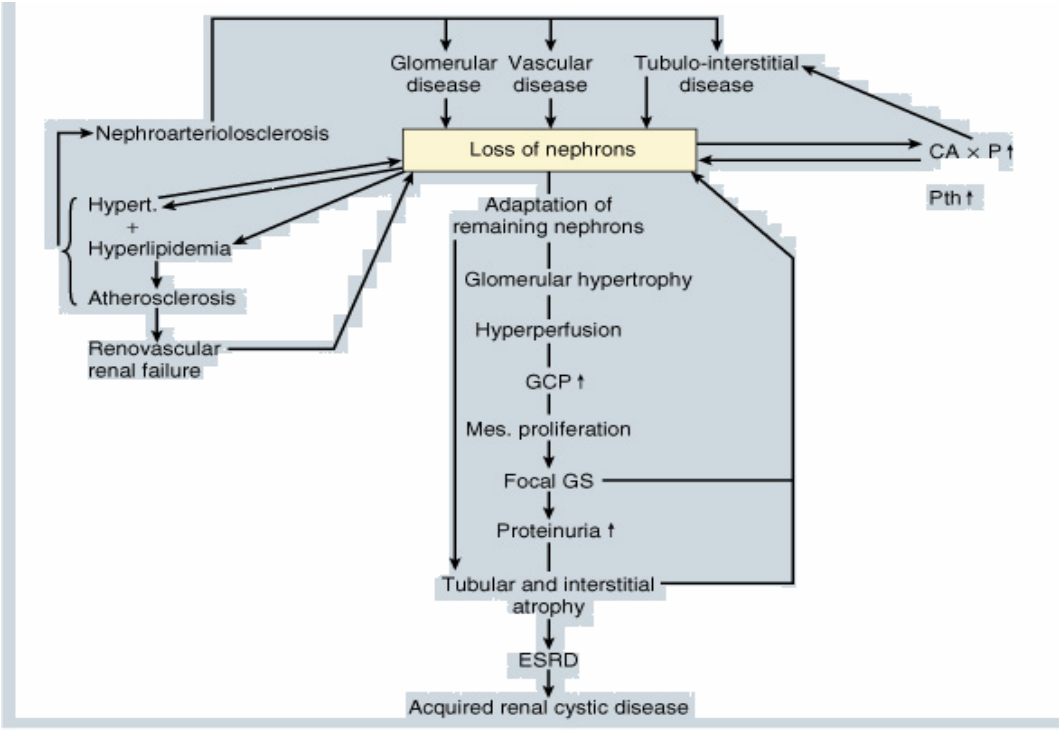
A rise in plasma creatinine from a baseline value of 0.6 mg/dL to 1.2 mg/dL in a patient, although still within the reference range, actually represents a loss of 50% of functioning nephron mass**.(Drey N et al., 2003).**

The residual nephron hyperfiltration and hypertrophy, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction**.(Doolan et al., 1998).**

This is believed to occur because of increased glomerular capillary pressure, which damages the capillaries and leads initially to focal and segmental glomerulosclerosis and eventually to global glomerulosclerosis. This hypothesis has been based on studies of five-sixths nephrectomized rats, which develop these lesions that are identical to those observed in humans with CKD**. (Levey et al, 2005).**

Pathophysiology of CRF is illustrated in Figure (1) that shows causes of renal failure are glomerular diseases, vascular diseases, and tubulo-intersitial diseases.

Fig.1 Pathophysiology of CRF



Factors other than the underlying disease process and glomerular hypertension that may cause progressive renal injury include the following**:(Drey et al, 2003).**

Systemic hypertension

Acute insults from nephrotoxins or decreased perfusion

Proteinuria

Increased renal ammoniagenesis with interstitial injury

Hyperlipidemia

Hyperphosphatemia with calcium phosphate deposition

Decreased levels of nitrous oxide

Causes of CRF

Vascular disease as renal artery stenosis, cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)–positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)–positive vasculitides, antineutrophil cytoplasmic antibody (ANCA)–negative vasculitides, atheroemboli, hypertensive nephrosclerosis, renal vein thrombosis.

Primary glomerular disease as membranous nephropathy, immunoglobulin A (IgA) nephropathy, focal and segmental glomerulosclerosis (FSGS), minimal change disease, membranoproliferative glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis. **(Winkelmayer et al, 2005)**

Secondary glomerular disease as Diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, scleroderma, Goodpasture syndrome, Wegener granulomatosis, mixed cryoglobulinemia.

Postinfectious glomerulonephritis as endocarditis, hepatitis B and C, syphilis, human immunodeficiency virus (HIV), parasitic infection, heroin use, gold, penicillamine, amyloidosis, light chain deposition disease, neoplasia, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), Henoch-Schönlein purpura, Alport syndrome, reflux nephropathy **(Fox et al, 2004)**

Tubulointerstitial disease as Drugs (eg, sulfa, allopurinol), infection (viral, bacterial, parasitic), Sjögren syndrome, chronic hypokalemia, chronic hypercalcemia, sarcoidosis, multiple myeloma cast nephropathy, heavy metals, radiation nephritis, polycystic kidneys, cystinosis.

Urinary tract obstruction as urolithiasis, benign prostatic hypertrophy, tumors, retroperitonealfibrosis,urethralstricture,neurogenicbladder**.(Winkelmayer et al,2005) (Fox et al, 2004)**

Clinical Picture:

Patients with chronic kidney disease stages 1-3 (GFR >30 mL/min) are generally asymptomatic and do not experience clinically evident disturbances in water or electrolyte balance or endocrine/metabolic derangements. Generally, these disturbances clinically manifest with chronic kidney disease stages 4-5 (GFR <30 mL/min).
Uremic manifestations in patients with chronic kidney disease stage 5 are believed to be primarily secondary to an accumulation of toxins, the identity of which is generally not known**.(Ruggeneti et al, 2001)**

Normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production.
It starts early in the course of disease and becomes more severe as the GFR progressively decreases with the availability of less viable renal mass.
No reticulocyte response occurs. RBC survival is decreased, and tendency of bleeding is increased from the uremia-induced platelet dysfunction. Other causes of anemia in chronic kidney disease patients include chronic blood loss, secondary hyperparathyroidism, inflammation, nutritional deficiency, and accumulation of inhibitors of erythropoiesis. (**Silver , 2000).**

Anemia is associated with fatigue, reduced exercise capacity, impaired cognitive and immune function, and reduced quality of life.

Anemia is also associated with the development of cardiovascular disease, the new onset of heart failure, or the development of more severe heart failure.
Anemia is associated with increased cardiovascular mortality.**(Adamson ,Eschbach 1998).**

The ability to maintain potassium (K) excretion at near normal levels is generally maintained in chronic kidney disease patients as long as both aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with chronic kidney disease is increased potassium excretion in the GI tract, which also is under control of aldosterone.

Therefore, **Hyperkalemia** usually develops when the GFR falls to less than 20-25 mL/min because of the decreased ability of the kidneys to excrete potassium. It can be observed sooner in patients who ingest a potassium-rich diet or if serum aldosterone levels are low, such as in type IV renal tubular acidosis commonly observed in people with diabetes or with use of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs). **(Bakris , Weir 2000).**

Hyperkalemia in chronic kidney disease can be aggravated by an extracellular shift of potassium, such as that occurs in the setting of acidemia or from lack of insulin. Hypokalemia is uncommon but can develop among patients with very poor intake of potassium, gastrointestinal or urinary loss of potassium, diarrhea, or diuretic use.
(Bakris , Weir , 2000).

Metabolic acidosis often is mixed, normal anion gap and increased anion gap, the latter observed generally with chronic kidney disease stage 5 but with the anion gap generally not higher than 20 mEq/L.
In chronic kidney disease, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium. In chronic kidney disease stage 5, accumulation of phosphates, sulphates, and other organic anions are the cause of the increase in anion gap. **(Warnock,1998).**

Metabolic acidosis has been shown to have deleterious effects on protein balance, leading to a negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, reduced albumin synthesis, and a lack of adaptation to a low protein diet.

Hence, this is associated with protein-energy malnutrition, loss of lean body mass, and muscle weakness. The mechanism for reducing protein may include effects on ATP-dependent ubiquitin proteasomes and increased activity of branched chain ketoacid dehydrogenases. **(Dalmez , Slatopolsky 1999).**

In the NHANES III prevalence study, **Hypoalbuminemia** (a marker of protein- energy malnutrition and a powerful predictive marker of mortality in dialysis patients as well as in the general population) was independently associated with low bicarbonate as well as the inflammatory marker C reactive protein.
Metabolic acidosis is a factor in the development of renal osteodystrophy, as bone acts as a buffer for excess acid, with resultant loss of mineral.
Acidosis may interfere with vitamin D metabolism, and patients who are persistently more acidotic are more likely to have osteomalacia or low-turnover bone disease. **(Pradeep Arora, 2010)**

The evidence for the benefits and risks of correcting metabolic acidosis is very limited, with no randomized controlled trials in pre-ESRD patients, none in children, and only 3 small trials in dialysis patients.
These trials suggest that there may be some beneficial effects on both protein metabolism and bone metabolism, but the trials were underpowered to provide robust evidence. Experts recommend alkali therapy to maintain the serum bicarbonate concentration above 22 mEq/L.**(Levey et al, 2005).**

Inflammation and hemostasis may increase the risk of kidney function decline, but prospective studies are lacking. The Atherosclerosis Risk in Communities (ARIC) Study, a prospective observational cohort, observed markers of inflammation and hemostasis in 14,854 middle-aged adults.[2] The risk for decreased kidney function associated with the inflammatory and hemostasis markers was examined, using data from 1787 cases of chronic kidney disease (CKD) that developed between 1987 and 2004.**(Adamson, Eschbach 1998).**

After adjustments for various factors, such as demographics smoking, blood pressure, diabetes, lipid levels, prior myocardial infarction (MI), antihypertensive use, and alcohol use, the above study revealed that the risk for chronic kidney disease rose with increasing quartiles of white blood cell (WBC) count, fibrinogen, von Willebrand factor, and factor VIIIc.The investigators found a strong inverse association between serum albumin level and chronic kidney disease risk. The study's findings suggested that inflammation and hemostasis are antecedent pathways for chronic kidney disease. **(PradeepArora,2010)**

Salt and water handling by the kidney is altered in patients with chronic kidneydisease.Extracellular volume expansion and total-body volume overload results from failure of sodium and free water excretion. This generally becomes clinically manifested when the GFR falls to less than 10-15 mL/min, when compensatory mechanisms have become exhausted**. (Hans Strid et al., 2002).**

As kidney function declines further, sodium retention and extracellular volume expansion lead to peripheral and, not uncommonly, pulmonary edema and hypertension.-At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion. (**Levey et al, 2005).**

Renal bone disease is a common complication of chronic kidney disease and results in both skeletal complications (eg, abnormality of bone turnover, mineralization, linear growth) and extraskeletal complications (eg, vascular or soft tissue calcification).

Different types of bone disease occur with chronic kidney disease, as follows:

(1) High turnover bone disease due to high parathyroid hormone (PTH) levels;

(2) Low turnover bone disease (adynamic bone disease);

(3) Defective mineralization (osteomalacia);

(4) Mixed disease

(5) Beta-2-microglobulin associated bone disease. **(Slatopolsky et al., 2002).**

Secondary hyperparathyroidism develops because of hyperphosphatemia, hypocalcemia, decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25 - dihydroxyvitamin D, or calcitriol), intrinsic alteration in the parathyroid gland that give rises to increased PTH secretion as well as increased parathyroid growth, and skeletal resistance to PTH. **(Ghazali et al, 2000).**

Calcium and calcitriol are primary feedback inhibitors; hyperphosphatemia is a stimulus to PTH synthesis and secretion. **(Guerin et al., 2000).**

Phosphate retention begins in early chronic kidney disease; when the GFR falls, less phosphate is filtered and excreted, but serum levels do not rise initially because of increased PTH secretion, which increases renal excretion. As the GFR falls toward chronic kidney disease stages 4-5, hyperphosphatemia develops from the inability of the kidneys to excrete the excess dietary intake. Hyperphosphatemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol, so serum calcitriol levels are low when the GFR is less than 30 mL/min. Increased phosphate concentration also effects PTH concentration by its direct effect on parathyroid gland posttranscriptional effect. **(Bleyer et al., 1999).**

Hypocalcemia develops primarily from decreased intestinal calcium absorption because of low plasma calcitriol levels and possibly from calcium binding to elevated serum levels of phosphate.**(Amann et al., 1999).**

Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and secretion. As these stimuli persist in chronic kidney disease, particularly in the more advanced stages, PTH secretion becomes maladaptive and the parathyroid glands, which initially hypertrophy, become hyperplastic. The persistently elevated PTH levels exacerbate hyperphosphatemia from bone resorption of phosphate. (**Block et al., 1998).**

If serum levels of PTH remain elevated, a high bone turnover lesion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as renal osteodystrophy. These lesions develop in patients with severe chronic kidney disease and are common in those with ESRD**. (Cannata , 2000).**

The prevalence of adynamic bone disease in the United States has increased, and it has been described before the initiation of dialysis in some cases.-The pathogenesis of adynamic bone disease is not well defined, but several factors may contribute, including high calcium load, use of vitamin D sterols, increasing age, previous corticosteroid therapy, peritoneal dialysis, and increased level of N-terminally truncated PTH fragments. -Low turnover osteomalacia in the setting of chronic kidney disease is associated with aluminum accumulation and is markedly less common. Dialysis-related amyloidosis from beta-2-microglobulin accumulation in patients who have required chronic dialysis for at least 8-10 years is another form of bone disease that manifests with cysts at the ends of long bones.(**Bleyer et al., 1999).**

Other manifestations of uremia in ESRD, many of which are more likely in patients who are inadequately dialyzed, include the following: **(Pradeep Arora,2010)**

- Pericarditis - Can be complicated by cardiac tamponade, possibly resulting in death.
- Encephalopathy - Can progress to coma and death
- Peripheral neuropathy
- GI symptoms - Anorexia, nausea, vomiting, diarrhea
- Skin manifestations - Dry skin, pruritus, ecchymosis
- Fatigue, increased somnolence, failure to thrive
- Malnutrition
- Erectile dysfunction, decreased libido, amenorrhea
- Platelet dysfunction with tendency to bleeding

Management

Unlike other forms of end-stage organ failure, renal failure is unique in having three modalities of therapy: (1) hemodialysis (2) peritoneal dialysis, and (3) renal transplantation. Each form of renal replacement therapy (RRT) has its unique risks and benefits.**(Cannata , 2000).**

Kolff first employed hemodialysis in the late 1940s for the treatment of acute renal failure.The development of vascular access by Scribner in the early 1960s enabled the use of hemodialysis as a chronic therapy. However, it was not until 1973, when the U.S. Congress approved Medicare funding for hemodialysis patients, recognizing end-stage renal disease (ESRD) as a "catastrophic illness," that hemodialysis achieved widespread availability. Currently, there are approximately 350,000 patients on dialysis in the United States, and the ESRD population is projected to grow by about 7% per year. ***(Rossert and Wauters , 2002)***

All three modalities of RRT have evolved significantly over the last four decades. The selection of a particular form of RRT is made according to the clinical setting and patient preference. It is important for the physician and the patient to recognize that these modalities should be viewed as alternative and complementary therapies, allowing flexibility of care under different clinical circumstances. **(Bleyer et al, 1999).**

The key is to identify patients with progressive renal failure early, so as to enable them to make an educated choice that fits their lifestyle and medical situation. Planning and establishing access early decrease emergency hospitalizations and complications and significantly reduce cost. Early evaluation also enables identification of potential living donors so that preemptive transplantation can be performed.**(Nina Tolkoff-Rubin,2007)**

Prognosis

The prognosis for patients with ESRD is poor; the mortality rate of dialysis patients averages 20% per year and is greater than that of patients with colorectal cancers and only somewhat better than that of those with lung cancer.Cardiovascular disease is the most common cause of mortality in CKD. It is present in many patients even at the early stages of CKD, and 90% of those beginning dialysis therapy will have left ventricular hypertrophy or dysfunction.**(William E. Mitch,2007)**

Several mechanisms have been implicated as causes of this association, including hypertension and older age; the median age of patients beginning dialysis in the United States is approximately 65 years. Other contributors are diabetes, anemia, increased homocysteine and low-density lipoprotein cholesterol levels, vascular calcification, and poorly identified factors.Regarding the continued loss of GFR, epidemiologic studies indicate that one third of patients with stage 4 CKD will progress to ESRD within 3 years. Patients with stage 3 CKD also have a significant risk of developing ESRD, but the average time to reach ESRD is longer. **(Cannata , 2000).**

Such data are of limited value for the CKD patient and his or her physician because both are interested in knowing when the patient will reach stage 5 CKD.Because the rate of loss of kidney function varies widely even in patients who have the same type of kidney disease, it is critically important to monitor the course of declining kidney function in each CKD patient.**(Guerin et al, 2000).**

Fortunately, the rate of progression is linear in most individuals, so the prognosis of CKD can be predicted from a plot of GFR or 1/serum creatinine versus time . Monitoring the course of CKD not only has prognostic value; it also can be used to evaluate the efficacy of therapy or to determine when investigation should be undertaken for complications that accelerate the loss of kidney function (e.g., nephrotoxic agents or the presence of obstruction).Factors that should be regularly evaluated include the presence of symptoms of advancing CKD or uremia, changes in body weight, blood pressure and the presence of edema, SUN concentration, urine albumin–to-creatinine ratio, hemoglobin level, serum albumin concentration, serum calcium concentration, phosphorus concentration, and electrolyte values. Changes in these factors should be investigated**. (WilliamE. Mitch,2007)**

Chapter Two

Cardiovascular changes in renal failure patients

Introduction:

Chronic kidney disease (CKD) affects approximately 13% of the U.S. population and is associated with increased risk of cardiovascular complications. Once renal replacement therapy became available, it became apparent that the mode of death of patients with advanced CKD was more likely than not related to cardiovascular compromise**. (Fadi G. Hage et al, 2009)**

Further observation revealed that such compromise was related to myocardial disease (related to hypertension, stiff vessels, coronary heart disease, or uremic toxins).
Early on, the excess of cardiovascular events was attributed to accelerated atherosclerosis, inadequate control of blood pressure, lipids, or inflammatory cytokines, or perhaps poor glycemia control. In more recent times, outcome research has given us further information that relates even lesser degrees of renal compromise to an excess of cardiovascular events in the general population and in those with already present atherosclerotic disease.**(Rajesh Venkataraman et al, 2009)**

As renal function deteriorates, certain physiologic changes occur (perhaps due to hemodynamic, inflammatory, or metabolic changes) that decrease oxygen-carrying capacity of the blood by virtue of anemia, make blood vessels stiffer by altering collagen or through medial calcinosis, raise the blood pressure, increase shearing stresses, or alter the constituents of atherosclerotic plaque or the balance of thrombogenesis and thrombolysis**.(Gilbert J. Zoghbi et al, 2009)**

At further levels of renal dysfunction, tangible metabolic perturbations are recognized as requiring specific therapy to reduce complications (such as for anemia and hyperparathyroidism), although outcome research to support some of our current guidelines is sorely lacking.
Understanding the process by which renal dysfunction alters the prognosis of cardiac disease might lead to further methods of treatment. **(Fadi G. Hage et al, 2009)**

There is increasing recognition that chronic kidney disease (CKD) of any degree portends a worsened prognosis for coronary artery disease (CAD) patients and that long-term outlook in CKD patients is closely related to cardiovascular events. **(Keith et al, 2004)**

The value of most therapeutic interventions is less certain for CKD versus non-CKD patients because the former have typically been excluded from randomized trials. **(Keith et al, 2004)**

Chronic kidney disease has reached epidemic proportions. More than 320,000 patients had dialysis-requiring CKD in 1998; by 2010, this number may exceed 650,000 patients.
Patients with mild to severe decrease in glomerular filtration rate (GFR) constitute a larger group, estimated in 1998 to be 13.3 million.
Finally, there are many CKD patients without decreased GFR (5.9 million in 1998)
The prevalence of CAD in CKD patients is high and is a major cause of morbidity and mortality. In hemodialysis (HD) or peritoneal dialysis patients, prevalence is estimated at 40% with a 9% annual cardiovascular mortality. **(MacMahon et al, 2007)**

Renal transplant recipients (RTRs) have a lower CAD prevalence (15%) with an annual cardiovascular mortality of 0.54%, twice the general population . This lower prevalence may be due to patients with fewer comorbidities and lower CAD likelihood being chosen for transplantation.
The need for nomenclature uniformity has led to a recent CKD classification based on estimated GFR **.(Mark et al, 2006)**

The GFR has been estimated by two formulae:

Cockcroft-Gault equation:

GFR= (140- age)x lean body weight (kg) / 72x serum Cr
(85 for females not 72)

Modification of Diet in Renal Disease study equation:

GFR/1.73 m2 = 170x pt creatine(mg/dl)exp[-0.999]xAge exp[-0.176]xSUrea (mg/dl)x[-0.170]x((Albumin[g/dl])exp[+0.136])

Chronic kidney disease increases cardiovascular event risk as shown in figure (2) and portends a worse outcome if an event occurs. **(London et al, 1997)**

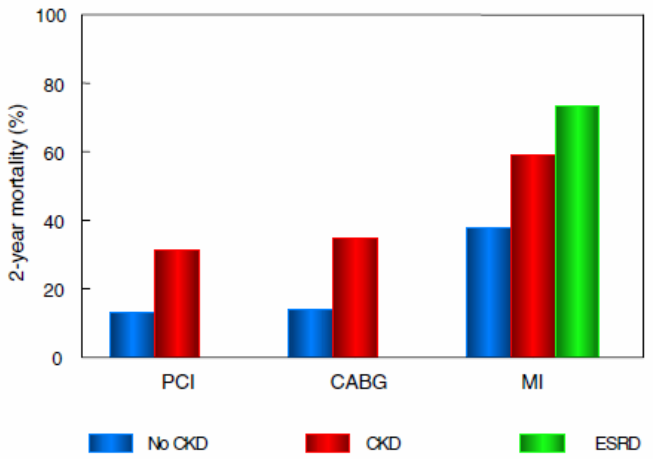


Figure 2 Mortality Is Increased in CKD Patients After MI, PCI, and CABG

The following figure (2) shows increased incidence of mortality in CKD patients after myocardial infarction, PCI

A study of 3,106 acute myocardial infarction (AMI) patients showed in-hospital mortality of 2% in normal renal function,6% mild CKD, 14% moderate CKD, 21% severe CKD, and 30% in dialysis patients ($p \leq 0.001$) with a similar trend long -term.
A meta-analysis of ST-segment elevation AMI thrombolytic trials showed inverse correlation between 30-day mortality and renal function**.**
(RajivGupta et al, 2004)

Patients with mild to moderate CKD and non–ST-segment elevation acute coronary syndrome (ACS) showed higher 30- and 180-day mortality than non-CKD patients.
One-year mortality after AMI was 59% in dialysis patients and 24% in RTRs .
In a post-AMI Medicare cohort comprised of 130,099 patients, one-year mortality was 24%without CKD, 46% with mild CKD, and 66% with moderate CKD ($p \leq 0.001$).
Among CKD patients undergoing coronary angiography followed long-term, the hazard ratio of AMI or death was 2.3 for GFR ≤60 ml/min and 5.1 for GFR ≤30ml/min. **(Yochai Birnbaum et al, 2004)**

The CKD patients with "normal" angiography demonstrated increased AMI (5.2% vs. 0.7% in non-CKD patients, $p \leq 0.01$) and mortality (24.7% vs. 3.9%, $p \leq 0.001$) rates. **(Barry F. Uretsky et al, 2004)**

Chronic kidney disease (CKD) is associated with cardiovascular (CV) disease and mortality.
It is not known whether cardiac rhythm disturbances are more prevalent among individuals with CKD or whether resting electrocardiogram findings predict future CV events in the CKD setting.**(Johnston et al, 2006)**

Data were obtained from the Cardiovascular Health Study, a community-based study of adults aged >65 yr. After exclusions for prevalent heart disease, atrial fibrillation, implantable pacemaker, or antiarrhythmic medication use, 3238 participants were analyzed. CKD was defined by an estimated GFR <60 ml/min per 1.73 m2.Outcomes were adjudicated incident heart failure (HF), incident coronary heart disease (CHD), and mortality.**(Babazono et al, 2007)**

Participants with CKD had longer PR and corrected QT intervals compared with those without CKD; however, differences in electrocardiographic markers were explained by traditional CV risk factors and CV medication use.
After adjustment for known risk factors, each 10-ms increase in the QRS interval was associated with a 15% greater risk for incident HF (95% confidence interval [CI] 1.04 to 1.27), a 13% greater risk for CHD (95% CI 1.04 to 1.24), and a 17% greater risk for mortality (95% CI 1.09,1.25) among CKD participants. Each 5% increase in QTI was associated with a 42% (95% CI 1.23 to 1.65), 22% (95% CI 1.07 to1.40), and 10% (95% CI 0.98 to 1.22) greater risk for HF, CHD, and mortality, respectively.
Associations seemed stronger for participants with CKD; however, no significant interactions were detected. Resting electrocardiographic abnormalities are common in CKD and independently predict future clinical CV events in this setting. **(Bryan Kestenbaum et al, 2007)**

Epidemiology of Cardiovascular Disease in Patients with CKD

Hemodialysis patients (stage 5 CKD) have extremely high morbidity and mortality from CVD. Based on data from the U.S. Renal Data System Coordinating Center Case-Mix Adequacy Study, the prevalence of clinical coronary heart disease (CHD) in hemodialysis patients is 40%, and CVD mortality is 10 to 30 times higher than in the general population despite stratificationbygender,age,race, and the presence of diabetes**.**
(Hunsicker et al, 2005)

The aging of the U.S. population and the epidemic of diabetes have greatly increased the incidence of mild to moderate CKD in the U.S. A prospective population-based study of subjects 65 years old followed patients with CKD for an average of 7 years; CKD, defined as creatinine 1.5 mg/dl in men and1.3 mg/dl in women, was found in 11% of participants.
Those with CKD were more likely to develop CVD, congestive heart failure, or peripheral vascular disease. This relationship persisted after adjusting for traditional risk factors, including age. Similar findings were reported in the Atherosclerosis Risk in Communities Study, which demonstrated that a decreasing GFR was independently associated with the development of atherosclerotic CVD .**(Chalmers et al, 2007)**

The link between dyslipidemia and increased CVD risk in patients with CKD has been difficult to establish in large part due to the myriad other cardiovascular risk factors observed in patients with CKD, including increased oxidative stress,inflammation, physical inactivity, anemia, vascular calcification, endothelial dysfunction, and reduced nitric oxide availability. **(Chalmers et al, 2007)**

Epidemiologic studies have suggested that hemodialysis patients with higher total cholesterol levels have lower mortality; however, these findings are not statistically significant when corrected for inflammation and nutrition.
(Charles R. Harper,2008)

Actually many patients with renal impairment don't reach the dialysis stage because they die of the cardiovascular complications as shown in figure (3).

(Keinth et al ,2004)

The following figure (3) shows the distribution of the causes of death in patients with ESRD

Figure (3)

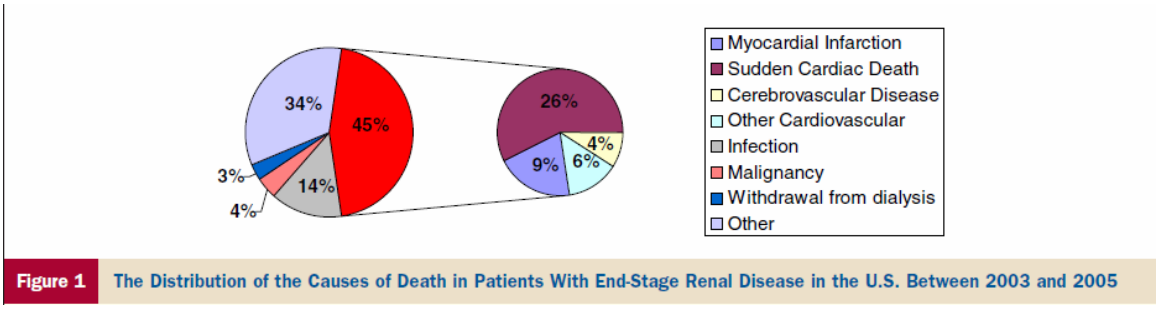


Figure 1 The Distribution of the Causes of Death in Patients With End-Stage Renal Disease in the U.S. Between 2003 and 2005

In order to understand the relationship between renal failure and cardiovascular complications, risk factors could be divided into：as shown in figure (4)(**Gaede et al, 2003)**

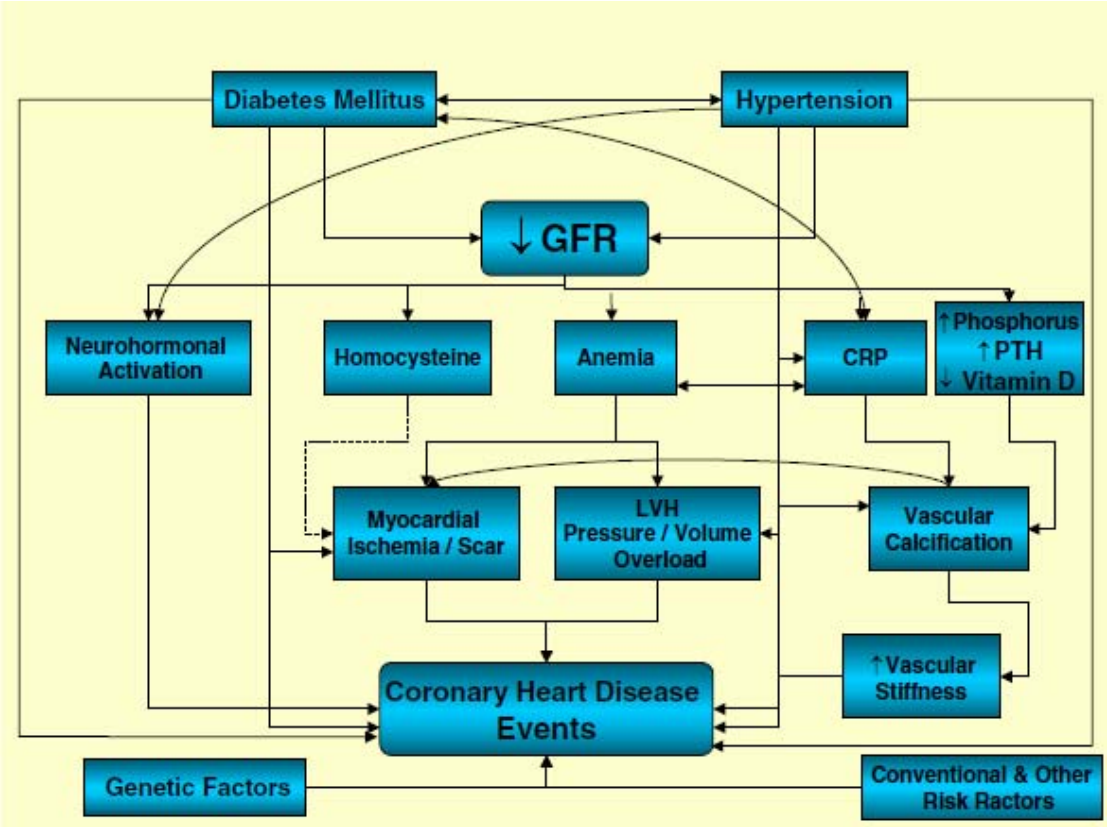
A) Traditional risk factors: these include:

1. Hypertension
2. Left ventricular hypertrophy
3. Dyslipidemia
4. Diabetes and insulin resistance
5. Sudden cardiac death syndrome
6. Albuminuria and hypoalbuminemia

B) Non traditional or novel risk factors:

1. Vascular calcification and inflammation
2. Endothelial dysfunction
3. Asymmetrical diethylarginine (ADMA)
4. Hyperhomocystenemia

Figure(4) Traditional and non traditional risk factors of cardiovascular diseases



A) TRADITIONAL RISK FACTORS:

1-Hypertension as a cardiovascular risk in renal failure patients:

Hypertension is the most common cause of of renal failure in general population, it is estimated that 60% of the renal failure patients had hypertension as main etiological factor .
It was found that in hypertensive renal failure patients ,there is intimal hyperplasia of the blood vessels ,most remarkably in the renal medium and small sized vessels, the so called nephroangiosclerosis **,**this process is then propagated to the aorta and to other arteries such as the coronaries and become major contributer to cardiovascular morbidity ***(*Bonett et al, 2003)**

As a potentially modifiable risk factor, the impact of hypertension on cardiovascular disease in patients with CKD is of great interest.
As kidney impairment progresses there is increasing activation of the RAS in response to glomerular sclerosis and interstitial disease as well as fluid overload and increased arterial stiffness, all of which contribute to hypertension**. (Cooper et al, 2001)**

Essential hypertension itself causes microvascular damage in the renal vascular bed causing kidney damage and hence, through RAS activation, exacerbating essential hypertension.
Hypertension is known to alter renal physiological function with increased filtration fraction of sodium and increased renovascular resistance seen in hypertensive patients. **(Lewis et al, 2001)**

Poor hypertension control clearly leads to increasing risk of cardiovascular morbidity and mortality and increasing riskof declining kidney function.
A 'vicious circle' is created with worsening kidney function itself then contributing to hypertension.
Hypertension is widespread among an otherwise healthy general population, especially in the elderly where approximately two thirds of people will be hypertensive**.(Makino et al, 2007)**

The majority of patients with CKD are hypertensive, with the prevalence increasing with increasing severity of CKD such that in the most severe stages of CKD (eGFR ≤ 30 mL/min) over 90% of patients are hypertensive.
(de LS, Chan et al, 2005)

As CKD progresses there is also increasing loss of the physiological nocturnal 'dip' in blood pressure, which is in itself a marker for the presence of LVH.
Studies have clearly shown a significant reduction in the rate of progression of CKD when hypertension is treated.
Particularly this has been demonstrated in major studies investigating blockade of the RAS with ACEi in both proteinuric and nonproteinuric CKD and with angiotensin II receptor blockers. **(Wanner , Krane et al, 2005)**

Many studies have demonstrated a reduction in the rate of progression of CKD with drugs blocking the RAS, compared to the same blood pressure reduction achieved with other antihypertensive regimens.
This alludes to the importance of blocking angiotensin II which is a powerful an endothelial growth factor in the renal vascular bed, as well as the body's most powerful vasoconstrictor.
There is not currently a full understanding of the pathophysiology of the effects of hypertension on the kidney in patients with CKD; however the major effect is likely to be a progressive increase in intra-renal vascular resistance which may precede any changes in kidney structure**.(Pfeffer et al, 2005)**

The Hypertension Detection and Follow Up Program followed over 10,000 general population patients over 5 years in a randomized controlled trial comparing usual antihypertensive care with a stepped program of drug interventions to achieve reduction in diastolic blood pressure of 10 mm Hg (or ≤90 mm Hg in those patients whose baseline diastolic blood pressure was ≥100mm Hg).**(Ford et al, 1998)**

As well as a 17% reduction in mortality, this trial established that the incidence of decline in kidney function was less in the stepped blood pressure treatment group than in other patients. **(Shulman et al, 1998)**

The incidence of decline in kidney function was greatest in men and older adults as well as those with higher baseline diastolic blood pressure. The incidence of significant kidney impairment was low in this community based study, however an elevated serum creatinine was a potent independent risk factor for mortality.
The lower rate of kidney impairment in the intensive blood pressure treatment group demonstrates the value of aggressive hypertension management in patients with CKD even in the early stages of kidney dysfunction.
(Shulman et al, 1998)

A smaller US study of patients with treated hypertension and initially normal serum creatinine levels also demonstrated that 15% of patients, went on to develop kidney dysfunction despite adequate blood pressure control.
(Rostand , Brown et al, 1989)

Altered kidney function is an adverse prognostic factor in populations with essential hypertension as well as in other patient populations, such as those with advanced congestive cardiac failure or a previous myocardial infarction. Even in the absence of a known primary kidney pathology, markersfor kidney dysfunction (reduced eGFR, microalbuminuria and overt proteinuria) should be investigated in these populations because of the adverse prognostic implications of kidney dysfunction. **(Albouze et al, 1993)**

In a study of patients with identified primary kidney diseases, elevated mean arterial blood pressure was independently correlated with a decrease in kidney function over time.**(Hannedouche et al, 1993)**

Thus both in patients with essential hypertension and in those with primary kidney diseases and secondary hypertension, controlling blood pressure is an important means of reducing the rate of kidney decline aswell as cardiovascular risk.
There is still debate about the ideal target level of blood pressure for patients with CKD. A meta-analysis of randomized controlled trials of ACEi showed that whilst increasing systolic blood pressure, above 120 mm Hg, proportionately increased the risk of progressive kidney dysfunction; increased risk was also seen with systolic blood pressures below 110 mm Hg.
(Keith ,2004)

This finding can probably be explained by relative hypoperfusion of the kidney in patients with low systolic blood pressure secondary to heart failure.
(Keith,2004)

Such studies might lead clinicians to assume that there is a very narrow range of blood pressure which can be considered 'ideal' for patients with CKD. The current British Renal Association guidelines suggest a target blood pressure of ≤130/80 mm Hg to be acceptable in patients with stable kidney function and a target blood pressure of ≤125/75 mm Hg in patients with proteinuric kidney disease. **(Jeremias et al, 2002)**

In practice, it is often very difficult to achieve reasonable blood pressure control without resorting to polypharma the side effects of which may not be acceptable to patients.

In elderly patients who have a high incidence of postural hypotension, more individualized blood pressure targets may need to be set. . **(Hansson et al, 1998)**

General population studies such as the Hypertension Optimal Treatment study suggest that there is a clear advantage of minor reductions in blood pressure in terms of cardiovascular outcomes and physicians should therefore take heart that even small blood pressure reductions may have great benefit for individual patients over time. **(Hansson et al, 1998)**

Similarly the Ramipril Efficacy in Nephropathy study demonstrated that adverse renal outcome (doubling of serum creatinine or the need for renal replacement therapy) was reduced with a minor reduction in blood pressure in theramipril arm of the study compared to the placebo arm**. (Patel et al, 2007)**

Overall average blood pressure achieved in this study was suboptimal compared to recent targets, again suggesting that any blood pressure reduction is important even if targets are not achieved. **(Julian Wright, Alastair Hutchison, 2009)**

2-Left ventricular hypertrophy

In patient populations on renal replacement therapy, LVH is an independent risk factor for cardiovascular related death which accounts for approximately 45% of mortality.
Even in the early stages of kidney impairment, the prevalence of LVH is higher than in the general population. **(Berl et al, 2005)**

In a prospective echocardiographic study by Levin of patients attending a renal insufficiency clinic, LVH was present in 27% of patients with a creatinine clearance over 50 mL/min.
In patients with clearances of 25 to 50 mL/min and less than 25 mL/min, the prevalence of LVH was 31% and 45% respectively. These were significant differences between the functional groups, with the major predictors of LVH in this study being systolic hypertension and anemia**.(Levin ,2003)**

The cardiomyopathy of kidney failure results largely from pressure and volume overload, leading to changes which are, at least in the early phase, adaptive compensations in order to maintain adequate stroke volume.
(**London , Parfrey , 1997)**

Pressure overload, resulting from hypertension and related to arterial stiffness and vascular calcification leads predominantly to concentric LVH.
Volume overload could be assumed to cause predominantly left ventricular dilatation, resulting from salt and water overload, but anemia is another factor which might contribute to dilatation of the ventricle**.(Chobanian et al, 2005)**

The resulting cardiomyopathy leads to both left ventricular systolic and diastolic dysfunction.
Systolic dysfunction in uremic patients has been well studied and it thought to be the result of premature myocyte death for which both IHD and the uremic environment are both predisposing factors.
Echocardiographic studies of patients at dialysis inception have revealed severe systolic dysfunction (LV ejection fraction of ≤25%) in 15% of patients, with 74% of patients having LVH and 32% of patients demonstrating LV dilatation. **(Foley et al, 1995)**

Such LV abnormalities have been shown to have a direct influence on prognosis once patients begin dialysis. Practically such findings underlie the congestive cardiac failure suffered by dialysis patients which is then greatly exacerbated by volume overload and hypertension – both highly prevalent in this patient population**.(Le Feuvre et al,2001)**

The advent of imaging techniques superior to echocardiography, such as cardiac magnetic resonance scanning has led to a new perspective on uremic cardiomyopathy.
LVH has been demonstrated by late gadolinium enhancement on magnetic resonance imaging to be the predominant form of uremic cardiomyopathy with subendocardial fibrosis secondary to ischemia being an equally common finding. **(Mark et al, 2006)**

Most studies have been performed in patients already on renal replacement programs, but the evolution of such left ventricular morphological changes a CKD progresses remains largely unstudied.

One might expect that early Correction of anemia and strict hypertension control may slow down the development of LVH in patients with CKD. **(Pascual , 1991)**

Such evidence already exists in dialysis patients with regards to the effect of increased hemoglobin levels, attained with the use of recombinant erythropoietin, leading to a decrease in LV mass and LV end diastolic volume, both surrogate markers for LVH**.(Pascual , 1991)(Silberberg, 1990)**

3-Dyslipidemia

Renal failure patients are more prone to develop dyslipidemia either due to the original illness and the progression of proteinuria . There are many abnormalities of lipid composition occurs in renal failure patients, those abnormalities contribute to vascular inflammation being augmented by the state of ongoing inflammation in renal failure patients ***(Trevisan et al ,2006)***

Abnormalities in lipid composition include the following:

-High density lipoprotein (HDL): HDL is a protective lipoprotein with antioxidant activity : its level and function is decreased in renal failure .
-Decreased production of the hepatic Abolipoprotein –A1and its replacement by Amyloid a Increased levels of apo c-III which is competitive inhibitor of the lipoprotein lipase with the resultant vasoconstriction.
-Increased level of triglycerides.
-Increased level of low density lipoprotein(LDL) with the resultant activation of the renin angiotensin system. **(Kaysen et al ,2004)**

But now the best indicator of cardiovascular risk associated with dyslipidemia is to measure the ratio of Apo-B (which is associated with increased risk and thought to be the most of the lipid markers to be associated with the cardiovascular risk to Apo –A1which is associated with decreased risk**.**

(Vazine et al ,2006)

It was thought in the past that lower cholesterol level in renal failure patients was associated with more cardiovascular morbidity and mortality. **(Dogoulet et al,1982)**.

Nowadays it is well known that this paradoxical relationship between cholesterol level in renal failure patients and cardiovascular morbidity and mortality is only true in the presence of systemic inflammation (high CRP) and this is may be explained by the cholesterol lowering effect of inflammation, however when CRP is not elevated the relationship is positive**. (Liu et al ,2004)**

Hypertriglyceridemia:

The triglyceride level is increased in renal failure patients.

The accumulation of triglycerides is the consequence of both:

1-High production rate :

An increased production of triglyceride-rich lipoproteins is possibly a consequence of impaired carbohydrate tolerance and enhanced hepatic VLDL synthesis**. (Kronkenberg et al ,2005)**

2-Low fractional catabolic rate

The reduced fractional catabolic rate is likely due to :

The decreased activity of two endothelium-associated lipases, namely, LPL and hepatic triglyceride lipase, which have the primary physiologic function of cleaving triglycerides into FFA for energy production or storage.

The cause of the decreased lipase activities in uremia is thought to be:

Depletion of the enzyme pool induced by frequent heparinization in hemodialysis (HD) patients.

Increase in the plasma apoC-III/apoC-II ratio, and the presence of other lipase inhibitors in plasma: ApoC-II is an activator of LPL, whereas apoC-III is an inhibitor of LPL. The increased apoC-III/apoC-II ratio is usually due to a disproportionate increase in plasma apoC-III. The impaired lipase activities in uremic plasma may also be caused by a decrease in LPL synthesis as a result of secondary hyperparathyroidism or suppressed insulin level **(Bonni et al, 2007)**

Lipid lowering drugs in renal failure patients:

Fibrates: despite the obvious risk of hypertriglyceredia in renal failure patients, it is not advised to use fibrates in renal failure patients as they are associated with high risk of rhabdomyolysis and instead dietary control of hypertriglyceridemia or other classes of lipid lowering drugs are recommended **(Tonille et al, 2007)**

Statins:
The use of statins as primary prevention of cardiovascular disease in advanced renal disease patients is not justified as there is already advanced atherosclerosis in those patients , however with mild renal impairment primary prevention with statins has a better outcome .
(Chonchol et al, 2007)

However the use of statins as secondary prevention in patients who have coronary heart disease was associated with lower cardiovascular mortality especially in diabetic dialyzed patients.***(Baigent et al , 2005)***

4-Diabetes and insulin resistance

Diabetic patients with CKD often present the most challenges for the nephrologist.
Such patients have a higher incidence of cardiovascular co -morbidities such as IHD and peripheral vascular disease than any other patient group with CKD.
The relationship between type 2 diabetes and hypertension is particularly strong with 79% of patients having either hypertension or abnormal circadian blood pressure cycles at the time of diagnosis.**(Keller , 1997)**

It is postulated that proteinuria reflects endothelial dysfunction so is a marker for increased risk of cardiovascular disease.
Mortality in diabetes patients becomes strikingly high with the onset of proteinuria. **(Makino et al, 2007)**

General measures to reduce vascular risk in diabetes patients apply with the addition of good diabetes control. **(Patel et al, 2007)**

Trials of intervention for diabetes patients with respect to kidney impairment have focused on reducing conversion of normalbuminuria to microalbuminura, delaying the onset of diabetes nephropathy in type 2 diabetes patients with microalbuminura and delaying progressive kidney impairment once diabetes nephropathy has occurred.
(Parving et al, 2001),(Brenner et al, 2001)

These interventions all involved blockade of the renin-angiotensin system (RAS). Interestingly, by the time patients have established diabetes nephropathy, intervention with RAS blocking agents has not been shown to alter cardiovascular risks overall, inferring that it is vital to commence treatment early in the pathway of kidney damage in patients with diabetes in order to affect their cardiovascular outcome. **(Lewis et al, 2001)**

A post-hoc analysis of the Irbesartan in Diabetic Nephropathy Trial did show an overall mortality benefit for those patients with systolic blood pressure ≤120 mm Hg compared to those patients with higher systolic blood pressure.
(Berl et al, 2005)
The Steno-2 trial demonstrated a 50% reduction in microvascular and microvascular complications in type 2 diabetes patients with microalbuminuira randomized to an intensive treatment arm with close attention paid to blood pressure, glycemic control, lipids and lifestyle measure; thus even indiabetes patients cardiovascular risk can be reduced with appropriate measures.
(Gaede et al, 2003)

Diabetes is a major cause of renal failure in the general population. It constitutes and additional risk for cardiovascular morbidity and mortality due to :

-Accelerated atherosclerosis and increased aortic arterial stiffness **:** in the diabetic dialyzed patients there is increased aortic stiffness as measured by the pulse wave velocity(PWV**)** ***(*****Kimoto et al ,2003)**

-Microalbuminuria: it has recently been shown that there is strong relationship between the urinary albumin to creatinine ratio and carotid intima media thickness and aortic stiffness and this leads to increased cardiovascular **.**
(Marc et al ,2007)

-The cardiometabolic syndrome: is currently estimated to affect 24% the adult population.

In addition to diabetes, which is the leading cause of end-stage renal disease (ESRD) in westernized societies, other metabolic and cardiovascular abnormalities associated with the cardiometabolic syndrome contribute to progressive renal disease, cardiovascular disease (CVD), and CVD mortality as shown in figure (5) of particular importance are hypertension and insulin resistance/hyperinsulinemia, which frequently coexist and contribute substantially to CVD and ESRD There appears to be a common genetic predisposition to both insulin resistance and hypertension**. (Mann et al, 2001)**

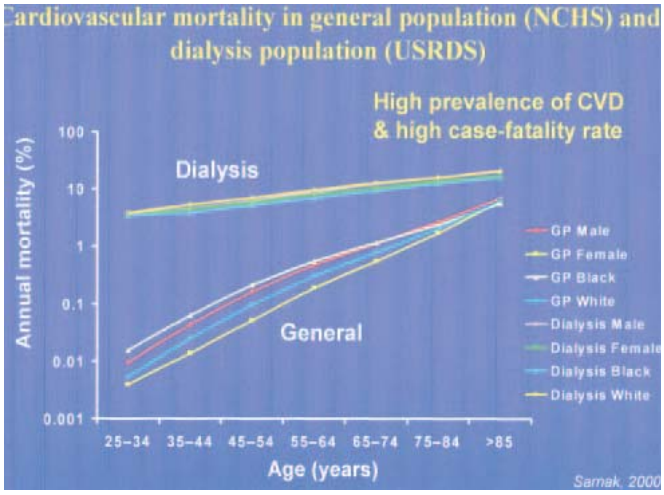


Figure (5) cardiovascular mortality in general population and dialysis population .

Furthermore, insulin resistance/hyperinsulinemia contributes to the elevated BP through several mechanisms, one of which is tissue angiotensin II (AngII) and aldosterone actions, leading to vascular resistance to the effects of insulin Other mechanisms include enhanced sympathetic nervous system (SNS) activity, dyslipidemia, atherosclerosis**,** enhanced oxidative stress, hypercoagulability, left ventricular hypertrophy (LVH), renal functional and structural changes and glomerulosclerosis, progressive renal disease, and eventually ESRD. (**Palaniapan,2003)**

Increased vascular inflammation and oxidative stress :

Oxidative stress has emerged as an important pathogenic factor in the development of long-term complications, such as atherosclerosis and nephropathy, in patients with diabetes.

Whereas multiple enzymes and processes can contribute to oxidative stress, recent studies indicate that a **multicomponent phagocyte-type NADPH oxidase** is a major source of reactive oxygen species (ROS) production in many nonphagocytic cells, including fibroblasts, vascular smooth muscle cells, endothelial cells, renal mesangial cells, and tubular cells**.(Tepel M et al, 2003)**

Under physiologic conditions, nonphagocytic NADPH oxidases have very low-level constitutive activity. However, enzyme activity is up regulated in diabetes. ROS production by the oxidase may serve a signaling role or may lead to oxidative damage.**(Jian Mei et al ,2003)**

5-Acquired long QT interval and sudden cardiac death

It was recently found that renal failure patients have increased risk of developing the so called **cardiac channelopathy** where there is loss of the redundant potassium channels in the cardiac myocytes and increased liability of inhibition of the remaining channels by drugs which prolong the QT interval . Prolongation of the QT interval is one of the important causes of sudden cardiac death syndrome in renal failure patients**(Straus et al ,2007)**

6-Albuminuria and hypoalbuminemia

It was found that both micro and macroalbuminuria are both independent risk factors for cardiovascular morbidity and mortality in diabetic as well as non diabetic renal failure patients and that its blockade delays the progression of cardiovascular complications **(De zeeuw et al ,2004)**

B)NON TRADITIONAL RISK FACTORS

1)INFALAMMATORY SYNDROME AND VASCULAR STRESS:

Between 30 and 50% of prevalent patients who are on hemodialysis (HD) have elevated serum levels of inflammatory markers. In some patients, this elevation is chronic, and in some, it is intermittent and generally is associated with breakthrough processes.**(Boaz et al, 2000)**

Furthermore, on many occasions, HD sessions trigger inflammation in a way that is not always identifiable with the conventional markers. Inflammatory markers are powerful predictors of mortality after adjustment for other factors. Inflammation also is responsible for other mortality risk factors, such as anemia, malnutrition, vascular disease,and left ventricular hypertrophy.

For lowering the high morbidity/mortality rate in patients who are on HD, inflammation must be tackled. How? First, by identifying the causes, then preventing or treating them.**(Pecoits-Filho et al, 2005)**

2)Oxidative stress

Among the nonconventional cardiovascular risk factors, oxidative stress and vascular calcification gradually are gaining importance. Glycoxidation products and advanced oxidation protein products show a close relationship with inflammatory markers such as CRP and IL-6 .Therefore, the end products of these processes could act as inflammatory markers. **(Ishimura et al , 2005)**

The generalized use of intravenous iron to treat anemia in HD units is noteworthy. Intravenous iron administration may release free iron that could react with hydrogen peroxide and generate free radicals. This results in an increase in advanced oxidation protein product levels, which are related to CRP levels, and in common carotid artery intima-media thickness. Therefore, treatment with intravenous iron could be considered as an additional inflammatory factor, as well as a risk factor for atherosclerosis in HD patients. **(Tovbin et al, 2002)**

Microorganisms may participate in the development of inflammation and vascular damage in the general population. Infection with Chlamydia pneumoniae or Helicobacter pylori and periodontal disease are the most frequent. In HD patients, the presence of IgG or IgA antibodies to C. pneumoniae is associated with a greater risk for cardiovascular events, and mortality is significantly higher **(Zoccali et al ,2003)**

Furthermore, the carotid artery intima-media thickness has been reported to be greater in patients with IgA antibodies compared with patients without antibodies , and the number of atherosclerotic plaques is related to the titer of IgG antibodies in smokers but there is no such relationship in nonsmokers. **(Kato et al, 2004)**

Periodontal disease is frequent in HD patients and is related to age, diabetes, smoking, HD duration, malnutrition, and inflammation **(Chen et al, 2006)**

IgG antibodies to some periodontal bacilli are related to higher CRP levels . Moreover, CRP levels and erythrocyte sedimentation rate significantly decrease after periodontal treatment . Periodontitis, therefore, is a frequent occult source of chronic inflammation that could contribute to the atherosclerosis process and resistance to erythropoietic agents.

(Kadiroglu et al ,2006)

The type of HD vascular access is of prime importance for the evolution of HD patients. Patients with an indwelling catheter have higher comorbidity and a poorer survival on HD .However, its relationship with the inflammatory state has not been assessed sufficiently. It was demonstrated recently that patients with an indwelling tunnelled catheter have higher CRP levels and greater resistance to erythropoietin than those with arteriovenous grafts (AVG) or an arteriovenous fistula, who have the lowest values **(Movilli et la ,2006)**

Furthermore, patients with clotted AVG have elevated CRP, advanced glycation end products, and endothelial adhesion molecule levels .This demonstrates that clotted vascular access may play an important role in the inflammatory process. The elimination of these clotted grafts may result in a significant improvement in inflammation parameters. These findings suggest the need to monitor inflammation markers in patients with old clotted AVG, so they must be removed when in doubt. **(Allon et al, 2006)**

The effect of hemodialysis technique

HD technique may contribute to maintaining the inflammatory state in many HD patients.

Several theoretical mechanisms may be implicated:

(1) The retention or non elimination of pro inflammatory molecules usually eliminated by the kidney.

(2) Potentiation of oxidative stress;

(3) Stimulation of antigen-presenting cells, mainly monocytes, either directly or through contaminants. These cells in HD patients usually are preactivated, expressing CD-14 and CD-16 phenotypes in a greater proportion than in the general population (**Ramirez et al ,2006)**

3)VASCULAR CALCIFICATION

Prevalence of vascular calcification in renal failure patients:

Vascular calcification is highly correlated with cardiovascular disease mortality, especially in patients with ESRD. Vascular calcification is now recognized as a marker of atherosclerotic plaque burden as well as a major contributor to loss of arterial compliance and increased pulse pressure seen with age, diabetes, and renal insufficiency. **(Rodriguez et al, 2005)**

The predisposition to vascular calcifications in patients with chronic kidney disease (CKD) was mentioned for the first time in the 19th century when Virchow described the appearance of metastatic calcifications in patients with kidney failure. However, this complication of CKD has been neglected because its impact on patient outcome was poorly known until recently.

The subject has gained great interest in recent years as many studies described that a high percentage of patients with CKD show vascular calcifications, including those who are younger than 30 yr, stressing also its likely impact on morbidity and mortality. **(Blatcher et al, 2001)**

The various types and localizations of vascular calcifications have an impact on cardiac mortality not only by increasing and complicating coronary atherosclerosis but also by increasing the stiffness of the main arteries, which in turn affects heart function and risks the perfusion and oxygenation of the heart **(Rodriguez et al, 2005)**

The high prevalence of vascular calcification has been studied, and it is known better in the setting of patients with stage 5 CKD. However, a high prevalence of vascular calcifications also has been demonstrated in the earliest phases of CKD. A recent study showed that 40% of patients (mean age 52 yr) with CKD and a mean GFR of 33 ml/min showed 40% of coronary artery calcifications compared with 13% in control subjects of similar age with no renal impairment **(Russo et al ,2004)**

The differences between the vascular calcification that are observed in the normal population and in patients with CKD are not only the type and the localizations of the calcification but also the early age at which vascular calcification begin in patients with CKD .This fact, together with the influence of several risk factors, will have a great impact on the rate, extension, and severity of the vascular calcification and also in mortality, which is known to increase according to the number and the severity of vascular calcification. And is almost 20 times higher in patients with CKD than in general population. **(Blatcher et al, 2001)**

Pathogenesis and mechanism of vascular calcification:

Calcification in the vessel walls occurs in two sites: The intima and the media.

The intimal calcification is a consequence of the inflammation and calcification of the atherosclerotic plaques; their presence is associated with atherosclerotic burden, and it is initiated early in life and progresses. They frequently are localized in two functionally relevant arteries, such as the aorta and the coronaries**. (Goldsmith et al, 2004)**

The medial calcification occurs in the elastic lamina of large- and medium-small size arteries; they are frequent in patients with CKD, but diabetes and age also are associated with an increase of medial calcification.

Both types of calcification are present in patients with CKD, but the complications of these two types of vascular calcifications are different: The former is mainly associated with occlusion of the vessels, and the latter is associated with vascular stiffness. In the end, both count, and they are partly responsible for the increase of mortality in patients with CKD. **(Kettler et al, 2005)**

The mechanism by which the process of vascular calcification is produced is complex, and it does not consist of a simple precipitation of calcium and phosphate but is instead an active and modifiable process in which, step by step, the vascular smooth cells undergo apoptosis and vesicle formation changes the phenotype of smooth vascular cells into osteoblast-like cells, inducing matrix formation and also attracting local factors that are involved in the mineralization process.

Uremic vascular calcification may be interpreted as the result of the dysregulation of the current equilibrium between promoters and inhibitors, in which several uremic factors—with phosphorus at the top of the list—may induce the phenotypic modifications mentioned before.

The promoters of vascular calcification: these are a group of risk factors which could be divided into: **(Shafer et al, 2003)**

Modifiable risk factors:

1) Serum phosphate and serum calcium- phosphate product
2) Hyperparathyroidism and hypoparathyroidism
3) High dose of vitamin D metabolites
4) Dyslipidemia ,hyperfibrinoginemia high CRP low albumin
5) Hypertension
6) Habits

Non modifiable risk factors:

1) Old age
2) Diabetes
3) Race
4) Time of dialysis

Inhibitors of vascular calcification

In humans and other mammals, serum concentrations of calcium and phosphate exceed the calcium-phosphate solubility product by several times, but intravascular precipitation does not take place. This fact clearly stresses the important role played by the physiologic inhibitors of the calcification that counterbalance the widely known effect of the promoters of calcifications. The list of promoters and inhibitors of the calcification process is large, and it increases every year. **(Hofbauer et al, 2004)**

Promoters of vascular calcification

Serum phosphate and serum calcium phosphate product:

Concentrations of extracellular Ca and P commonly found in serum of patients on dialysis induce VSMC(vascular smooth muscle cell) calcification and that this effect is potentiated in the absence of serum. It was noted that elevated both calcium and phosphate levels have synergistic effect than the isolated elevation of any of them.Therefore ,In the presence of increased P, even modest increases in Ca can substantially exacerbate calcification, which is induced by nucleation of BCP(bony calcium phosphate) in vesicles that are released from both viable and apoptotic VSMC. (**Joanne.L et al, 2004)**

The main effect of elevated calcium and phosphate product is its effect on the **vascular smooth muscle cell** (VSMC) which might be affected in the following ways: **(Hofbauer et al, 2004)**

VSMCS can resist calcification in the presence of serum but loses this ability in the absence of serum which emphasizes the role of systemic inhibitors of calcification.

In the presence of hyperphosphatemia and hypercalcemia VSMCS undergo on of the following process all of which aid in vascular calcification:

(Moe et al , 2004)

Apoptosis with the release of apoptotic bodies.
Increased formation of microvesicles(MV)
Change into chondrocyte or osteocyte like cells.

Parathyroid hormones and vitamin D metabolites:

Over the last half a century, scientists have come to appreciate the importance of vitamin D prescription for people with renal disease. Vitamin D and its analogues have profoundly altered the natural history of deforming 'renal rickets'. Observational studies have found significant associations between use of vitamin D compounds and improved survival. **(Dubrez et al , 2004)**

Now there is clinical and experimental evidence that the abnormalities of calcium, phosphorus and parathyroid hormone observed in chronic kidney disease are associated with increased mortality. . Some of these abnormalities may be affected by treatment with vitamin D compounds.**(Block et al , 2004)**

International guidelines have therefore reflected the need to target improvement of biochemical targets, including parathyroid hormone, phosphorus and calcium, which implies use of both pharmacological (vitamin D and its analogues, calcimimetics and phosphate binders) and non-pharmacological strategies (long-hours dialysis and dietary restriction).

The management of bone disease/secondary hyperparathyroidism by targeting tight near-to-normal levels of these biochemical markers is now standard practice and well reflected by policy in clinical nephrology but renal osteodystrophy is not all what matters .

That vitamin D compounds suppress circulating parathyroid hormone levels has been identified in clinical studies, but evidence also demonstrates that these compounds may increase serum calcium and phosphorus. Such elevations of calcium and phosphorus are identified, again in observational studies, as correlates and predictors of increased all-cause and cardiovascular mortality/morbidity, possibly through up regulation of vascular calcification. **(Moe et al , 2008)**

This means that although there is a broad acceptance of vitamin D compounds and other therapies for bone disease in chronic kidney disease, considerable uncertainty persists particularly relating to the potential harms of these agents and, more importantly, whether vitamin D compounds really have an effect on important clinical outcomes, outside altering the levels of biochemical markers.

(Strippoli et al , 2006)

Even the relationship between administration of the newer vitamin D analogues and and the reduction in the parathormone levels could not be proven as there is controversy as regard this .however there is increasing evidence that vitamin D therapy causes elevation in the serum phosphate levels **(Tonille et al ,2007)**

Now advocates for vitamin Duse as replacement in renal failure patients claim that it is indispensable as renal failure is actually a state of vitamin D depletion and that under treatment with vitamin D leads to severe bony osteodystrophy.

(**Arenas et al ,2006)**

On the other hand opponents of vitamin D use in renal failure patients state that :

there is no proven efficiency as regard parathormone reduction besides ,it may aggravate cardiovascular morbidity through hyperphosphatemia hormone replacement is not always safe as cited by hormone replacement in post menopausal women and erythropoiten replacement. **(Phrommintikul et al , 2007)**

4) Hyperhomocysteinemia

Hyperhomocysteinemia is associated with an increased incidence of cardiovascular events in ESRD and RTRs.
Hyperhomocysteinemia may produce endothelial dysfunction; smooth muscle proliferation; platelet aggregation; activation of factors V, X, and XII; and modulation of tissue plasminogen activator, all creating a prothrombotic environment.
Plasma homocysteine increases, often to very high levels (≥100 mol/l; normal ≤12mol/l) with GFR ≤70 ml/min**.(Mark et al, 2006)**

Homocysteine is metabolized by either transsulfuration with pyridoxine as cofactor or by remethylation with transcobalamin and methyltetrahydrofolate, the active form of folate, as cofactors.
Deficiency of these water-soluble vitamins may develop from losses during dialysis and, coupled with poor oral intake and decreased homocysteine renal clearance,promoted hyperhomocysteinemia. **(Rajiv Gupta et al, 2004)**

Optimizing medical management of cardiovascular diseases

Here is underutilization of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), glycoprotein IIb/IIIa receptor antagonists, diagnostic coronary angiography, thrombolytic therapy, and PCI in CKD patients with AMI or ACS**. (Freeman et al, 2003)**
This may relate to physician concern regarding bleeding risk, worsening of renal function, lack of evidence for use of certain drugs, associated comorbidities, and generally worsened outcomes in CKD patients. Dose adjustment in cardiac medications may be necessary **. (Berger et al, 2003)**

Table (1) shows a table of dose modification of selected cardiovascular drugs

Table 4. Dose Modification of Selected Cardiovascular Drugs Commonly Used in CAD in CKD

Drug Class	Specific Drug	Adjustment for CKD (% Dose Compared With Normal GFR Dose*)		Supplement for HD†	Comments
		10–50 ml/min	10 ml/min		
Beta-blocker	Atenolol	50	25	25–50 mg	Carvedilol, metoprolol, labetalol, propranolol, esmolol: no change
	Sotalol	30	15–30	80 mg/dose after HD	
	Nadolol	50	30	40 mg	
ACEI	—	50–75	25–50	20–30%/dose after HD	
ARB	—	100	75	None for fosenopril or benazepril	—
Ca-blockers	—	100	100	None	—
Adrenergic modulators	Methyldopa	q8–12 h	q12–24 h	250 mg	Clonidine, doxazosin, prazosin: no change
Vasodilators	Hydralazine	q8 h	q8–16 h	None	Minoxidil, nitroprusside: no change
Diuretics	Thiazides	100	Avoid	NA	Furosemide, bumetanide, torasemide, metolazone: no change
	Spironolactone	q12–24 h	Avoid	NA	
	Triamterene	100	Avoid	NA	
	Ethacrynic acid	q8–12 h	Avoid	NA	
Lipid-lowering agents	Rosuvastatin	100	25	U	Atorvastatin, simvastatin, lovastatin, fluvastatin, pravastatin, gemfibrozil, colestipol, cholestyramine, ezetimibe: no change
	Fenofibrate	25–50	Avoid	Avoid	
	Nicotinic acid	50	25	U	
Anticoagulants/lytic	LMWH	100	50 or avoid	U	Unfractionated heparin, warfarin, streptokinase, t-PA: no change
	Bivalirudin	80	10–30	U	
Antiplatelet agents	Eptifibatide	100 bolus; 50 infusion	Avoid	None	Aspirin, abciximab, clopidogrel, ticlopidine: no change
	Tirofiban	50–100	50		
Anti-arrhythmics	Disopyramide	q12–24 h	q24–48 h	None	Adenosine, amiodarone, lidocaine, ibutilide, moricizine, propafenone: no change
	Flecainide	100	50–75	None	
	Bretylium	25–50	25	None	
	Procainamide	q6–12 h	q8–24 h	200 mg	
	Mexiletine	100	50–75	None	
	Quinidine	100	75	None	
Inotropes	Dopamine	100	50–75	U	Dobutamine: no change
	Epinephrine	100	50–75	U	
	Milrinone	100	50–75	U	
	Nesiritide	100	50–75	U	

ANTICOAGULATION

Management of ACS in CKD patients is the same as in the general population with few exceptions.
Aspirin is recommended, although no prospective efficacy or safety data have dealt specifically with CKD patients. **(Tonille et al ,2007)**

Unfractionated heparin is preferred over low molecular- weight-heparin, which may accumulate in renal failure and for which adequate data are unavailable.
Direct thrombin inhibitors are cleared partially by the kidney, urging caution until more data are available.
A metaanalysis suggests that at least for bivalirudin, the drug is equally, or more, effective than unfractionated heparin and produces less bleeding. **(Chew et al, 2003).**

Safety data on glycoprotein IIb/IIIa inhibitors are limited as a result of the exclusion of CKD patients from most clinical trials.
Among mild to moderate CKD patients in the Platelet-Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, tirofiban plus heparin was well tolerated and effective in reducing ACS complications .
Among mild CKD patients in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, bleeding risk and treatment effect with eptifibatide were similar to that in patients with normal renal function **(Reddan et al, 2003).**

A retrospective study in mild CKD PCI patients showed no significant differences in bleeding or the combined end point of death and AMI between abciximab and control . Thienopyridine studies have excluded CKD patients, so efficacy and safety in this group are inferred**.(Jeremias et al, 2002)**

MANAGEMENT OF HYPERTENSION

The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure recommends that CKD patients should have a blood pressure≤130/80 mm Hg. **(Chobanian et al, 2003).**

The National Kidney Foundation recommends ≤125/75 mm Hg for CKD patients with proteinuria ≤1 g/day . **(Bakris et al, 2000).**

However, the relationship between blood pressure and mortality in HD patients may exhibit a "U"-shaped distribution wherein not only high (≥180 mm Hg) but also low (≤110 mm Hg) systolic blood pressure is associated with increased mortality . **(Zager et al, 1998)**

Hypertension in CKD patients, especially those on dialysis, is volume-dependent. Hence maintenance of fluid balance is paramount. Examination of neck veins,edema, and body weight can aid in managing fluid status.
ACEI: Angiotensin-converting enzyme inhibitors decreased 30-day mortality (relative risk 0.64) in dialysis patients with AMI, an effect similar to non-dialysis patients **(Berger et al, 2003).**

Angiotensin-converting enzyme inhibitors decrease the progression of nephropathy in type 1 and 2 diabetes (Lewis EL,etal1993)(Ravid M,etal1998) and non-diabetic renal disease. **(Jafar et al, 2001).**

In the Heart Outcomes Prevention Evaluation (HOPE) trial, risk reduction for cardiovascular death, all-cause mortality, and heart failure hospitalizations with ramipril was greater for CKD than non-CKD patients **(Mann et al, 2001).** These agents should be used cautiously because they may induce hyperkalemia in nondialysis patients with mild to severe CKD.

ARBS:ANGIOTENSIN RECEPTOR BLOCKERS**.**

Renoprotection from angiotensin receptor blockers has been demonstrated in CKD patients but cardioprotection has not. Renoprotection appears to be independent of blood pressure reduction**. (Brenner et al ,2001)**

In a randomized trial of 1,513 CKD patients with type 2 DM, nephropathy progression was reduced by losartan but cardiovascular death incidence was similar to placebo. (**Brenner et al, 2001).**

In a trial of irbesartan, amlodipine, or placebo in 1,715 CKD patients with hypertension and type 2 DM, irbesartan afforded renoprotection but not cardioprotection. **(Lewis et al, 2001).**

Based on lack of proven cardioprotective effect of angiotensin receptor blockers in CKD patients, ACEI are preferred when possible.

BETA-BLOCKERS: Beta-blockers appear to retain their cardioprotective effects in CKD patients.
In an analysis of a Medicare database of over 200,000 mild CKD patients, there was a 35% reduction in mortality with beta-blockers**. (Gottlieb et al, 1998).**

TREATMENT OF HYPERLIPIDEMIA:

Target serum low-density lipoprotein cholesterol in CAD patients is≤100 mg/dl.
Statin dose reduction is required in RTRs taking cyclosporine or tacrolimus.
It is not clear whether isolated hypertriglyceridemia or low levels of high-density lipoprotein cholesterol should be treated with drugs in CKD patients. **(Michael Abecassis et al, 2008)**

TREATMENT OF HYPERHOMOCYSTEINEMIA:

Recommended daily allowances of folate (5 mg/day), transcobalamin (0.4mg/day), and pyridoxine (50 mg/day) normalize homocysteine level in mild to moderate CKD patients and RTRs, but only mildly affect homocysteine levels in dialysis patients.
Although higher homocysteine levels are associated with increased cardiovascular events in CKD patients, data demonstrating reduction in ischemic events or death with treatment in CKD or the general population are lacking.**(Mark et al, 2006)**
Nevertheless, it seems reasonable to normalize plasma homocysteine if possible.

MANAGEMENT OF ANEMIA.

Anemia may increase angina severity and left ventricular hypertrophy and decrease exercise tolerance, and its correction improves these abnormalities **(Wizemann et al, 1992).**

The Normal Hematocrit Trial showed that patients with ESRD and CAD or heart failure treated with erythropoietin to a target hematocrit of 42% had a higher risk ratio (RR) (1.3) for the end points of death or nonfatal AMI compared with a targeted hematocrit of 30% **(Besarab et al, 1998).**

Alternatively, a large Medicare study of HD patients using erythropoietin demonstrated decreased risk of cardiac mortality with a hematocrit of 30% to 33%, and an even lower risk with 33% to 36% **(Ma et al, 1999).**

TREATMENT OF HYPERPHOSPHATEMIA.

Control of calcium-phosphate product and hyperparathyroidism seem reasonable goals although efficacy data are lacking. Lowphosphate diet and use of phosphate binders may be helpful.**(Bleyer et al, 1999)**

ROLE OF ANTIOXIDANTS.

Antioxidants for cardioprotection have demonstrated conflicting results. The Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease (SPACE) trial demonstrated that vitamin E use in HD patients was associated with a 54% decrease in the combined end point of AMI, IHD,stroke, symptomatic peripheral vascular disease, and unstable angina. **(Boaz et al, 2000).**

Other studies have not demonstrated a beneficial effect of vitamin E. **(Yusuf et al, 2003).**

N-acetylcysteine in HD patients decreased the composite end point of AMI, cardiovascular death, need for revascularization, ischemic stroke, and symptomatic peripheral vascular disease versus placebo (28% vs. 47%, p≤ 0.03).
Although efficacy trials with antioxidants have been disappointing in non-CKD patients, the increased oxidant stress in CKD may provide the environment for antioxidants to be cardioprotective.
Clearly more data are required before any antioxidant can be recommended. **(Tepel , 2003)**

Revascularizing CKD patients.(PCI)

There is a striking lack of comparison of CAD treatments in CKD patients. Small studies using balloon angioplasty in HD patients have shown initial angiographic success of 56% to 96% with high restenosis rates (60% to 81%). Procedural advances and stent use have produced better angiographic success rates(90%) and lower restenosis rates (31% to 36%) **(Le Feuvre C, 2004).**

Drug-eluting stents may reduce restenosis rates further, although data are currently unavailable.
Mortality risk during PCI hospitalization increases with CKD as well as demand appears additive. **(Best ,2002)**

The CKD patients have higher one-year mortality after PCI than non-CKD patients , a trend observed through four -year follow-up.
In 5,327 post-PCI patients, one-year mortality was 1.5% (RR 1.5) with CCr 70 to 90 ml/min, 3.6% (RR 2.3) with CCr 50 to 69 ml/min, 7.8% (RR 3.7) with CCr 30 to 49 ml/min, 18.3% with CCr≤30 ml/min, and 19.9% (RR 8.9) in dialysis patients (p ≤0.001**).(Mehran ,2003)(Gruberg et al, 2002)(Feuvre et al, 2003)**

Percutaneous coronary intervention use in AMI showed a higher 30-day death rate (7.5%) in CKD versus non-CKD patients (0.8%, p ≤0.0001).
In multivariable analysis, CKD had the highest RR (5.7) for mortality of all factors studied. **(Sadeghi et al, 2003)**

The CKD patients undergoing saphenous vein graft intervene interventions also show a higher in-hospital and one-year mortality. **(Gruberg et al, 2003**)

Chronic kidney disease patients with ST -segment elevation AMI showed a lower 30-day mortality with thrombolysis (8.3%) than PCI (37.1%, p≤ 0.04), emphasizing the uncertainty of the preferred AMI treatment in CKD patients. **(Dragu et al, 2003)**

CORONARY ARTERY BYPASS GRAFT SURGERY (CABG).

Coronary artery bypass graft surgery perioperative mortality in dialysis patients is approximately 7% to 10%, at least three to four times non-CKD patients, and five-year mortality is estimated at 48% versus 15% in non-CKD patients . **(Nishida et al, 2001)**

Most studies are retrospective, have small sample size, and are unadjusted. In studies with adjustment, CKD remains a highly significant predictor for decreased long-term survival. Not unexpectedly, HD-dependentdiabetics suffer worse long-term outcomes after CABG than non-diabetics . **(Dacey et al 2002)**

Coronary artery bypass graft surgery outcomes in mild or moderate CKD patients are limited. Chronic kidney disease patients (vs. non-CKD patients) had longer in-hospital and intensive care unit stay and more frequent postoperative dialysis. **(Hosoda et al, 2001)**
In a prospective 1,427-patient study, sCr ≥1.5 mg/dl increased the length of hospital stay and the need for postoperative dialysis .
In-hospital mortality increased with a rise in preoperative sCr (2.3%, sCr≤1.5 mg/dl; 18.5%, sCr≤1.7 mg/dl).
In a prospective study of 2,222 mild CKD patients, 7.7% had postoperative renaldysfunction associated with prolonged intensive care unit and hospital stays and increased mortality. **(Weerasinghe et al, 2001).**

Long-term outcomes in the Bypass Angioplasty Revascularization Investigation (BARI) showed a higher risk of allcause(RR 2.2) and cardiac (RR 2.8) deaths and increased cardiac admissions in CKD patients who underwent CABG or PCI, with 70% with CKD and DM dead by 7 years. **(Szczech , 2002)**

Another analysis of mild to moderate CKD patients, in hospital CABG mortality was 11% and actuarial survival at 10years was 32%, similar to dialysis patients **(Nakayama et al, 2003)**

There have been very few studies addressing CABG outcomes in RTRs. In a study of 131 RTRs, there was a perioperative mortality of 3.2% with no deaths during five-year follow up. In 45 RTRs undergoing PCI or CABG, actuarial survival at 1, 3, and 5 years was 93%, 78%, and 60% **(Dresler et al, 1997)(Ferguson ,1999)**

COMPARISON OF CABG AND PCI.

Studies comparing CABG with PCI in HD patients are all non-randomized and retrospective. There may be an increased perioperative mortality but better long-term survival and freedom from angina with CABG compared with balloon angioplasty **. (Keeley et al, 2003)**

A preliminary report from a large prospective trial comparing stenting and CABG in patients with multi-vessel disease suggests similar outcomes. **(Ix et al, 2002)**

A non-randomized study in CKD patients with estimated GFR≥60 ml/min with ACS showed that PCI was associated with improved survival compared with CABG or medical therapy**. (Herzog , Ma, Collins ,2002)**

Conclusions

CKD is a serious health problem worldwide that leads to devastating CHD morbidity and mortality.
The mechanisms that lead to these events are diverse and far more complicated than in patients with normal renal function. **(Agirbasli et al, 2000)**

CHD is uniquely different in CKD from that in the general population, with earlier onset in life, more rapid progression, a closer association with calcification, increased vascular stiffness, resistance to statin medications, higher complications with percutaneous and surgical revascularization, and higher rates of sudden death. **(Ivens et al, 2001)**

Chapter Three

Renal transplantation

Introduction and brief history about renal transplantation:

Kidney transplantation has dramatically evolved from a life-saving yet unproven therapy for patients with renal failure to a mature field that is the preferred treatment for those suffering from ESRD**.(Todd E. Pesavento,2009)**

Kidney transplantation is the most desired and cost-effective modality of renal replacement therapy for patients with irreversible chronic kidney failure (end-stage renal disease, stage 5 chronic kidney disease). **(Michael Abecassis et al, 2008)**

For many, it is difficult to envision any discussion of renal disease without considering the impact of transplantation**.(Friedman et al, 2009)**

For children with congenital abnormalities, delaying the inevitable progression to ESRD until a successful preemptive transplant can be preformed is now standard therapy.

For those individuals with immunologic diseases that have failed therapy, transplantation
is still an option, but the concern over recurrence of their native disease must be considered.

For the elderly or those patients with diabetes, extending their lives, improving their quality of life, and the resultant reduction of overall medical costs with transplantation have significant public health benefits**.**

However, these current widely held concepts were not universally accepted in the recent past.

Concern about the cost of renal transplantation and long-term outcomes relegated it as a therapy that was still without a clear place in the continuum of care for chronic renal disease**.**
The first successful kidney transplant was performed in 1954 between two identical twins by Dr Joseph Murray.
Over the next decade, remarkable advancements occurred that allowed transplantation to be offered to a broader range of patients, with organs emanating from distantly related live donors to deceased donors**.(Stange , Sumner ,2009)**

By 1965, amazing short-term graft survival had been achieved, reaching nearly 80% from living donor sources and approaching 65% for deceased donor recipients.
(Murray ,1992)

Because of the concern about the initial cost of renal transplantation and its still unproven long-term advantage, many physicians still viewed dialysis as the preferred treatment method for chronic renal failure. This view was summarized nicely in an editorial by Rennie in 1978, when he discussed the societal impact of dialysis and transplantation.

He stated "A successful transplant means less expense during the period in which the graft is functioning, but the risk to life is greater…So even although it offers a much better quality of life while it works, a transplant in most cases can be considered only a temporary respite from the basic form of treatment, which is dialysis" **(Rennie ,1978)**

This prevailing opinion was finally changed by the landmark article by Wolfe *et al.* in 1999. To address the valid concerns of many that it was solely caused by selection bias that transplant patients had superior outcomes to those on dialysis. **(Wolfe et al, 1999)**

Among some of their findings, they were able to quantify the magnitude of benefit of transplantation compared with remaining on dialysis even in high-risk groups such as the elderly and those with diabetes**.(McCullough et al, 2009)**

Patients wait listed for a transplant had a 49% lower risk of death compared with the entire group on dialysis when adjusted for age, diabetes, and other factors.

For patients receiving a deceased donor renal transplant, their risk of death was even more impressive, with a 69% reduction in risk. When comparing only those patients on the wait list *versus* those who received a transplant, the benefits were early and marked. **(Keith et al, 2009)**

Even after taking into account the risk of surgery, early complications, infections, and cardiac events, the relative risk death after transplantation equaled that of remaining on dialysis after only 106 d. Long term, there was a 68% lower risk of mortality as shown in Figure**(6) .(Wolfe et al, 1999)**

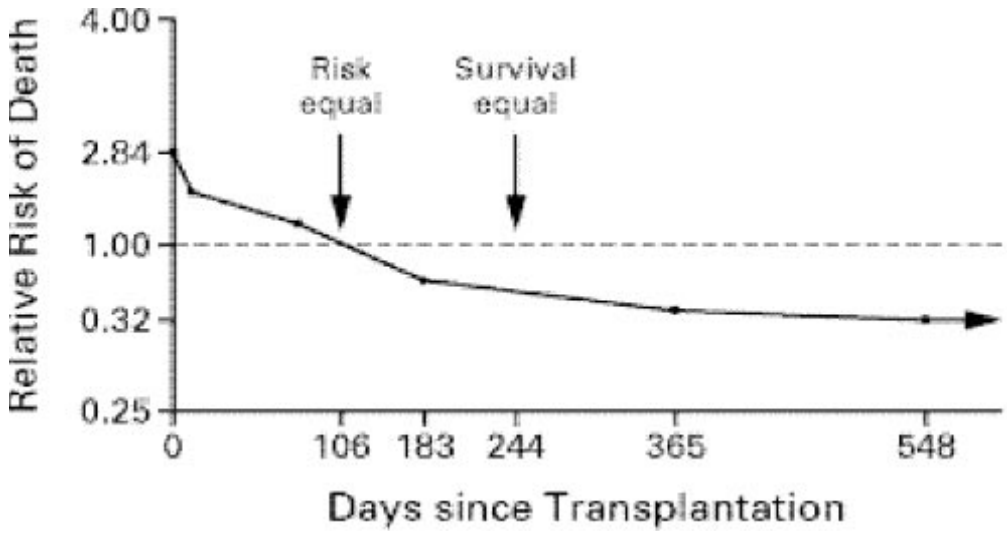


Figure (6)
Adjusted relative risk of death among 23,275 recipients of a first cadaveric transplant. The reference group was the 46,164 patients on dialysis who were on the waiting list (relative risk, 1.0). Values were adjusted for age, gender, race, cause of ESRD, year of placement on the waiting list, geographic region, and time from first treatment for ESRD to placement on the waiting list. The points at which the risk of death and the likelihood of survival were equal in the two groups are indicated.
A log scale was used. Used by permission from Wolfe**.(Todd E. Pesavento,2009)**

Using data from Ohio State University, were the first to show that there was a significant negative effect on post-transplant mortality with increasingly long dialysis times before transplantation **.(Cosio et al, 1998)**

They showed that after 7 yr of follow-up, those patients who were never dialyzed before receiving their transplant had only a 7% mortality compared with 23% for those who dialyzed for≤3 yr and 44% for those dialyzing for ≥3 yr**.**
(Meier-Kriesche et al, 2000)

This remarkable effect on mortality seemed to be caused by two major causes: a higher infection rate on dialysis and worsened cardiac risk factors, namely a higher prevalence of left ventricular hypertrophy and cardiomegaly with increasingly long dialysis times. **(Port et al, 2000)**

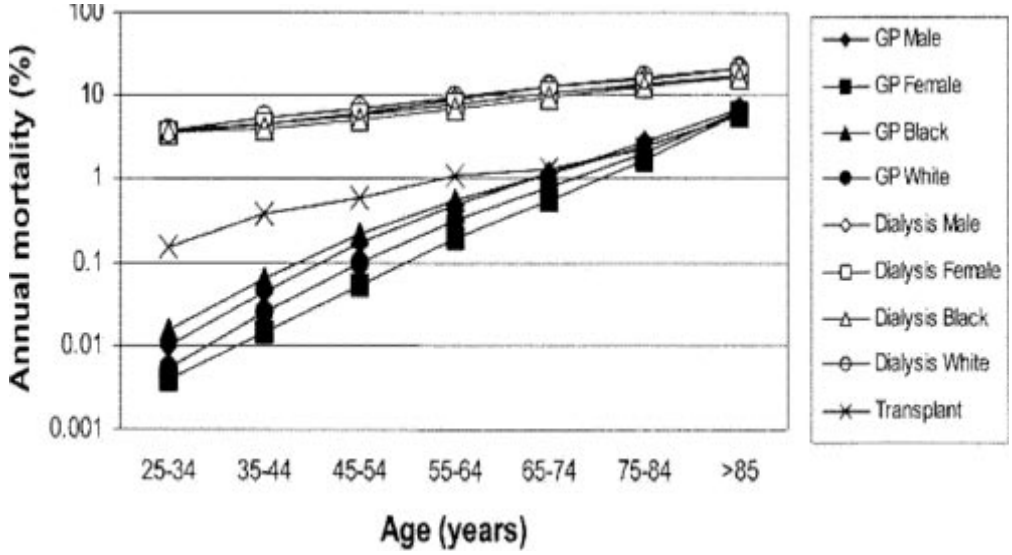
Numerous studies have shown at figure (7) the marked impact of ESRD on patient survival compared with transplantation and the general population.

This impact is most dramatic in younger patients where annual mortality rates are100 times greater in the patients with ESRD compared with the general population**.(Sarnak , 2003)**

Even in older patients where mortality rates would be expected to high, transplantation has a dramatic impact on survival has shown that, even in patients older than age 70, transplantation offers a 41% lower risk of death compared with those that remain wait listed. **(Singh et al, 2009)**

Older patients (≥49 yr of age) now account for nearly 60% of the active waiting list compared with just 45% 10 yr earlier, and for patients 65 yr and older, there has been a 78% increase **(Rao et al, 2007).**

Figure (7)

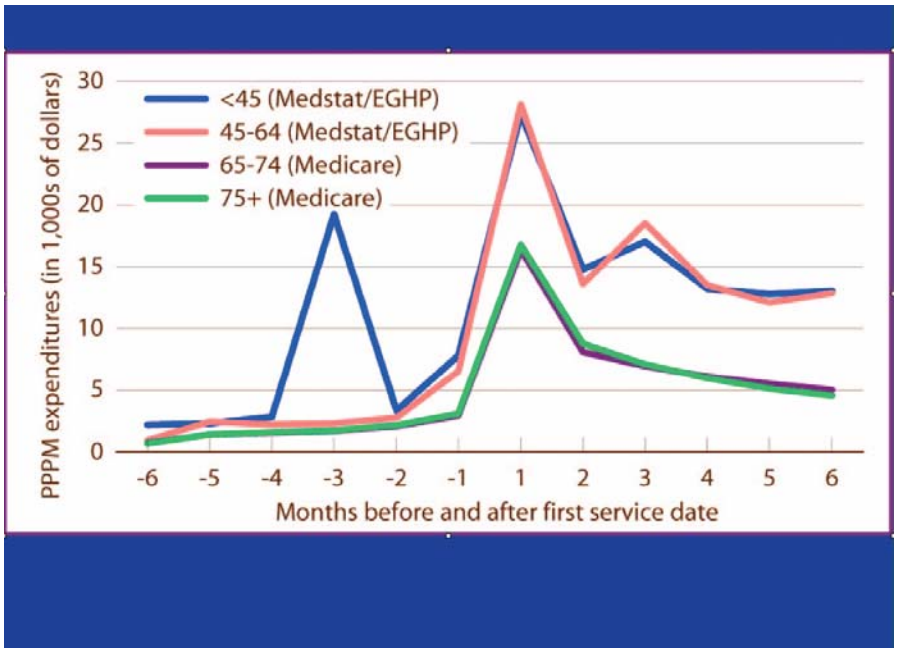


Cardiovascular mortality rate in the general population and in kidney failure treated by kidney transplantation or dialysis**. (Singh et al, 2009)**

Preemptive Transplantation

It is now well established that early kidney transplantation is associated with optimal outcomes in terms of patient and graft survival. **(Innocenti et al, 2007)**

Whereas mortality within the first year of initiation of RRT has steadily declined for patients who are on peritoneal dialysis and those who receive transplants, early mortality on hemodialysis remains high and relatively unchanged since the mid-1990s. (Figures 8 and 9). These data indicate the importance of effective transitioning of patients between CKD and ESRD care and have provided impetus for the " Fistula First" initiative of the Center for Medicare and Medicaid Services (CMS) **(National Vascular Access Improvement Initiative,2007).**
When a patient begins RRT, or transitions from one modality of care to another, there is a dramatic decline in quality-of-life measures **(Watnick S. et al, 2003)**



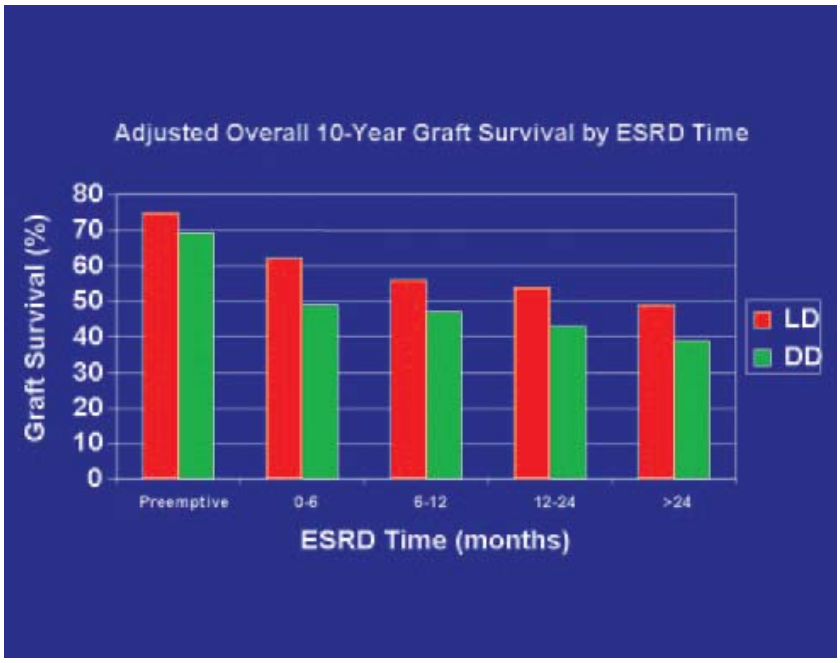
Figure(8). Expenditures associated with institution of long-term dialysis for patients transitioning from chronic kidney disease (CKD) care to renal replacement therapy (RRT) in 2003, by age. Per-person per-month expenditures for the transition to ESRD Medicare, incident patients with Medicare as primary provider; Medstat/employee group health plan [EGHP], patients enrolled for full year in both 2003 and 2004 **((US Renal Data System,2007).**

Furthermore, of patients who were on dialysis for ≥1 yr, only 24% returned to work after transplantation, compared with at least one half of those who received a transplant preemptively **(Gaston , Thomas , 2005).**

It is also clear that duration of disability before transplantation influences return to- work rates and preservation of family dynamics **(Muerher, Becker ,2005).**

Figure (9). Decline in functional status associated with institution of dialysis, recovery, then a secondary decline associated with transplantation. Preemptive transplantation, by reducing transitions from two to one, has the potential to decrease substantially the adverse impact of RRT on quality-of-life measures **(Rebecca Hays, 2007).**

For appropriate candidates, figure (10) shows kidney transplantation from a Living donor or deceased donor provides the best outcomes among available modalities of RRT; time spent on dialysis awaiting referral for transplantation increases mortality and compromises outcomes after transplantation **(Meier-Kriesche , Kaplan ,2002).**



Figure(10) Impact of duration of time undergoing dialysis on allograft survival at 10 yr after transplantation for recipients of kidneys from living (LD) and deceased (DD) donors **(Meier-Kriesche , Kaplan B,2002.)**

Kidney transplantation improves survival for patients with end-stage renal disease (ESRD), compared with remaining on the transplant waiting list **(John F. Hurdle et al, 2006).**

Recent improvements in immunosuppression have reduced the incidence of acute rejection but have had little effect on chronic allograft nephropathy and late graft loss. **(Bradley C. Baird et al, 2006)**

This is important for two reasons. First, the loss of a primary renal allograft is associated with significant mortality, especially in recipients with type-I-diabetes mellitus (DM) **(Greg Stoddard et al, 2006)**

Second, allograft failure is now one of the leading causes of being listed for transplant, one whose influence will continue to grow as more transplant recipients cycle back through renal replacement therapy (RRT). Strikingly, recipients with repeat transplantation after graft failure showed a substantial improvement in survival over their wait-listed counterparts on dialysis: a 45% reduction in the 5-year mortality for Type I DM patients and a 23% reduction for non-diabetic patients **(Alfred K. Cheung et al, 2006).**

Still, an important question remains about the timing of the re-transplant. In general, pre-emptive transplant (i.e. without exposing the patient to dialysis) seems to be advantageous for graft survival **(Lev L. Barenbaum et al, 2006)**

The length of time on dialysis prior to the first transplant is a predictor of the graft and recipient survival, however relatively short duration of dialysis does not change either graft or recipient outcome **(Goldfarb-Rumyantzev et al, 2005).**

It is unclear if the general advantage associated with pre-emptive transplantation holds for patients with a prior kidney transplant. There is no clear evidence in the literature whether patients who failed a previous transplant should be re-transplanted pre-emptively or be allowed to 'cool down' on dialysis before the next transplant. **(Kasiske et al ,2002)**

Effect of Preemptive Transplantation on Graft Failure

Preemptive transplantation was associated with a lower rate of delayed graft function (dialysis in the first week after transplantation) compared with non preemptive transplantation, for both cadaver donor (8.4 *versus* 25.6%; $P \geq 0.001$) and living donor transplants (2.6 *versus* 6.1%; $P \leq 0.001$).

In univariate (unadjusted) analysis, preemptive transplantation was associated with improved patient and graft survival for recipients of both cadaver and living donor allografts. **(Kasiske et al, 2002)**

Transplantation of a kidney from a living donor without previous long-term dialysis was associated with a 52 percent reduction in the risk of allograft failure during the first year after transplantation (rate ratio, 0.48; P=0.002), an 82 percent reduction the second year (rate ratio, 0.18; P=0.001), and an 86 percent reduction during subsequent years (rate ratio, 0.14; P=0.001), as compared with transplantation after dialysis**. (Kevinc. Mange et al, 2001)**

It is not surprising that preemptive transplantation was relatively more likely among children, given that every effort is made to transplant children as soon as possible to improve their growth and development.**(Papalois et al, 2000)**

Even so, among all cadaver donor-preemptive transplants, only 8.7% were to patients less than 18 yr old, and 3.3% of non preemptive transplants were to patients less than18 yr old.Thus, giving children priority to encourage preemptive transplantation does not divert large numbers of cadaver donor kidneys from adults.**(Vats et al, 2000)**

Long-Term Need for Immunosuppression

Immunosuppressive drugs that have been introduced since 1995 have led to combination therapies that have significantly lowered the rates of acute rejection. **(Meier-Kriesche et al, 2004)**

Induction therapies with various antilymphocyte antibodies also reduce the rate and intensity of acute rejection and possibly prevent the onset of chronic rejection. **(Vincenti ,2003)**

Over the past two decades, empirical trials have led to protocols of combination therapy that reduce side effects yet maintain graft survival. A major challenge in regard to long-term immunosuppression is the need for expanded multicenter trials of various combination therapies and for the development of inexpensive and noninvasive tools to define and monitor responses along the spectrum of immunity toward, ultimately, tolerance.**(Li B et al, 2001)**

All immunosuppressive drugs have specific side effects and additively contribute to an overall state of immunosuppression, which leads to an increased risk of infections and various specific malignant conditions. **(Denton,1999)**

Such immunosuppressive drugs probably contribute to the increased risk of cardiovascular disease, which is the most common cause of premature death in transplant recipients. **(Sarnak et al, 2003)(Bostom et al, 2002)**

Excessive total immunosuppression causes a susceptibility to infectious diseases, especially to DNA viruses such as cytomegalovirus, Epstein–Barr virus, and the more recently recognized polyomavirus, which causes nephropathy and renal allograft loss.**(Fishman ,2002)**

New candidates for treatment such as T-cell–depleting agents and T-cell blockade, all of which are used to modify the immune responses, are under study, and some transplant biologists believe that combinations of drugs without side effects will eventually be available**. (Kreis et al, 2004)**

For example, the use of target-of-rapamycin inhibitors as a way to avoid the use of calcineurin inhibitors in recipients of kidney transplants has recently been reported to improve long-term renal function, decreasing the pathologic changes of chronic allograft nephropathy**.(Mota et al, 2004)**

Several studies have demonstrated that whenever induction therapy is used, acute rejection rate are lowered. **(Legorreta et al, 2006)**

Among patients who are at low immunologic risk, anti–IL-2 receptor (IL-2R) antibodies provide a better efficacy/safety profile than more toxic polyclonal antibodies, including rabbit anti-human thymoglobulin (RATG) , and lymphocyte-depleting mAb, such as OKT3 **. (Chuang et al, 2006)**

Conversely, among patients who are at high immunologic risk—recipients of second grafts, hypersensitized patients, and black patients—RATG offers better anti rejection activity than no induction therapy or induction with non depleting antibodies **(Wong et al, 2006).**

Preliminary results indicate that RATG is associated with a lower rate of recurrence of immune glomerular diseases than anti–IL-2R antibodies or Campath-1H, consistent with its immunomodulatory activity on B cells and its stimulatory effect on regulatory T cells **(Treg) (Lopez et al, 2006).**

Whether these effects translate into a better long-teroutcome remains to be established. A major shortcoming of RATG, when given at conventional dosages, is an increased risk for cytokine-release syndrome and posttransplantation lymphoproliferative disorders. **(Zand et al, 2005)**

Attempts have been made to reduce the RATG dosage without affecting its efficacy in preventing acute rejection **(Khauli et al, 2006).**

A single pulse of 4 to 6 mg/kg RATG was as effective as a single 6- to 9-mg/kg preventing acute graft rejection in live-donor kidney transplant recipients. To safely reduce the dosages of RATG further, others proposed a novel approach that is based on the combination of an anti–IL-2R antibody and low-dosage RATG (3 mg/kg). **(Ciancio, Sageshima , Burke et al, 2006)**

Similarly, a prospective study in patients who were at high immunologic risk documented that this combination of induction therapies was as effective as standard-dosage RATG alone in limiting episodes of acute rejection but safer and less expensive**.(Ruggenenti et al, 2006)**

With the use of this strategy, anti–IL-2R antibodies may contribute to overall mmunosuppression by inhibiting IL-2–mediated signaling in activated T lymphocytes that are spared from depletion by RATG, without affecting the function of Treg**(Nelson et al, 2005)**

Future regimens that combine anti– IL-2R antibody and low-dosage RATG might increase calcineurin inhibitor or steroid-sparing protocols, saving costs and reducing toxicity. **(Baan et al, 2006)**

Maintenance Therapy

The most widely used maintenance immunosuppressive regimen is standard triple therapy **(Ekberg et al, 2006)**

1- Cyclosporine A [CsA] or Tacrolimus
2- An antimetabolite (mycophenolate mofetil [MMF] or Azathioprine),
3- Corticosteroids. **(John Pirsch, William D. Simmons, Hans Sollinger,2003)**

Drugs used in renal transplantation

Antithymocyte Globulin (ATGAM)

Azathioprine

Cyclophosphamide

Cyclosporine-A

Methylprednisolone

Mycophenolate Mofetil

Prednisone

Tacrolimus

Basiliximab

Daclizumab

Tolerance

The achievement of immunologic tolerance has been the focus of transplant medicine since the first successful kidney transplant programs in the 1950s. **(Kawai et al, 2006)**

Despite success in experimental models, translation of these results into the clinical setting has been slower than predicted as new barriers to tolerance have been encountered. Difficulties and hopes emerge also from the overview of ongoing studies on tolerance induction in humans that were presented at the WTC. **(Kawai et al, 2006)**

Most of the work in this field has been done on behalf of the Immune Tolerance Network. Induction of mixed chimerism by a nonmyeloablative conditioning regimen has been attempted in patients who were given combined bone marrow and kidney transplantation from one-haplotype–mismatched, related donors.**(Sachs et al, 2006)**

Long term follow up

The primary focus of immunosuppressive therapy in renal transplant patients is optimal management of the renal allograft.

In the first year after transplantation, the primary clinical goal is to prevent acute rejection and graft failure**.(Stephanie R. Earnshaw et al, 2008)**

In subsequent years, transplant recipients should receive ongoing surveillance of graft function as well as reevaluation of the efficacy, toxicity, and costs of immunosuppressive regimens**.(Kasiske et al, 2000)**

Long-term deterioration of renal function with consequent cardiovascular disease progression and ultimately graft loss or patient death2 is the current challenge in kidney transplantation.These cascading events have not only clinical consequences but also economic implications**.(Christopher N. Graham et al, 2008)**

Prolonged dialysis and subsequent retransplantation are associated with increased direct and indirect costs that affect both society and individual patients. Regimens associated with high short-term survival rates are not necessarily associated with high long-term survival rates. **(Mulay et al, 2005)**

Thus, treatment with immunosuppressive regimens needs to be adapted over time to optimize short- and long-term outcomes**.(Kreis et al, 2004)**

Chapter Four

Cardiovascular diseases post renal transplantation

Cardiac Evaluation before Kidney Transplantation

Candidates for kidney transplantation undergo an extensive evaluation of health status before surgery **(Steven Fishbane,2005).**

An important component is a rigorous consideration of the subject's cardiovascular health.
Among the reasons that cardiac disease is particularly relevant to the pretransplant evaluation is the need to fully assess and manage perioperative risk.**(Kasiske et al ,2003)**

There are excellent published clinical practice guidelines that link evidence to specific recommendations for the cardiac evaluation of patients undergoing noncardiac surgery.

Although written for general patient populations, many of these principles can be applied directly to the potential renal transplant recipient**. (Eagle et al, 2002).**

Beyond perioperative risk, the potential transplant recipient has other characteristics that make cardiac evaluation important.

First, cardiovascular disease is the major cause of death in this population.
Almost half of deaths within 30 d of transplantation are due to cardiac events.
(Stewart et al ,2000)

Second, the long-term posttransplant need for immunosuppressive medications may complicate the process of atherosclerotic risk reduction .
Both steroids and calcineurin inhibitors can increase BP and aggravate dyslipidemia. In addition, clinicians may tend to under-treat with statin drugs because of interactions with calcineurin inhibitors**.(Ojo et al, 2000)**

Third, kidneys for living or cadaver transplants are a precious and scarce resource.
Because cardiovascular death is a major reason for eventual graft loss, the balance of risk and benefit for decisions related to cardiac testing may be shifted with this difficult resource utilization/ethical issue in mind.
(Steven Fishbane,2005)

The American College of Cardiology (ACC) recommends a stepwise approach to the selection of tests for risk assessment before non cardiac surgery .
(Berger et al, 2002).

It is recommended that patients in the major group go directly to coronary angiography.

Patients with intermediate predictors should be stratified on the basis of functional status.
The ACC recommends that patients with good function proceed to surgery, with poor function noninvasive stress testing recommended.
The American Society for Transplantation has guidelines refined more specifically for pretransplant evaluation, recommending risk stratification and noninvasive stress testing for candidates at high cardiac risk.
(Kasiske et al, 2003).

Noninvasive cardiac tests (specifically dipyridamole thallium/ sestamibi scintigraphy [DSS] or dobutamine echocardiography [DE]) have been fairly well studied in patients with ESRD.

A recent meta-analysis found that transplant candidates with positive noninvasive stress tests may have a greater risk for future cardiac events.

For prediction of cardiac death the pooled results indicated a sensitivity of 80%, but a specificity of only 59**%** **(Rabbat et al, 2003).**

The primary finding was that DSS had a sensitivity and specificity of only 58% and 67%, respectively, and DSE had a sensitivity of only 44%, with a better specificity of 87%.

The noninvasive tests performed with similar poor accuracy for the prediction of future cardiac events**.(De Lima et al, 2003)**

Only coronary angiography can reasonably exclude the presence of significant coronary artery disease in many high-risk transplant candidates.
But the risks of this test include radiocontrastinduced nephropathy (RCIN) , atheroembolic disease, and other important complications **(Lindholt ,2003).**

For the patient on dialysis who is undergoing pretransplant evaluation, the risk for RCIN may be less important, and coronary angiography would be a reasonable starting test for many high-risk patients.
In contrast, the high-risk candidate who seeks preemptive living donor transplantation before dialysis poses a difficult problem**. (Saklayen et al, 2003)**

The risk for RCIN may be great enough that the patient may reach ESRD as a result of the procedure.
Thus, the clinician is left with two disappointing choices: Wait for coronary angiography until the patient starts dialysis, or proceed and confront the risk of inducing RCIN and premature ESRD**.(Ammann et al, 2003)**

Better noninvasive tests are needed and improved technology should lead the way to a better future in this difficult area of clinical decision-making.
The ideal test would be highly accurate and would not require the use of radiocontrast media. **(Steven Fishbane,2005).**

Comorbid Conditions in Kidney Transplantation

Although the impact of comorbidity on outcomes in ESRD has been evaluated extensively, its contribution after kidney transplantation has not been well studied. It is believed that comorbidity assessment is critical to the informed interpretation of kidney transplant outcomes. **(Christine et al, 2005)**

Although a significant body of literature discussing the effects of comorbid conditions on patients with ESRD and their access to kidney transplantation exists.
The consequences of patient comorbidity on kidney transplant outcomes have not been well studied**. (Di Iorio , 2004)**

A few reports have evaluated the effects of single comorbid conditions, such as diabetes or cardiovascular disease, on transplant outcomes.
(Woo et al, 2002)

Baseline comorbidity is often considered in preoperative risk stratification ; however, patient outcomes after kidney transplantation to date have focused on immunologically relevant donor, recipient, and also transplant procedure characteristics. **(Romero et al, 2001)**

It was suggested previously that nonimmunologic factors, including comorbid conditions and the complications of chronic kidney disease, are more predictive of patient mortality after kidney transplantation than immunologic and transplant-related factors **(Gill et al, 2002).**

The Charlson Comorbidity Index as shown in figure (11) was used to assess the comorbid conditions of 715 patients who underwent kidney transplantation at the Starzl Transplant Institute between January 1998 and January 2003.
The impact of pretransplantation comorbidity on the development of acute cellular rejection after transplantation and on patient and graft survival was examined. **(Christine et al, 2005)**

Figure (11) shows Distribution of Charlson Comorbidity Index (CCI) score.

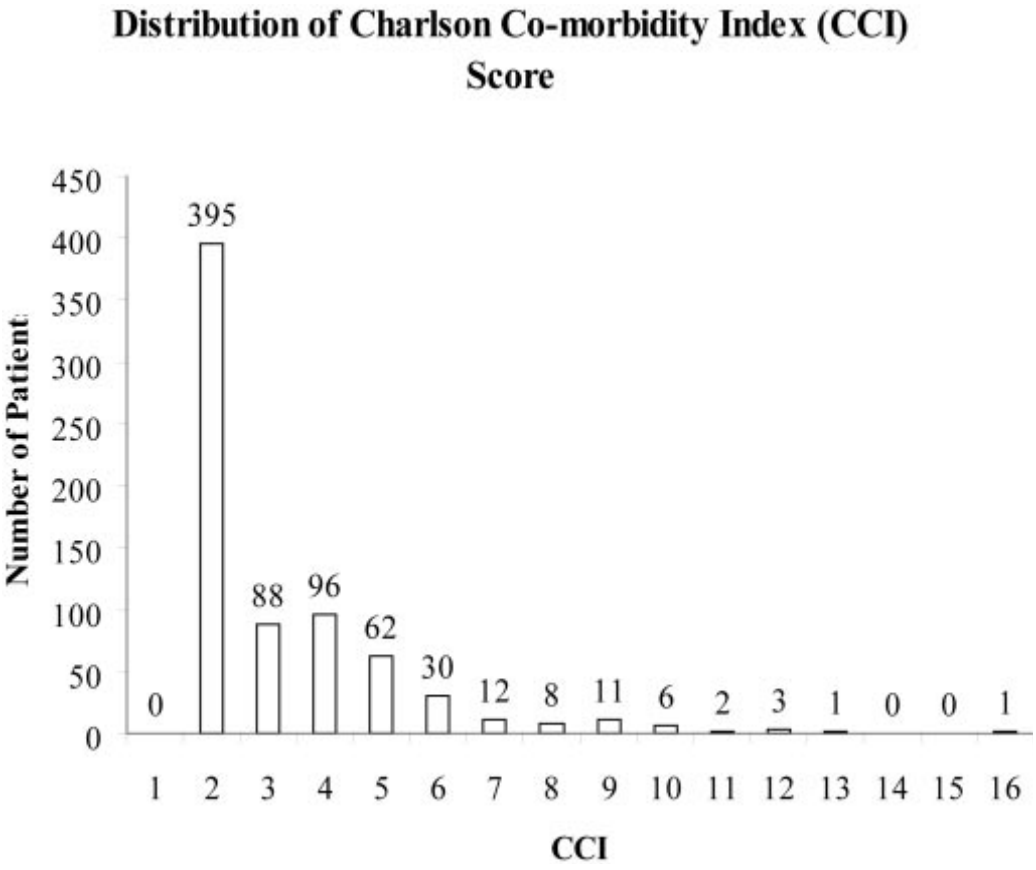


Figure (11) Distribution of Charlson Comorbidity Index (CCI) score.

Cardiovascular Disease in Transplant Recipients

Kidney transplantation is the renal replacement therapy of choice for most patients with ESRD, not only improving quality of life but also offering extended life expectancy compared with dialysis. **(Neipp et al, 2006)**

Immunosuppressive therapies have significantly improved allograft outcomes, yet, for many patients, the advantages of renal transplantation do not result in a normal life span.
Compared with the general population, renal transplant recipients (RTR) are at higher risk for morbidity and mortality, largely as a result of cardiovascular disease (CVD). **(Anushree C. Shirali, and Margaret J. Bia,2008)**

Kidney transplantation reduces mortality and cardiovascular deaths, more so than dialysis, although survival for both remains worse than in non renal disease populations.
This may be for reasons of preexisting cardiovascular disease acquired during renal progression or dialysis; however, recent population data suggest even minor kidney dysfunction (which is almost universal in graft recipients) is associated with increased cardiovascular risk.
(Eberhard Ritz and Christoph Wanner,2008)

A cardiovascular disease event in a transplant recipient may be the result of a pre transplantation disease process, a direct effect of immunosuppressant medications, or the result of exposure to a variety of traditional and nontraditional risk factors after transplantation.
Although the understanding of post transplantation cardiovascular disease remains incomplete, there is evidence that the impact of post transplantation cardiovascular disease has been decreased, through increased attention to this problem**. (John S. Gill,2008)**

Although increased awareness of cardiovascular disease (CVD) has resulted in a reduction in CVD-related deaths over time, CVD remains the major known cause of death in transplant recipients and is a significant barrier to improving long-term outcomes in kidney transplantation. **(Meier-Kriesche et al, 2001)**

The high risk for CVD in transplant recipients is in part explained by the high prevalence of conventional CVD risk factors (*e.g.*, diabetes, hypertension, dyslipidemia**)** in this patient population.**(Anzdata Registry Report 2006)**

However, a significant portion of CVD risk in transplant recipients is unexplained by these factors and may be related to pre transplantation exposure to chronic kidney disease (CKD)-related risk factors.
Ongoing exposure to CKD-related risk factors as a result of impaired allograft function, or to transplant-specific risk factors including those related to the use of immunosuppressant medications or infection**.(USRDS,2005)**

There are two major and overlapping categories of CVD:
(**John S. Gill**,**2008**)

1- **Disorders of cardiovascular perfusion** in**clud**ing:

Atherosclerotic CVD

Ischemic heart disease [IHD]

Cerebrovascular disease

Peripheral vascular disease

2- **Disorders of cardiac function** in**clud**ing:

Congestive heart failure (CHF)

Left ventricular hypertrophy

Epidemiology and Risk Factors

By 36 months after transplantation, nearly 40% of patients have experienced a CV-related event.Although acute myocardial infraction occurs after transplantation, especially in the elderly and patients with diabetes, CV events related to congestive heart failure (CHF) are more common**.(Kasiske et al, 2006)**

Indeed, after infection, CHF is the most common cause of hospital admissions after renal transplantation. Clearly, management of CVD after transplantation should include modifying risk factors that contribute to CHF as well as ischemic heart disease**. (Anushree C. Shirali, and Margaret J. Bia,2008)**

Traditional risk factors for CVD in the general population remain relevant for transplant recipients.

Some of these, such as diabetes and hypertension, are likely to be preexisting conditions, although, along with other diseases, particularly hyperlipidemia and anemia, they can also arise *de novo* from the unintended effects of immunosuppression. **(Fellstrom et al, 2005).**

There is now general consensus that worsening kidney function is also an independent risk factor for cardiac disease. Although renal replacement by transplantation can abrogate that effect, allograft dysfunction is still an important risk factor for all-cause and CV mortality. **(Ducloux et al, 2004)**

In addition, proteinuria itself is a risk factor for CVD. Fernando-Fresnedo *et al.* found in a single-center retrospective analysis that transplant recipients with proteinuria carry a relative risk of 2.45 for development of CVD when compared with patients without proteinuria. **(Fernandez-Fresnedo et al, 2002)**

Markers of inflammation, such as hyperhomocysteinemia, C-reactive protein (CRP), and advanced glycation end products, are independently linked to CVD in some studies of RTR **(Hartog et al, 2006).**

Risk Factors of CVD : (Anushree C. Shirali,and Margaret J. Bia,2008)

Risk factors for the development of CVD after kidney transplantation

1- Traditional Risk Factors

- Modifiable/potentially modifiable

Obesity
Diabetes
Hypertension
Hyperlipidemia
Smoking

- Non modifiable

Gender
Age
Family history

2- Transplant-Associated Risk Factors

Immunosuppression CKD

Proteinuria Anemia

3- Emerging Risk Factors

Inflammation
CRP/ AGE
Homocysteine

Obesity

Now a global public health epidemic, obesity is also affecting the RTR population.

Obesity can be stratified according to body mass index (kg/m2):
(Hartog et al, 2006)

Overweight (25 to 29.9)
Obese (30 to 34.9)
Morbidly obese (_35).

Increasing numbers of obese and overweight patients are now presenting for transplant than ever before and there is further weight gain after transplantation.
(El-Agroudy et al, 2004)

Recent data from a contemporary cohort of the United Network for Organ Sharing database indicated that 50% of transplant patients could be classified as obese .

Obesity can predispose to insulin resistance, diabetes, ischemic heart disease, and reduced graft survival **.(Jindal , Zawada Jr,2004)**

Obesity in transplant patients is also being increasingly recognized in the context of the metabolic syndrome, which is defined in table (2). When examined at 6 yr after transplantation,up to 63% of RTR meet the criteria for metabolic syndrome, with an associated decrease in kidney allograft survival and increased number of CVD events **.(Courivaud et al, 2007)**

Table (2) shows Risk factors for metabolic syndrome

Risk Factor	Defining Criteria
Abdominal obesity	Waist circumference: ≥35 in (88 cm) for women; ≥40 in (102 cm) for men
BP	≥130/85 mmHg or use of antihypertensive agents
Triglycerides	≥150 mg/dl or drug therapy for high triglycerides
HDL cholesterol	Men ≥40 mg/dl for men; ≥50 mg/dl for women
Insulin resistance	Fasting blood glucose≥110 mg/dl or treatment for diabetes

Adult Treatment Panel III (ATP III) defines metabolic syndrome in the presence of three or more of these factors. **(Courivaud et al, 2007)**

Athough the use of steroids clearly plays a role, improvementin appetite and freedom from dialysis-related dietary restrictions also contribute to posttransplantation weight gain**.(Jindal, Zawada, 2004)**

In reports of steroid-avoidance protocols, small decreases in weight gain after transplantation were noticed in some but not all studies.
In a carefully controlled study, Painter *et al.* reported that neither weight nor body fat composition was different at 1 yr in patients in a steroid-avoidance protocol *versus* those who were maintained on steroids.**(Painter et al, 2003)**

These findings are consistent with the fact that obesity precedes transplantation in many patients .
Thus, although steroids can stimulate appetite and are blamed for obesity by both patients and physicians, there is not convincing evidence that steroid-free regimens should be used specifically to avoid posttransplantation weight gain.
(Rajab et al, 2006)

Lifestyle Modification for Prevention and Control of Obesity

It is well appreciated that diet and exercise form the backbone of lifestyle changes needed to achieve and support sustained weight loss. Van den Ham *et al* found that physical activity was more important than steroid dosage in post transplantation weight gain**. (Van den Ham et al, 2000)**

Dietary counseling needs to be incorporated into routine visits. Although patient motivation drives adherence toboth diet and exercise, weight loss programs can help patients achieve weight loss goals**.(Tsai , Wadden et al, 2005)**

Effective drug therapy for obesity is limited, partly because of the complex pathogenesis.
Orlistat is a pancreatic lipase inhibitor that blocks fat absorption. It is modestly effective in promoting weight loss when compared with placebo in nontransplant patients **(Li , Maglione et al, 2005).**

No similar studies exist for RTR, but there are case reports of subtherapeutic calcineurin inhibitor (CNI) levels in patients who used orlistat.
Physicians should be mindful of its potential use among patients, especially because orlistat recently became available without a prescription.
(Barbaro et al, 2002)

Antidepressants may be useful for depressed patients who have an emotional component of weight gain, particularly selective serotonin reuptake inhibitors such as fluoxetine and sertraline, which, unlike other antidepressants, are less likely to cause weight gain. St. John's wort, an herbal preparation used as part of an alternative prescription for depression, decreases CNI levels by potent cytochrome P450 induction. Transplant patients should be cautioned against its use, because it has been linked to acute rejection episodes **(Ernst ,2002).**

Cigarette Smoking

Smoking clearly increases the risk for CVD death in kidney transplant recipients, and there is evidence that the smoking-related risk for death issipates 5 yr after smoking cessation.Transplantation represents an opportunity to initiate smoking cessation successfully. The combined use of pharmacologic and nonpharmacologic strategies may be most effective, and there are no significant interactions between the commonly used drugs for smoking cessation and immunosuppressant medications.
(Kasiske , Klinger ,2000)

Tobacco use, which occurs in approximately 25% of RTR, is an independent risk factor for CVD and confers a 30% risk for graft loss as a result of premature CVD .In fact, smoking has been demonstrated to be a risk for death with a functioning graft as great as that due to diabetes**.(Aker et al, 1998)**

This risk can be reversed with smoking cessation. RTR who stopped smoking ≥5 yr before transplantation had a 34% risk reduction in CVevents.
Thus, the commitment to modify this risk factor needs to begin long before transplantation**.(Cosio et al, 1999)**

The most successful approaches to smoking cessation involve both pharmacologic therapy (usually nicotine replacement therapy [NRT]) and sustained behavioral therapy (counseling).The important role of the physician in this process needs to be emphasized.**(Thorndike et al, 2007)**

Long-term smoking is a sign of chemical dependence on nicotine, providing the rationale for NRT as pharmacologic therapy.Several modalities exist, including transdermal patches, gum, and inhalers, with all displaying nearly equal efficacy.**(Silagy et al, 2004)**

Dyslipidemia

Dyslipidemia is present in 50 to 60% of kidney transplant recipients . Next table (3) summarizes the current thresholds for the diagnosis of dyslipidemia as defined by the KDOQI guidelines.Dyslipidemia is strongly associated with atherosclerotic CVD in CKD and non-CKD populations **(Kasiske ,2005).**

Dyslipidemia is clearly linked to the use of corticosteroids, CNI, and sirolimus. Compared with cyclosporine, tacrolimus has been associated with better lipid profiles, whereas sirolimus has been associated with a greater incidence and severity of dyslipidemia. Other factors that contribute to dyslipidemia include weight gain, decreased kidney function, proteinuria, beta blockers, and diuretics **(Pham ,etal2007).**

Table (3)Definition of dyslipidemia in adult kidney transplant recipients: **(Kasiske,2005).**

Dyslipidemia (mg/dl)	Goal (mg/dl)
TG more than500	TG lessthan500
LDL 100 to 129	LDL lessthan100
LDL morethan130	LDLlessthan100
TG morethan 200 and non-HDLmorethan130	NonHDLlessthan130

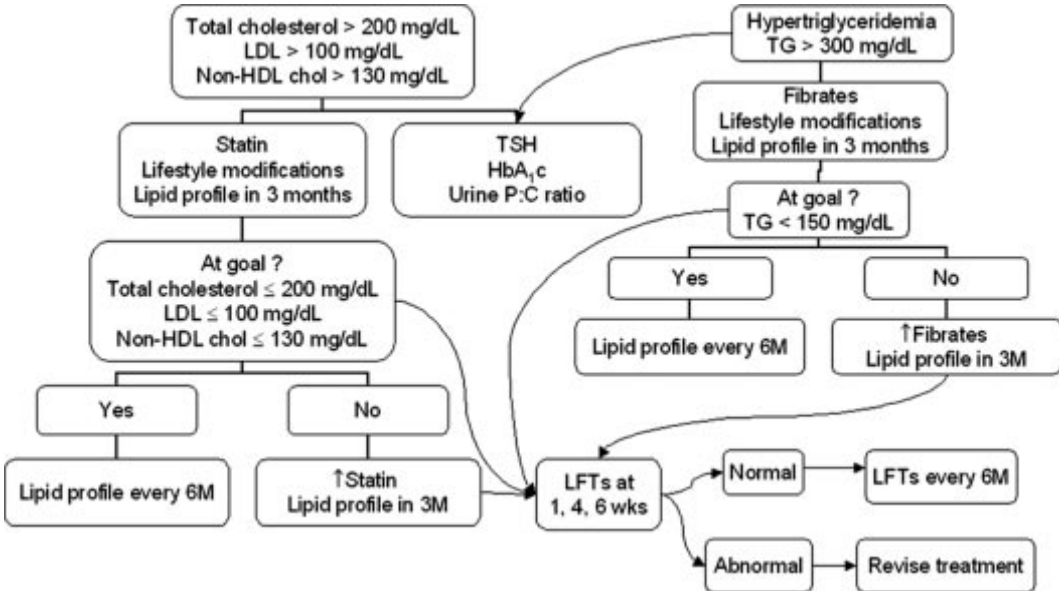
The KDOQI guidelines recommend that all adult and adolescent transplant recipients be tested for dyslipidemia (complete fasting lipid profile including total cholesterol, LDL, HDL,and triglycerides) .

Testing should be done when patients are stable after transplantation and at least annually thereafter.In addition, testing should be done 2 to 3 mo after a change in immunosuppressant medications or conditions that are known to cause dyslipidemia (*e.g.*, change in proteinuria or GFR**). (Pham et al, 2007)**

On the basis of the Adult Treatment Panel III (ATP III) classification, the working group considered RTR in the highest CVD risk category and suggested goal lipid levels accordingly **(Kasiske et al, 2004).**

Goals for therapy are outlined in the next figure (12) and include both lifestyle modifications and drug therapy.

In RTR, a goal of LDL ≤100 mg/dl is recommended, but in transplant patients with diabetes or previous CVD, one could justify an LDL goal of ≤70 mg/dl, which has been shown to be even more protective in preventing cardiac events in non-RTR **(Grundy et al, 2004).**



Figure(12)
Management of dyslipidemias in renal transplant recipients. HbA1c, glycosylated hemoglobin; LFTs, liver function tests; TG, triglycerides; TSH, thyroxin-stimulating hormone.

Role of Immunosuppressive Agents

Steroids, even at maintenance dosages, contribute to hyperlipidemia in RTR , and improved lipid profiles have been reported in most steroid-free or steroid-withdrawal studies .
Risk for acute rejection with late steroid withdrawal and lack of long-term follow-up in steroid-avoidance trials suggest the need for caution in choosing a steroid-free regimen to improve lipid profile. **(Alexander et al, 2004)**

Cyclosporine and tacrolimus both can contribute to hyperlipidemia, but cyclosporine has a greater effect.In fact, switching from cyclosporine to tacrolimus to improve hyperlipidemia, especially in a patient who is intolerant to statin therapy, can significantly improve levels of cholesterol and LDL **(Newcombe et al, 2005).**

Sirolimus has the greatest effect on lipid profiles and elevates both cholesterol and triglycerides in a dosage-dependent manner. Because of the antiproliferative effect of sirolimus on the vascular endothelium, some have postulated that elevated lipid levels are not as much of a risk in patients who take sirolimus, with some clinical data to support this hypothesis.
The antimetabolite immunosuppressants, namely mycophenolate mofetil and azathioprine, are not associated with *de novo* development of dyslipidemias. **(Fernandez-Fresnedo et al, 2004)**

Lifestyle modifications presented in the National Cholesterol Education Project Plan III (NCEP III) are appropriate goals for transplant patients and include diet, weight reduction, and increased physical activity .Diet composition should contain≤200 mg/d cholesterol, ≤7% saturated fat, plant sterols (2 g/d), and increased soluble fiber (10 to 25 g/d) **(Cupisti et al, 2004).**

Trans fats should also be avoided. Although benefits in lipid profile in RTR have been demonstrated in small studies , most transplant patients need drug therapy to reach lipid profile goals**.(Blum et al, 2002)**

Drugs that treat hyperlipidemia are listed in Table 3. Among different statins, atorvastatin is the most potent and along with pravastatin and fluvastatin does not need dosage adjustment for renal insufficiency. Most statins are metabolized by the same cytochrome P450 system (CP3A4) as cyclosporine, leading to an accumulation of the former in plasma and resulting in a greater frequency of rhabdomyolysis **(Lemahieu et al, 2005).**

Data on tacrolimus are sparse, although pharmacokinetic studies in a limited number of patients on concomitant atorvastatin and tacrolimus therapy did not show a significant interaction between the two **(Lemahieu et al, 2005).**

Fluvastatin is metabolized by CP2C9, whereas pravastatin metabolism relies on sulfation; therefore, both should theoretically be safer to use . The potential for rhabdomyolysis also increases as the liphophilicity of the compound increases, because the more lipid-soluble statins are more likely to in extrahepatic tissues and cause toxicity **(Nogueira, Weir ,2007).**

Among statins in current use, table (4) shows simvastatin and lovastatin are the most liphophilic compounds, whereas atorvastatin and fluvastatin are less so and pravastatin is hydrophilic .

In considering these differences among statins, fluvastatin, pravastatin, and atorvastatin seem to have a more favorable safety profile over simvastatin and lovastatin.**(Neuvonen et al, 2006)**

Table (4) Classes of lipid-lowering drugs and their effects

Drug Class	LDL Cholesterol	HDL Cholesterol	Triglycerides	Adverse Effects
Statins (HMG-CoA reductase inhibitors, *e.g.*, atorvastatin)	↓↓↓↓	↑↑	↓↓	Rhabdomyolysis, myositis elevated LFT,
Fibrates (*e.g.*, gemfibrozil)	↓↓	↑↑↑	↓↓↓	increased levels with CNI use
Bile acid sequestrants	↓↓	↔	↓↓	Elevated creatinine,b
Nicotinic acid	↓↓	↑↑	↓↓	erectile dysfunction
Cholesterol absorption inhibitor (*e.g.*, ezetimibe)	↓↓	↔	↔	Interferes with absorption of CNI, GI distress Flushing, hyperglycemia GI distress

Hypertension

Hypertension after renal transplantation is defined according to criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, and Evaluation of High Blood Pressure (JNC VII) as systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP)≥90 mmHg **(Chobanian et al, 2003).**

Given this definition, 75 to 90% of kidney transplant patients have hypertension **(Ojo , 2006)**

A figure that has changed little in recent years. In a large cohort (29,751 patients) in the Collaborative Transplant Study, reported that up to 55% of kidney transplant patients did not reach the goal for BP control.**(Opelz et al, 2006)**

Each 10-mmHg incremental rise in SBP independently increases the risk for death and deathcensored graft failure in RTR by 18 and 17%, respectively **(Kasiske et al, 2004).**

Hypertension is also associated with poor long-term graft survival.
(Opelz et al, 1998).

K/DOQI guidelines suggest goal BP≤130/80mmHg for all RTR with decreased targets considered appropriate for patients with proteinuria.
European best practice guidelines specify BP≤125/75 mmHg in patients with proteinuria**. (Anushree C. Shirali and Margaret J. Bia,2006).**

HTN is a risk factor for allograft failure, death with a functioning allograft, atherosclerotic CVD, and disorders of cardiac function.
The pathogenesis of HTN in transplant recipients is linked to pretransplant factors including pretransplant HTN, the type of primary kidney disease, and excess renin output from native kidneys**.(John S. Gill,2008)**

Posttransplantation factors include the quality of the donor organ, delayed graft function, acute rejection, transplant renal artery stenosis, the level of allograft function (GFR), chronic immune and nonimmune injury, recurrent or *de novo* glomerulonephritis in the allograft, and excessive weight gain**.**
(Chobanian et al, 2004).

Both calcineurin inhibitors (CNI) and glucocorticoids contribute to HTN.
HTN was significantly lower before the introduction of CNI **(Anjum et al, 2004).**

CNI cause afferent arteriolar vasoconstriction by sympathetic stimulation and by upregulation of the local renin-angiotensin-aldosterone system. CNI also decrease vasodilator prostaglandins and nitric oxide and increase vasoconstrictor cytokines **(Zhang et al, 2003).**

Glucocorticoids contribute to HTN by causing sodium and water retention. .
(John S. Gill,2008)

The CNI (cyclosporine more than tacrolimus) contribute to hypertension *via* vasoconstriction and salt retention, and improvement in hypertension has been reported when dosage is reduced or the drug is eliminated **(Mota et al, 2004).**

Mechanisms by which steroids contribute to hypertension include salt retention, weight gain, and mineralocorticoid effect. Improvement in hypertension has been reported in steroid-withdrawal and steroid- avoidance trials
(Rajab et al, 2006).

Lifestyle Modification for BP Control:

Lifestyle modification for hypertension control includes diet and exercise. Nontransplant patients who followed the Dietary Approaches to Stop Hypertension (DASH) diet were demonstrated to have a decrease in SBP (11.4 mmHg) and DBP (5.5 mmHg) **(Mitka, 2007).**

This diet, which features a high intake of fruits and vegetables and a low intake of fats, is now recommended for all patients with hypertension by national guidelines, including JNC VII. The new DASH diet recommends a sodium intake of 1600 mg/d. **(Chobanian et al, 2004).**

Unfortunately, despite its proven efficacy, evidence suggests that the DASH diet is seldom followed.In a study of 4386 hypertensive patients, Mitka reported that only 22% of patients were following this diet. **(Mitka , 2007)**

No single class of antihypertensive agents has proved to be superior for all RTR, and the choice depends on the particular patient.The use of calcium channel blockers (CCB) is popular as first-line therapy , because they are often used to counteract the vasoconstrictive effects of cyclosporine as well as posttransplantation hyperuricemia**(Kuypers et al, 2004).**

In studies in which improved allograft function has been reported with the use of dihydropyridine (DHP) CCB compared with angiotensin-converting enzyme inhibitors (ACEI) ,the results are likely explained by the hemodynamic effects of ACEI to decrease GFR and may not represent an advantage for long-term survival**.(Chanard et al, 2003)**

There are some concerns about the use of CCB. In a retrospective, single-center analysis. found that DHP CCB imposed a relative risk of 2.26 for major ischemic heart disease events, independent of other variables, including BP.
(Kasiske et al ,2004)

Furthermore, there is a greater risk for proteinuria with these agents compared with ACEI in nontransplant patients with CKD. Edema can be a major problem with the use of DHP CCB in RTR, and the non-DHP CCB can delay metabolism and elevate the levels of cyclosporine and tacrolimus .
(Kuypers et al, 2004.)

Classes of drugs to be used are listed in table (5)The use of ACEI and angiotensin II receptor blockers (ARB) in RTR is more widespread now than in the past**. (Kuypers et al, 2004.) Table (5)**

Parameter	Diuretics	CCB	ACEI/ARB	_ Blockers
Selected examples Considerations for initiating use in RTR Adverse effects Interactions with immunosuppressive drugs	Loop: furosemide Thiazide: HCTZ Volume overload Volume depletion	Non-DHP: diltiazem, verapamil DHP: amlodipine, nifedipine Minimizes CNI EDEdema with DHP All non-DHP CCB increase CNI levels	ACEI: lisinopril ARB: losartan vasoconstriction Proteinuria, CHF, LVHPreferred in patients with known IHD Elevated K_, anemia, elevated creatinine	Selective: lopressor Nonselective: carvedilol vasoconstriction Proteinuria, CHF, LVHPreferred in patients with known IHD Bradycardia, ED

The cardioprotective and renoprotective effects of renin-angiotensin system blockade in the general population and in patients with CKD make the use of these agents attractive in the RTR population; however, limited prospective data in the transplant population confirm these benefits.

Regarding cardioprotection found equal benefits of lisinopril and nifedipine in reducing left ventricular mass index after transplantation.This trial was not powered to study CV events or mortality. **(Heinze et al, 2006)**

Regarding renoprotection, data compiled from many studies document decreased proteinuria in RTR with the use of ACEI. In a meta-analysis of the use of ACE/ARB in ≥1500 RTR who were enrolled in RCT reported a 0.47-g/d reduction in proteinuria. **(Hiremath et al, 2007)**

Although caution has been advised in using these agents too early after transplantation, we and others have reported no deleterious effect of these drugs on GFR when used in the early posttransplantation period.Whether these agents are renoprotective aside from improving proteinuria, as they are in patients with CKD, is controversial. **(Weir , 2004)**

In one report involving 2031 RTR from a single center, improvement in 10-yr actual patient survival (74 *versus* 53%; $P \leq 0.002$) and graft survival (59 *versus* 41%; $P \leq 0.001$) was reported in patients who were *versus* were not on ACEI/ ARB therapy **(Mitterbauer et al, 2006).**

Shortly thereafter, in another report involving 17,209 RTR in the Collaborative Transplant Study, no benefit on ACEI or ARB use could be demonstrated. **(Chanard et al, 2003).**

Adverse effects such as anemia, hyperkalemia, and decrease in GFR must be monitored with patients who are taking these agents.Because the combination of afferent arteriolar vasoconstriction from CNI and efferent arteriolar vasodilation as a result of reninangiotensin system blockade can predispose to acute kidney injury, we routinely advise our patients to discontinue their ACEI/ ARB if they are acutely ill and at risk for volume depletion**.** **(Formica et al, 2004)**

In RTR, multiple drugs are often used to meet BP goals **(Lorenz et al, 2004).**

The addition of α_-β blockers (labetalol or carvedilol) or centrally acting drugs (clonidine) is often needed to achieve control.

Selective α-1 blockers (*e.g.*, doxazosin) may be helpful in men who also have prostatism, but monotherapy is associated with a higher incidence of heart failure **(Formica et al, 2004).**

β_ Blockers are used for patients with ischemic heart disease.

In addition, diuretics are often used and are associated with increases in episodes of pre renal azotemia. The inhibitory effects of many of these drugs on sexual function, especially thiazides, β _ blockers, and clonidine, must be considered and discussed with the patients**.(Francis et al, 2007)**

New-Onset Diabetes

With the increasing incidence of diabetes in the ESRD population, ≤20% of recent transplant recipients have existing disease at the time of transplantation .

The rate of new-onset diabetes after transplantation (NODAT) is also on the rise, with prevalence in a contemporary US Renal Data System cohort estimated at 9.1, 16.1, and 24% at 3, 12, and 36 mo after transplantation, respectively **(Snyder et al, 2003).**

Obesity, hepatitis C infection, black and Hispanic ancestry, and older recipient age are associated with NODAT **(Kasiske et al, 2003).**

In addition, there is appreciation that the increasing prevalence of metabolic syndrome after renal transplantation independently predicts development of NODAT . **(Ducloux et al, 2005)**

RTR with NODAT have as high a risk for CVD as patients with diabetes before transplantation. RTR with impaired fasting hyperglycemia also experience a higher risk for death from CVD **(Porrini et al, 2006).**

Prevalence rates have varied in previous reports because of varying definitions of diabetes.

In 2003, the transplant community issued international consensus guidelines (ICG) that suggested that screening for NODAT be based on the American Diabetes Association criteria for diagnosing diabetes **(Wilkinson et al, 2005).**

The American Diabetes Association issued revised criteria in 2003 , which are detailed in table (6). Screening by fasting plasma glucose is recommended in all RTR weekly in the first month after transplantation, then at the 3, 6, and 12 mon visits. **(Snyder et al,2003).**

Table (6) Current definition of glucose intolerance and diabetes

Parameter	Fasting Glucose	Random Glucose	2-H GTT
Normal	≤100 mg/dl	N/A	≤140 mg/dl
Impaired	100 to 125 mg/dl Consider 2-h GTT	N/A	140 to 199 mg/dl
Diabetes	≥126 mg/dl	≥200 mg/dl	≥200 mg/dl

All abnormal values should be confirmed with testing on a separate day.
(Cosio et al, 2005)

Although screening with the more sensitive glucose tolerance testing has been advocated in certain at-risk populations, fasting glucose is still used in most transplant centers. **(Armstrong et al, 2006)**

The ICG recommend that glycemic control in established diabetes be based on glycosylated hemoglobin (HbA1c) ≤6.5% and fasting plasma glucose 90 to 130 mg/dl **.(Crutchlow et al, 2007)**

K/DOQI guidelines are similar, except that HbA1c≤7% is considered acceptable **(Porrini et al, 2006).**

Testing for HbA1c is not recommended in first 3 mo after transplantation .

Glycemic control may be difficult for patients to achieve but is an essential part of reducing adverse outcomes. In non-RTR, a 1% drop in HbA1c decreases CV mortality by 15 to 20% **(Selvin et al, 2004).**

***Role of Immunosuppressive Agents*:**

Prednisone and the CNI (tacrolimus more than cyclosporine) contribute to glucose intolerance and NODAT . **(Kasiske et al, 2003)**

Steroids are a known cause of insulin resistance, and the CNI impair insulin secretion. The tendency for a greater prevalence of diabetes with tacrolimus *versus* cyclosporine is diminished with steroid-free protocols and with the lower dosages of tacrolimus being used today **(Meier-Kriesche et al, 2006).**

Although higher dosages of steroids clearly lead to more diabetes, could demonstrate no difference in insulin sensitivity between 5 mg of prednisone and a prednisone-free protocol. **(Midtvedt et al, 2004)**

Sirolimus does not have a marked effect on glucose metabolism, but a decrease in insulin sensitivity has been reported , as well as a worsening of glucose tolerance when sirolimus is added to a calcineurin-based protocol.
(Romagnoli et al, 2006).

Again, caution is advised in considering modifying immunosuppression to improve glucose tolerance because of the risk for rejection**.**
(Teutonico et al, 2005)

Lifestyle Modification for Prevention and Treatment of NODAT:

There is strong evidence in non-RTR that lifestyle modification through weight loss and exercise for overweight individuals can prevent diabetes more dramatically and in a more sustained manner than any pharmacologic agent.

In a recent study of patients with overt diabetes, the combination of weight resistance training and aerobic exercise (30 min three times weekly) was more effective than either alone in leading to a 1% decrease in HbA1c . **(Lindstrom et al, 2006).**

Although there is no direct evidence in RTR, it seems logical to assume that lifestyle modification would play an important role in the treatment and prevention of diabetes in this population as well. **(Sigal et al, 2007)**

In addition to lifestyle modification, stepwise initiation of oral monotherapy, oral combination therapy, and/or insulin therapy may be required to maintain targets for glycemic control as in table (7). **(Van Hooff et al, 2005)**

The choice of initial oral therapy depends on patient characteristics and physician preference, because no RCT are available to compare drug classes in guidelines addressed drug therapy for diabetes in patients with CKD, which are also appropriate for RTR. The classes of drugs are detailed in Table 6.

The risk for hypoglycemia is highest with insulin and insulin secretagogues such as sulfonylureas and is potentiated with renal insufficiency. **(Citterio et al ,2006)**

Thus, drugs that have hepatic clearance are preferred over those that have renal clearance.

Classes of drugs used to treat diabetes in RTR (**Cosio et al, 2005)**

Class	Drug	Dosing Recommendations	Adverse Effects/Drug Interactions
Second-generation sulfonylureas	Glipizide Glyburide Glimiperide	Preferred agent Not recommended Begin with low dosage	Hypoglycemia
Thiazolidinediones	Pioglitazone Rosiglitazone	None	Volume retention/edema, CHF
Meglitinide	Repaglinide Nateglinide	Preferred agent Renally cleared; begin with low dosage	Levels may be increased with statin/fibrate use
Biguanides	Metformin	Not recommended, especially with reduced GFR	Lactic acidosis
α -Glucosidase inhibitors	Acarbose	Not recommended with creatinine≥2.0 mg/dl	GI distress
GLP-1 (incretin mimetic)	Exenatide	None	No published data on Interactions
DPP-IV inhibitor	Sitagliptin	Reduce dosage: 50% for GFR 30 to 50 75% for GFR ≤30	No published data on Interactions
Insulin	Rapid acting: regular, lispro, aspart Intermediate acting: NPH Long acting: glargine	None	Hypoglycemia

Table (7) shows Classes of drugs used to treat diabetes in RTR

Proteinuria

Proteinuria is prevalent in 20 to 40% of transplant recipients. The evidence to treat proteinuria specifically to reduce CVD risk is lacking**.**
(Fernandez-Fresnedo et al, 2004)

Proteinuria is believed to be a marker of endothelial dysfunction, and there are ample observational data showing that proteinuria is clearly associated with an increased risk for CVD in transplant and nontransplant patients.
(Wachtell et al, 2003)

However, there are limited data from controlled studies demonstrating that treatment of proteinuria decreases the risk for CVD **(Ibsen et al, 2005).**

Controlled trials in the nontransplantation setting clearly demonstrate that proteinuria reduction is renoprotective; therefore, there is a stronger rationale to treat proteinuria to preserve allograft function. To date, no controlled trials in transplant recipients have demonstrated that proteinuria reduction preserves allograft function**.(John S. Gill,2008)**

Anemia

The recent KDOQI guidelines on anemia management contain a dedicated discussion of posttransplantation anemia **.(Rigatto et al, 2003)**

Although anemia is associated with CVD in both transplant and nontransplant patients, there is no clear evidence that correction of anemia reduces the risk for CVD events.

The main proven benefit of anemia treatment with erythropoiesis-stimulating agents in dialysis-treated and non–dialysis-treated patients with CKD is avoidance of transfusions and improved quality of life**(Imoagene-Oyedeji et al, 2006).**

There are no controlled studies demonstrating improvement in CVD, quality of life, or the need for transfusions in transplant recipients.

Prospective interventional studies are needed to define the benefits of anemia treatment on posttransplantation CVD and other clinically meaningful outcomes.
(Anushree C. Shirali and Margaret J. Bia, et al, 2008)

Hyperhomocysteinemia

Several studies have documented that hyperhomocysteinemia is an independent risk factor for CVD in transplant recipients **(Ducloux et al, 2001).**

Controlled trials in the nontransplantation setting have shown no benefit to treatment of hyperhomocysteinemia **(Bonaa et al, 2006).**

Results of the ongoing Folic Acid for Vascular Outcome Reduction in Renal Transplantation (FAVORIT) study will provide definitive evidence regarding the benefit of treatment in transplant recipients **(Bostom et al, 2006).**

C-Reactive Protein

An elevated concentration of C-reactive protein (CRP) is independently associated with increased risk for CVD events in transplant recipients **(Winkelmayer et al, 2004).**

This finding is consistent with studies in the general population demonstrating an association between CRP and ischemic heart disease.

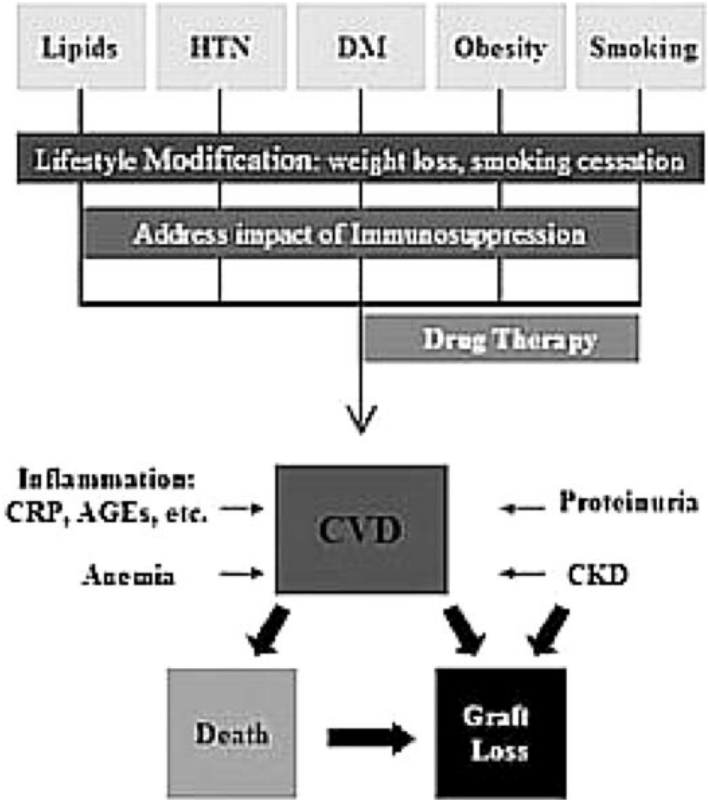
CRP levels were lowered with the use of statins, and this reduction in CRP was associated with a reduced risk for CVD independent of the lipid-lowering effect **(Ridker et al, 2005).**

Further studies are warranted to determine the role of targeted therapies to lower the levels of inflammatory markers to reduce CVD risk**. (John S. Gill,2008)**

Summary of risk factors:

A summary of factors associated with CV risk and their management is depicted in Figure(13). Although there is good evidence documenting the high incidence of CVD in RTR and the risk factors involved, only one trial (the ALERT study) has addressed whether reduction in these risk factors improves patient or allograft survival; therefore, most recommendations for prevention and treatment are extracted from studies in the CKD and general populations.
(Anushree C. Shirali and Margaret J. Bia,etal2008)

Figure (13) A summary of factors associated with CV risk and their management



Chapter Five

Cardiovascular changes in renal transplantation in children

A successful kidney transplant remains the most effective renal replacement therapy for children with end-stage renal failure. **(Salvatierra et al, 2002).**

During the last two decades renal transplantation has become routine treatment for uremic children.

However, there are many technical, immunologic, metabolic and psychological factors that make the results in children and adolescents different from those in adults.**(Najarian et al, 2000).**

A major difference between children and adults relates to the causes of ESRD; structural abnormalities of urinary tract and focal segmental glomerulosclerosis with its high risk with recurrence predominates in pediatric patients.Pediatric renal transplantation presents a number of challenges, especially in the younger age group. Graft and patient survival were often reported to be not so good in young recipients compared with older children and adults, but the results have been improved **(Ettenger , 2004).**

Long-term consequences of cardiac alteration in children with chronic renal failure and after renal transplantation are largely unknown. In chronic uremia, cardiomyopathy manifests itself as systolic dysfunction, concentric left ventricular hypertrophy (LVH) or left ventricular dilatation. **(Alfrey et al, 2004)**

The correction of uremic state by renal transplantation leads to normalization of left ventricular contractility, regression of LVH and improvement of cavity volume and so dialysis patients with uremic cardiomyopathy would benefit from renal transplantation.

Cardiac abnormalities are observed in most children and adolescents with ESRD after renal transplantation. These are important causes of morbidity and mortality in this population. In pediatric patients who died in Europe on renal replacement therapy between 1987 and 1990, a cardiovascular cause of death was noted in 51% of dialyzed and 37% of transplanted subjects **(Ehrich , 1992).**

Cardiac alterations appear to be less prevalent in pediatric than in adult patients with CRF, but no recent comprehensive study on their frequency has been published in the pediatric age group. **(Scharer , 1999).**

In adult patients the myocardial lesions induced by CRF are often accompanied by cardiovascular risk factors such as atherosclerosis, essential hypertension, diabetes, myocardial infarction or endocarditis, which are rarely observed in the young. As these factorsbecome more and more relevant with advancing age, early recognition of cardiac abnormalities and preventive measures are imperative in children with CRF and after transplantation **(Scharer , 1999).**

The development of heart failure and uremic cardiomyopathy is partially explained by hypertension, diabetes mellitus, anemia, hypoalbuminemia or hyperparathyroidism. Unrecognized volume overload and the arteriovenous access may also contribute to left ventricular dilatation. Inadequate dialysis may predispose to cardiomyopathy, particularly as uremia per se has an adverse impact on cardiac myocytes.
(Weisenee , 1993).

Renal transplantation will correct uremia, anemia, hypoalbuminemia, hyperparathyroidism and volume overload, but other risk factors may persist, such as high blood pressure, ischemic heart disease, hyperlipidemia, functioning arteriovenous access and diabetes mellitus **(Kasiske , 1988).**

After renal transplantation, left ventricular contractility improves in selected patients with systolic dysfunctions, even in those with severe symptomatic disease. Some investigators have demonstrated improvement in LVM and volume following transplantation while others have not. **(Sahagun , 2001)**

The long-term outcome of pediatric renal transplantation recipients has improved dramatically in the past 3 decades, as a result of the use of more potent immunosuppressive agents and a decline in mortality from infections.

However, the expected life span is shortened, compared with an age-matched population, mostly as a result of accelerated cardiovascular disease (CVD). Heart disease is the second most common cause of death in children after infection, and is the leading cause of death in young adults who have undergone renal transplantation.**(McDonald et al, 2004)**

These children in many cases can lead a full and normal life, but they may have a 10-fold increased risk for cardiac death compared with their peers. Although the cardiovascular morbidity and mortality in renal transplant recipients are much lower than in dialysis patients, they still remain unacceptably high.
(Parekh et al, 2002)

The clinical characteristics of childhood-onset renal insufficiency are very different from those of adult-onset disease; therefore, risk factors and markers for CVD in children and young adults who are living with a kidney transplant need to be assessed .Research efforts and resources now are being invested in studying the causes and treatment strategies of CVD in adult transplant recipients **.**
(Levey et al,1998)

Some of the traditional risk factors for cardiac disease and death, such as

Hypertension
Obesity
Leftventricular hypertrophy (LVH)
Diabetes
Hyperlipidemia
Hyperhomocysteinemia are more common in renal transplant recipients.
(Mitsnefes et al, 2004).

This may be due to persistence of a problem that predated transplantation or may result from renal insufficiency or the use of immunosuppressive medications **(Jardine et al, 2005).**

Other potential risk factors for heart disease are emerging, such as evidence of inflammation (elevated C-reactive protein [CRP] and fibrinogen) ,
cardiac markers (troponins, B-type natriuretic protein [BNP], and N-terminal pro-BNP) **(Lipshultz et al, 2003)**

And other factors, such as lipoprotein (a), Elevated calcium _phosphate product, and cardiac calcifications **. (Tsimikas et al, 2005)**

The prevalence of these risk factors has not been studied in the pediatric renal transplantation population.Many studies have shown that risk factors for CVD are common in adults with renal failure and after transplantation.

Although cardiovascular mortality is relatively high in pediatric renal transplant recipients, it does not necessarily follow that the same risk factors are to be found in children and young adults. **(Jardine et al, 2005)**

Most adults with renal failure have established atherosclerosis or clinical cardiac abnormalities before reaching ESRD, and in some,diabetes or chronic hypertension is the cause of renal impairment .
The clinical characteristics of childhood-onset renal insufficiency are very different from those of adult-onset disease; therefore, risk factors and markers for CVD in children and young adults who are living with a kidney transplant need to be assessed. **(Mitsnefes et al, 2004)**

Traditional Risk Factors

Hypertension

Hypertension was a common finding in the examined population, with more than half of the patients taking antihypertensive medications and 13% with uncontrolled hypertension, which mostly was systolic.

These frequencies are slightly lower than those noted in previous studies of pediatric renal transplant recipients, possibly as a result of the lower prevalence of obesity and that all patients in our group are white **(Shatat , Flynn,2005).**

It has been suggested that lowering BP goals below the 90th percentile, or below 120/80, in adults should be recommended in patients with CKD to decrease risk for CVD, as well as to slow the decline of renal graft function **(Lurbe E. et al, 2004)**

With this goal in mind,38% of patients had elevated SBP and 12% had elevated DBP. Inpatients with chronic renal disease, office BP measurementsmay underestimate the prevalence of hypertension. Ambula- tory BP monitoring is more sensitive and also may correlate better with LVMI in children **(Kimball et al, 2003).**

Obesity

Surprising, they did not find a high prevalence of obesity in our patients; in fact, only one individual fell into that category, although 18% of patients were defined as overweight.Physical conditioning, assessed by the 6-min walk, was acceptable in most patients, but lack of regular physical activity was associated with a higher BMI.
Of note, 17% of patients were underweight, either children with a BMI ≤5th percentile or young adults with a BMI of ≤18.5, which also may be associated with a higher risk for all-cause and cardiovascular mortality.
(Rachel Becker-Cohen et al, 2006).

Hyperlipidemia

Hyperlipidemia in pediatric renal transplantation recipients is well described.

Previous studies have shown a prevalence of 50%, even in studies that were performed as recently as 2000. **(Silverstein et al,2000)**

In contrast,they report a much lower frequency of lipid abnormalities. Even when applying the limit of 100 mg/dl LDL cholesterol concentrations (2.59 mmol/L), 70% of patients had normal values. **(Bilenko et al, 2005)**

Significantly higher serum total and LDL cholesterol concentrations were seen in patients who were treated with cyclosporine compared with those who were taking tacrolimus-based immunosuppression. This has been noted in studies that demonstrated improved lipid profiles after changing immunosuppression from cyclosporine to tacrolimus. **(Artz et al, 2004).**

In previous studies that examined dyslipidemia in transplant recipients, most or all of the patients were treated with cyclosporine, whereas the majority of our patients are receiving tacrolimus.This, as well as relatively normal BMI in our patients and low-dosage alternate-day corticosteroid treatment, may account partly for the differences in blood lipids compared with previous studies.
(Colak et al, 2002)

Diet also may play a role; although eating habits in Israel among Jews are closer to the Western rather than Mediterranean diet, saturated fat and cholesterol intake is lower and monounsaturated fat intake is higher among Arabs.

Looking separately at these two ethnic populations, there was a trend toward slightly lower LDL cholesterol levels in Arab patients, which did not reach statistical significance.**(Bilenko et al ,2005)**

Hyperhomocysteinemia

Hyperhomocysteinemia is common in renal insufficiency and after renal transplantation, with an inverse relationship between serum homocysteine concentration and GFR **(Feinstein et al ,2002).**

Although it is clear that elevated homocysteine concentration in adults with renal disease is associated with CVD, whether this just may be a surrogate marker for the degree of renal compromise or an independent risk factor remains to be established.Folic acid and vitamin B12 supplementation have been shown to decrease homocysteine levels in adults with chronic renal insufficiency and after renal transplantation.

They previously showed that folic acid supplementation can normalize homocysteine levels in children who are on hemodialysis .
(Rachel Becker-Cohen et al, 2006).

However, it remains unclear whether treatment with folic acid to decrease homocysteine concentrations in patients with renal disease can modify the risk for heart disease.

Hyperhomocysteinemia was a common finding in young renal transplant recipients in this study, despite normal vitamin B12 and folate concentrations in the majority of patients; the relationship to GFR is shown clearly.
(Mitsnefes et al ,2004).

Drug effects

Cyclosporine treatment was associated with elevated total and LDL cholesterol, hyperhomocysteinemia, but not BPI. Conversely,the patients who developed diabetes all were on tacrolimus therapy.These possibly deleterious effects on cardiovascular health need to be considered when choosing immunosuppressive therapy **(Artz et al ,2004)**

Chronic anemia in renal transplant recipients may be overlooked as a cause of LVH that contributes to cardiac morbidity and mortality **(El-Husseini et al, 2004).**

Treatment with recombinant erythropoietin of anemic patients who have ESRD has become the standard of care in Western countries.Post transplantation anemia, however, is a surprisingly frequent finding, even in patients with reasonable graft function, and occurs in children and young adults, as we demonstrate in our study**. (Rigatto et al, 2003)**

Anemia

Chronic anemia in renal transplant recipients may be overlooked as a cause of LVH that contributes to cardiac morbidity and mortality . Treatment with recombinant erythropoietin of anemic patients who have ESRD has become the standard of care in Western countries**. (Sheashaa et al ,2004)**

Post transplantation anemia, however, is a surprisingly frequent finding, even in patients with reasonable graft function, and occurs in children and young adults. Other causes of anemia need to be explored, such as iron deficiency or anemia as a result of treatment with antimetabolites**.(Foley et al, 2003)**

However, many renal transplant patients require erythropoietin therapy to restore hemoglobin to normal or near-normal levels.

Left ventricular hypertrophy

Cardiac disease has extensively been investigated in adult patients, but to a much lesser extent in children and adolescents with CRF and after renal transplantation. LVH is a strong and independent predictor of death and cardiac failure. **(Scharer , 1999).**

Concentric LVH usually results from LV pressure overload and is the most frequent manifestation of uremic cardiomyopathy in chronic uremia, being present in 42% of patients on starting ESRD therapy **(Foley et al, 1995).**

The degree of LVH is associated with hypertension and anemia. **(Harnett et al, 1995).**

Correction of uremia by renal transplantation was associated with 17% improvement in LVMI, similar to the degree of regression of hypertrophy observed on partial correction of anemia with erythropoietin.
The degree of regression of LVH may have been limited by hypertension, as a significant association was observed between fall in blood pressure and fall in LVMI. They reported that the degree of improvement in LV contractility after transplantation was 56% increase in fractional shortening and it was larger than that expected for correction of anemia **(Parfrey et al,1995).**

Reduction of the LVMI after renal transplantation has not been a universal observation, more recent studies did not find significant change in LVMI following transplantation **(McGregor et al, 2000)**

Also Mitsnefes et al. showed that there was no significant difference in the mean values for the LVMI in children and adolescents while on dialysis and after renal transplantation. **(Mitsnefes et al ,2004).**

The most common echocardiographic abnormality was the LVH (47.9%). This prevalence was higher in comparison to other studies as in the only large study performed by EDTA in children which reported incidence of 22% of post-transplant LVH **.(Johnstone et al, 1996).**

But recent reports indicate a high prevalence of LVH in children on dialysis and after renal transplantation, Mitsnefes et al. found that the prevalence of LVH was 56% among children and adolescents after renal transplantation.
(Mitsnefes et al ,2004).

On the other hand, Johnstone and his colleagues reported that LVH was more frequent and more severe in children after transplantation compared with those on hemodialysis or in preterminal renal failure.**(Johnstone et al, 1996).**

Left atrial enlargement was a common abnormality among our cases (31.5%) and this was also reported by others Rysz et al. concluded that abnormal function of left atrium in the course of uremia is not fully corrected after renal transplantation despite elimination of many cardiovascular complications observed in chronic renal disease**. (Rysz et al, 2002)**

Systolic dysfunction was also a prevalent abnormality in our series (13.7%). Harnett and his colleagues found that systolic dysfunction is present in 16% of patients on the initiation of ESRD therapy and they reported that it is a significant predictor of the development of cardiac failure and of mortality
(Harnett et al,1995).

The effect of pretransplant dialysis on the left ventricular function and structure had been documented previously as many risk factors associate dialysis as hypertension, hypervolemia, anemia, arteriovenous fistula, pericarditis, endocarditis, stimulation of the rennin–angiotensin system, sympathetic over-activity, hyperparathyroidism, metabolic acidosis, uremic toxins, acute phase reactant, B2 microglobulin, and hyperhomocysteinemia.The development of LVH during dialysis may persist after transplantation **(Scharer et al, 1999).**

Alvares et al. found an increased LVMI in children with prior hemodialysis before renal transplantation, especially if dialysis lasted for more than 2 yr and they concluded that although cardiac hypertrophy and dilatation is reversible after renal transplantation, it would seem that children may benefit from an earlier transplantation.**(Alvares et al, 1998)**

After transplantation, LVH is mainly dependant on the presence of hypertension.

A significant association was observed between fall in blood pressure and fall in LVMI. **(Peteiro et al, 1994)**

Also Mitsnefs et al found by multivariate analysis that hypertension was independent predictor for increased LVMI after renal transplantation in children and adolescents and they concluded that control of blood pressure might be an important factor in regression or prevention of progression of LVH in these patients. **(Mitsnefes et al ,2004).**

Also anemia was reported as independent predictor for LVH Alvares and his colleagues reported that correction of hematocrit correlated with reduction of LVMI after renal transplantation in children followed-up six children for 12 months after successful renal transplantation; the children showed persistent anemia despite dramatic improvement in biochemistry and they found no significant change in cardiovascular function. **.(Alvares et al, 1998)**

They concluded that anemia is the more dominant influence on cardiovascular function in end stage renal failure **(Morris et al, 1994).**

In conclusion LVH is a common problem among children and adolescents after renal transplantation. Early transplantation, control of hypertension and correction of anemia may bebeneficial regarding left ventricular function and structure.**(Amr A. El-Husseini et al, 2004)**

Patients and methods

Patients and methods

In this study 110 Egyptian patients were enrolled where they were divided into 6 groups :

Group I consists of 30 patients below age of 18years who had renal transplantation more than 6 months and less than one year duration.

Group II consists of 30 patients above age of 18years who had renal transplantation more than 6 months and less than one year duration .

Group III consists of 20 patients below age of 18years who were chronic renal failure patients on regular hemodialysis.

Group IV consists of 20 patients above age of 18years who were chronic renal failure patients on regular hemodialysis.

Group V consists of 5 subjects below age of 18years with normal kidney function.

Group VI consists of 5 subjects above age of 18years with normal kidney function.

A full medical history was taken from every patient.

All the patients were subjected to full clinical examination.

In all cases, we recorded age, body mass index (BMI) which is measured by body weight (in kg) divided by the square of their height (in m^2). The formulas universally used in medicine produce a unit of measure of kg/m^2 *(Gadzik J.,2006)*.

Complete blood count was measured by the automatic multiparameter blood cell counter.

Patients of group I and II had hemoglobin before transplantation and 6 months after transplantation.

Trans- thoracic echocardiography was done to all our patients

Patients of group I and II had trans- thoracic echocardiography before transplantation and 6 months after transplantation.

We measured ejection fraction(EF) before and after transplantation and recorded degree of improvement by (EF improvement percentage)

Exclusion criteria:

1- Patients older than sixty years old.

2- Patients with ischemic heart diseases.

3- Patients with diabetes mellitus.

4- Patients with liver cirrhosis.

5- Patients with COPD.

6- Patients with serum creatinine more than 1.5mg/dl after transplantation.

Statistical Methods:

Statistical Package for social science (SPSS) program version 9.0 was used for analysis of data. Data was summarized as mean, SD . T test for dependant and independent variables was used for analysis of two quantitative data. One Way ANOVA test was done for analysis of more than two variables followed by post HOCC test for detection of significance. Pearson correlation was also done.

P-value is considered significant if < 0.05*.

Master Table

Table (8)

Group I consists of 30 patients below age of 18years who had renal transplantation more than 6 months and less than one year duration.

NO	Age / years	sex	Durartion Of HDX	Weigth	heigth	BMI	Hg/pre	LVED/ PRE	LVES/ PRE	FS/ PRE	EF% PRE	Hg/ Post	Cr/ post	LVED/ post	LVES/ post	FS/ post	EF% post
1	8	M	3m	22	100	22	6.4	5.2	3.4	35	64	13	0.8	4.7	2.1	56	80
2	3.5	M	no	15	70	30.6	8.2	4.2	3	35	59	14.5	0.5	3.9	2.3	40	70
3	10	M	6m	25	100	25	7.5	4	2.7	30	65	15	0.9	4	2.7	30	65
4	14	F	3m	30	120	20.8	6.5	4.1	3	27	54	12.5	1.2	3.9	2.3	40	70
5	12	M	6m	25	100	25	7.3	3.4	3	29	55	14.4	1.4	4	2.7	35	65
6	10	M	6m	30	100	30	8.2	4.2	2.2	38	65	13.5	1.1	4	2.1	46	75
7	8	M	8m	23	85	31.8	8.5	2.8	1.9	32	45	12.5	0.8	3.5	2.1	40	65
8	9	M	12m	25	10	25	7.5	4.2	2.2	38	65	13.8	0.9	3.8	1.9	30	75
9	10	M	12m	22	90	27.1	9.1	5.2	3.4	35	64	14.2	0.8	4.7	2.1	56	80
10	8	F	6m	18	70	32.6	8.3	3.7	2.6	30	65	13.6	0.4	3.9	2.3	40	72
11	4	F	4m	20	85	27.68	6.5	4.8	2.8	40	65	12.9	0.6	3.47	1.7	51	80
12	6	M	6m	22	90	27.16	6	5.8	4	32	59	13.9	0.7	5.3	3.1	40	70
13	6	F	8m	18	80	28.12	6.5	5.7	4.1	26	54	14	0.8	4.8	2.3	35	66
14	8	F	6m	30	95	23.24	7.2	4.6	2.6	43	65	14.2	1	4.4	2.7	38	69
15	5	F	9m	18	80	28.12	6.5	4.2	2.6	39	70	14.5	0.8	3.5	1.6	54	86

NO	Age	sex	Durartion Of HDX	Weigth	heigth	BMI	Hg/pre	LVED/ PRE	LVES/ PRE	FS/ PRE	EF% PRE	Hg/ post	Cr/ post	LVED/ post	LVES/ post	FS/ post	EF% post
16	7	M	10m	20	75	35.5	7.2	5.7	4	30	56	13.5	0.7	5.2	3.1	40	70
17	2	M	6m	8	50	32	7.5	3.7	2.6	30	65	15	0.5	3.9	2.3	40	72
18	13	M	10m	35	110	28.9	5.5	4.3	3.2	25	51	12.8	0.9	3.8	2.1	35	65
19	9	F	6m	35	125	22.4	6.3	4.3	3.3	24	47	14.5	1.5	4	2.7	30	65
20	12	F	9m	50	140	25.5	7.5	6.1	4.7	23	45	13.6	0.8	4.8	3.1	34	62
21	13	M	No	45	135	24.69	6.5	4.8	3.1	34	62	12.9	1	3.8	1.8	52	80
22	12	F	6m	33	120	22.9	6.2	6	3.7	38	65	14.2	1.2	5.2	3.1	40	70
23	15	F	1m	50	156	20.5	6.5	5.2	3.7	29	56	12.6	1.1	4.3	2.6	40	70
24	14	f	6m	40	120	27.7	6.8	4.9	2.9	34	65	13.2	1.2	4.2	2.6	39	70
25	12	M	6m	50	140	25	6.2	4.9	2.8	35	59	14	0.8	4.2	2.1	40	68
26	15	F	4m	60	150	26.6	5	5	3.4	31	60	13	1	4.7	2.1	56	80
27	14	M	No	48	160	18.7	7	5.3	3.6	35	60	15	1	4.3	2.4	46	78
28	12	M	6m	30	120	20.8	6.5	4.3	3.2	25	51	14	0.9	4.3	2.3	37	70
29	8	M	6m	30	120	20	8	5.4	3.4	37	66	15	0.8	4.2	2.7	37	67
30	15	M	4m	40	150	17.7	5.5	4.2	2.3	40	70	16	1.5	4.3	2.3	44	75
												14			2.4	46	78

Table (9)

Group II consists of 30 patients above age of 18years who had renal transplantation more than 6 months and less than one year duration .

NO	Age	sex	Durartion Of HDX	Weigth	heigth	BMI	Hg/pre	LVED/ PRE	LVES/ PRE	FS/ PRE	EF% PRE	Hg/ post	Cr/ post	LVED/ post	LVES/ post	FS/ post	EF% post
1	25	M	10m	70	176	22.59	7.5	5.5	3.5	30	52	17	1.3	5.3	3.4	36	61
2	20	M	6m	80	170	27.68	6.5	6.2	5	20	40	13.5	1.5	5	3.6	40	63
3	33	M	36m	85	167	30.4	8.5	6.3	5	20	40	11.5	1.2	4	2.7	30	65
4	30	F	24m	60	162	22.86	7.5	7.1	5.1	28	54	13.2	1	5.3	3.6	40	63
5	35	M	12m	80	173	26.72	8.2	5	3.4	31	60	14.2	1.2	4.8	3.2	33	61
6	32	M	12m	65	175	21.22	6.3	5.8	4	32	59	11.9	1.3	5.5	3.7	33	61
7	38	F	6m	68	165	24.97	5.9	5.2	3.4	35	64	12.6	1.2	4.1	2.4	42	75
8	26	F	7m	60	159	23.73	5.5	5.7	4.1	26	54	17	1.5	5.3	3.7	30	55
9	25	M	12m	75	174	24.77	5.2	7.4	6.3	19	26	12	1.3	5.3	3.7	30	55
10	20	M	18m	63	165	23.12	6.3	6.1	4.7	23	25	11.5	1.2	6	3.9	34	62
11	30	M	7m	75	177	23.93	8.5	5.7	4	30	56	13.5	1.2	4	2.7	37	65
12	27	M	10m	75	180	23.13	7.5	5.5	3.5	30	52	12.6	1.5	4.3	2.7	37	67
13	22	M	12m	80	168	28.3	9.5	6	3.4	40	68	11.3	1.3	5.3	3.1	40	70
14	25	M	5m	65	160	25.39	6.5	4.86	3.2	34	63	13.2	0.9	4.2	2.8	40	68
15	21	M	10m	55	164	20.44	7.3	4.3	2.6	40	62	11.2	1.5	5.6	3.1	45	75

NO	Age	sex	Durartion Of HDX	Weigth	heigth	BMI	Hg/pre	LVED/ PRE	LVES/ PRE	FS/ PRE	EF% PRE	Hg/ post	Cr/ post	LVED/ post	LVES/ post	FS/ post	EF% post
16	25	M	12m	62	160	24.21	6.8	6.4	3.5	26.47	45	12.5	1	4.3	2.7	40	67
17	26	M	18m	89	175	29	6.2	5.9	3.8	35	64	13.5	1.2	5.2	2.9	37	74
18	27	M	7m	70	165	25.7	8.3	5.2	3.5	33	61	10.3	1	5.8	3.6	37	66
19	38	M	18m	89	170	30.79	7.9	5.3	3.2	35	65	12.5	1.2	4.4	2.7	38	69
20	26	F	7m	75	165	27.54	7.5	5.5	3.5	30	52	12.6	1.2	4.3	2.7	37	67
21	21	M	18m	55	150	24.4	6	6.3	5	20	40	14.2	0.9	4	2.7	30	65
22	23	M	12m	66	165	24.2	5.5	7.4	6.3	19	26	16	1.5	5.3	3.7	30	55
23	22	M	18m	68	170	23.5	4.5	7.1	5.1	28	54	11.5	1.9	5.3	3.6	40	63
24	34	M	10m	70	165	25.7	8	5.5	3.5	30	52	15	0.9	4	2.7	37	65
25	21	M	12m	75	160	29.2	7.5	5.7	4	30	56	16	1.1	5.3	3.4	36	61
26	35	M	12m	80	175	26.12	7	6	3.4	40	68	18	1.3	4.3	2.7	37	67
27	21	M	15m	50	160	19.5	6.5	5.9	3.8	35	64	12	1	5.2	2.9	40	74
28	22	M	8m	45	155	18.73	6	5.3	3.5	33	61	11.5	1.2	4.4	2.7	38	69
29	21	F	10m	50	154	21	6.3	6.3	5.1	19	38	13.5	0.9	5.5	3.5	30	52
30	32	M	18m	60	165	22	5.7	6.3	5	20	40	12.5	1	5.5	3.6	40	63

Table (10)

Group III consists of 20 patients below age of 18years who were chronic renal failure patients on regular hemodialysis

NO	Age /year	sex	Durartion Of HDX/year	Weigth	heigth	BMI	Hg/dl	LVED	LVES	FS	EF%
1	8Y	M	2Y	25	80	39	9	5.2	3.4	35	64
2	10Y	M	4Y	28	90	34.5	10	2.8	1.9	32	45
3	14Y	F	6Y	30	110	24.79	11	4.2	3	35	59
4	12Y	F	3Y	35	120	24.3	8.5	4.1	3	27	54
5	10Y	F	4Y	30	130	17.17	7.5	3.4	3	29	55
6	8Y	M	1.5Y	23	90	28.39	8	5.7	4.1	26	54
7	9Y	M	2Y	20	100	20	9	4.3	3.2	25	51
8	12Y	M	3.5Y	35	120	24.3	10	4.3	3.3	24	47
9	13Y	M	4.5Y	40	130	23.66	11	5.2	3.7	29	56
10	14Y	F	4Y	45	140	22.95	7.5	4.9	2.8	35	59
11	15Y	F	3.5Y	50	145	23.76	8.5	4.3	3.2	25	51
12	10Y	F	2.5Y	45	135	24.69	9	5.7	4.1	26	54
13	11Y	M	5.5Y	42	130	24.85	10	4.2	2.2	38	65
14	12Y	M	3.5Y	35	132	19.9	11	4.3	3.3	24	47
15	13Y	M	2.5Y	32	125	20.48	8.5	4.8	3.1	34	62
16	10Y	F	2Y	36	120	25	7.5	6	3.7	38	65
17	8Y	M	3.5Y	40	100	40	6.5	5.2	3.7	29	56
18	6Y	F	2Y	25	90	30.86	8.5	5.4	3.4	37	66
19	8Y	M	2.5Y	30	80	46.87	7.5	5.3	3.6	35	60
20	10Y	M	4Y	35	85	48.44	5.5	4.9	2.8	35	59

Table (11)

Group IV consists of 20 patients above age of 18years who were chronic renal failure patients on regular hemodialysis.

NO	Age	sex	Durartion Of HDX/year	Weigth/ Kg	Height/ cm	BMI	Hg/dl	LVED	LVES	FS	EF%
1	28	F	2	40	134	22.2	8.9	5.9	4.3	20	35
2	32	F	7	44	146	20.6	7.5	4.6	2.9	33	57
3	31	F	11	46	152	20	11.7	5.2	3.8	30	52
4	46	F	9	75	162	28.6	9	5.9	3.8	30	52
5	47	M	3	70	176	22.6	11	5.9	4.2	33	57
6	60	F	10	48	160	18.8	10.2	4.9	3.8	32	55
7	54	F	12	80	168	28.4	10.3	5.8	3.8	30	51
8	60	M	3	90	178	28.5	9.5	6	5.6	18	31
9	42	M	8	72	169	25.3	8.9	5.6	5.4	34	59
10	58	F	15	40	164	15	8.5	5.4	3.9	27	46
11	60	M	4	92	168	33	13.4	6.7	5.3	28	48
12	37	M	12	57	172	19.3	7.4	5.6	3.6	27	46
13	54	M	5	60	163	22.6	10.9	4.4	2.4	35	60
14	25	F	3.5	30	142	14.8	5.7	4.6	2.5	29	50
15	30	F	10	46	160	18	11.3	5.6	3.4	28	48
16	32	F	2.5	57	162	22	9.6	5.5	3.5	30	52
17	25	F	11	59	160	23	9.6	5.4	3	31	53
18	33	F	15	47	162	18	7.5	5.9	4.2	27	46
19	58	M	18	94	172	32	12.6	7.8	6.2	27	47
20	52	M	9	40	134	22.2	11	5.9	4.7	34	58

Table (12)

Group V consists of 5 subjects below age of 18years with normal kidney function.

NO	Age	sex	Cr	Weigth	heigth	BMI	Hg/dl	LVED	LVES	FS	EF%
1	32	M	1	86	172	29	11.9	5.3	3.6	36	61
2	33	M	0.9	100	180	31	12	5.2	2	37	63
3	25	M	0.8	80	165	23.4	15	4.8	3.1	37	63
4	27	M	1	72	176	23.3	14.2	4.5	3.2	39	67
5	34	M	0.8	62	168	22	13	5.3	3.7	41	70

Table (13)

Group VI consists of 5 subjects above age of 18years with normal kidney function.

NO	Age	Sex	Cr	Weigth	heigth	BMI	Hg/dl	LVED	LVES	FS	EF
1	13	M	0.6	40	140	20	14	4.8	3.9	41.17	70
2	12	M	0.5	30	135	16.6	15	3.8	2.8	44	75
3	10	M	0.4	35	145	16.4	13	3.9	2.9	38.2	65
4	14	M	0.6	40	150	17.7	15	4.1	2.7	42	73
5	11	M	0.7	35	135	19.2	14	4.2	2.6	44	75

Results

Table 1: Descriptive data of children with renal transplantation GroupI (30 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	2.0	15.0	9.8 ± 3.7
Duration of dialysis (yrs)	0.1	1.0	0.6 ± 0.2
Hemoglobin pre transplantation (g/dl)	5.0	9.1	6.9 ± 1.0
Weight pre transplantation (kg)	8.0	60.0	30.6 ± 12.5
Height pretransplantation (cm)	50.0	160.0	107.9 ± 28.4
BMI pre transplantation (kg/m^2)	17.7	35.5	25.8 ± 4.4
LVED pre transplantation (mm)	2.8	6.1	4.7 ± 0.8
LVES pre transplantation (mm)	1.9	4.7	3.1 ± 0.6
FS pre transplantation %	23.0	43.0	32.6 ± 5.3
EF pre transplantation %	45.0	70.0	59.7 ± 7.0
Creatinine post transplantation (mg/dl)	0.4	1.5	0.9 ± 0.3
Hemoglobin post transplantation (g/dl)	12.5	16.0	13.9 ± 0.9
LVED post transplantation (mm)	3.5	5.3	4.2 ± 0.5
LVES post transplantation (mm)	1.6	3.1	2.4 ± 0.4
FS post transplantation %	30.0	56.0	41.7 ± 7.6
EF post transplantation %	62.0	86.0	71.9 ± 6.1

Table 2: Descriptive data of adult with renal transplantation GroupII (30 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	20.0	38.0	26.8 ± 5.6
Duration of dialysis (yrs)	0.2	1.5	0.9 ± 0.4
Hemoglobin pre transplantation (g/dl)	4.5	9.5	6.9 ± 1.2
Weight pre transplantation (kg)	45.0	89.0	68.7 ± 11.4
Height pretransplantation (cm)	150.0	180.0	166.3 ± 7.3
BMI pre transplantation (kg/m^2)	18.7	30.8	24.7 ± 3.1
LVED pre transplantation (mm)	4.3	7.4	5.9 ± 0.7
LVES pre transplantation (mm)	2.6	6.3	4.1 ± 0.9
FS pre transplantation %	19.0	40.0	29.0 ± 6.6
EF pre transplantation %	25.0	68.0	52.0 ± 12.5
Creatinine post transplantation (mg/dl)	0.9	1.9	1.2 ± 0.2
Hemoglobin post transplantation (g/dl)	10.3	18.0	13.3 ± 1.9
LVED post transplantation (mm)	4.0	6.0	4.9 ± 0.6
LVES post transplantation (mm)	2.4	3.9	3.1 ± 0.5
FS post transplantation %	30.0	45.0	36.5 ± 4.1
EF post transplantation %	52.0	75.0	64.8 ± 5.9

Table 3 : Descriptive data of children with chronic renal failure GroupIII (20 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	6.0	15.0	10.7 ± 2.4
Duration of dialysis (yrs)	1.5	6.0	3.3 ± 1.2
Hemoglobin (g/dl)	5.5	11.0	8.7 ± 1.5
Weight (kg)	20.0	50.0	34.1 ± 8.0
Height (cm)	80.0	145.0	112.6 ± 21.3
BMI (kg/m^2)	17.2	48.4	28.2 ± 9.0
LVED (mm)	2.8	6.0	4.7 ± 0.8
LVES (mm)	1.9	4.1	3.2 ± 0.6
FS %	24.0	38.0	30.9 ± 5.0
EF %	45.0	66.0	56.5 ± 6.3

Table 4 : Descriptive data of adult with chronic renal failure GroupIV (20 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	25.0	60	43.9 ± 14.1
Duration of dialysis (yrs)	2.0	18.0	8.5 ± 4.7
Hemoglobin (g/dl)	5.7	13.4	9.7 ± 1.9
Weight (kg)	30.0	94.0	59.4 ± 19.2
Height (cm)	134.0	178.0	160.2 ± 12.7
BMI (kg/m^2)	14.8	33.0	22.7 ± 5.2
LVED (mm)	4.4	7.8	5.6 ± 0.8
LVES (mm)	2.4	6.2	4.0 ± 1.0
FS %	18.0	35.0	29.2 ± 4.3
EF %	31.0	60.0	50.2 ± 7.4

Table 5 : Descriptive data of control children GroupV (5 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	10.0	14.0	12.0 ± 1.5
Hemoglobin (g/dl)	13.0	15.0	14.2 ± 0.8
Weight (kg)	30.0	40.0	36.0 ± 3.9
Height (cm)	135.0	150.0	141.0 ± 6.1
BMI (kg/m^2)	16.4	20.0	18.0 ± 1.5
LVED (mm)	3.8	4.8	4.2 ± 0.4
LVES (mm)	2.6	3.9	3.0 ± 0.5
FS %	38.2	44.0	41.9 ± 2.3
EF %	65.0	75.0	71.6 ± 4.0
Creatinine (mg/dl)	0.4	0.7	0.6 ± 0.1

Table 6 : Descriptive data of adult controls GroupVI (5 patients)

Variables	Minimum	Maximum	Mean ± SD
Age (yrs)	25.0	34.0	30.2 ± 3.7
Hemoglobin (g/dl)	11.9	15.0	13.2 ± 1.3
Weight (kg)	62.0	100.0	80.0 ± 13.5
Height (cm)	165.0	180.0	172.2 ± 5.7
BMI (kg/m^2)	22.0	31.0	25.7 ± 3.8
LVED (mm)	4.5	5.3	5.0 ± 0.3
LVES (mm)	2.0	3.7	3.1 ± 0.6
FS %	36.0	41.0	38.0 ± 1.9
EF %	61.0	70.0	64.8 ± 3.4
Creatinine (mg/dl)	0.8	1.0	0.9 ± 0.09

Table 7: Comparison between data of children before and after renal transplantation

Variables	Before renal transplantation Mean ± SD	After renal transplantation Mean ± SD	P –value
Hemoglobin n (g/dl)	6.9 ± 1.0	13.9 ± 0.9	0.0001*
LVED (mm)	4.7 ± 0.8	4.2 ± 0.5	0.0001*
LVES (mm)	3.1 ± 0.6	2.4 ± 0.4	0.0001*
FS %	32.6 ± 5.3	41.7 ± 7.6	0.0001*
EF %	59.7 ± 7.0	71.9 ± 6.1	0.0001*

P-value is significant if < 0.05*

Table 8: Comparison between data of adult before and after renal transplantation

Variables	Before renal transplantation Mean ± SD	After renal transplantation Mean ± SD	P –value
Hemoglobin (g/dl)	6.9 ± 1.2	13.3 ± 1.9	0.0001*
LVED (mm)	5.9 ± 0.7	4.9 ± 0.6	0.0001*
LVES (mm)	4.1 ± 0.9	3.1 ± 0.5	0.0001*
FS %	29.0 ± 6.6	36.5 ± 4.1	0.0001*
EF %	52.0 ± 12.5	64.8 ± 5.9	0.0001*

P-value is significant if < 0.05*

Table 9: Correlation between EF (post transplantation) and improved EF% in children with other parameters

Variables	EF (post transplantation)		Improved EF	
	R	P - value	r	P – value
Age (yrs)	- 0.1	0.7	0.1	0.5
Duration of dialysis (yrs)	- 0.1	0.8	0.2	0.3
Hemoglobin (g/dl)	- 0.1	0.7	- 0.2	0.4
BMI (kg/m^2)	- 0.1	0.6	- 0.04	0.8

Table10: Correlation between EF (post transplantation) and improved EF% in adult with other parameters

Variables	EF (post transplantation)		Improved EF	
	R	P - value	r	P – value
Age (yrs)	0.2	0.4	- 0.3	0.1
Duration of dialysis (yrs)	0.1	0.8	0.2	0.4
Hemoglobin (g/dl)	0.2	0.1	- 0.3	0.1
BMI (kg/m^2)	0.1	0.6	- 0.1	0.7

Table 11: Comparison between EF(pre & post transplantation) and improved EF % in children and adult

Variables	Children Mean ± SD	Adult Mean ± SD	P - value
EF pre transplantation (%)	59.7 ± 7.0	52.0 ± 12.5	0.005*
EF post transplantation (%)	71.9 ± 6.1	64.8 ± 5.9	0.0001*
Improved (EF %)	12.2 ± 5.1	12.7 ± 9.8	0.8

P-value is significant if < 0.05*

Table 12: Comparison between data of children after renal transplantation, chronic renal failure and controls

Variables	After renal transplantation Mean ± SD	CRF Mean ± SD	Controls Mean ± SD	P -value
Hemoglobin (g/dl)	13.9 ± 0.9[a]	8.7 ± 1.5[b]	14.2 ± 0.8[a]	0.0001*
LVED (mm)	4.2 ± 0.5[a]	4.7 ± 0.8[b]	4.2 ± 0.4[a]	0.02*
LVES (mm)	2.4 ± 0.4[a]	3.2 ± 0.6[b]	3.0 ± 0.5[b]	0.0001*
FS %	41.7 ± 7.6[a]	30.9 ± 5.0[b]	41.9 ± 2.3[a]	0.0001*
EF %	71.9 ± 6.1[a]	56.5 ± 6.3[b]	71.6 ± 4.0[a]	0.0001*

P-value is significant if < 0.05*
Different symbol indicate significance

Table 13: Comparison between data of adult after renal transplantation, chronic renal failure and controls

Variables	After renal transplantation Mean ± SD	CRF Mean ± SD	Controls Mean ± SD	P -value
Hemoglobin (g/dl)	13.3 ± 1.9[a]	9.7 ± 1.9[b]	13.2 ± 1.3[a]	0.0001*
LVED (mm)	4.9 ± 0.6[a]	5.6 ± 0.8[b]	5.0 ± 0.3[a]	0.001*
LVES (mm)	3.1 ± 0.5[a]	4.0 ± 1.0[b]	3.1 ± 0.6[a]	0.0001*
FS %	36.5 ± 4.1[a]	29.2 ± 4.3[b]	38.0 ± 1.9[a]	0.0001*
EF %	64.8 ± 5.9[a]	50.2 ± 7.4[b]	64.8 ± 3.4[a]	0.0001*

P-value is significant if < 0.05*
Different symbol indicate significance

Statistical Methods:

Statistical Package for social science (SPSS) program version 9.0 was used for analysis of data. Data was summarized as mean, SD . T test for dependant and independent variables was used for analysis of two quantitative data. One Way ANOVA test was done for analysis of more than two variables followed by post HOCC test for detection of significance. Pearson correlation was also done.
P-value is considered significant if < 0.05*.

Figures

Fig 1 : Comparison between hemoglobin of children before and after renal transplantation

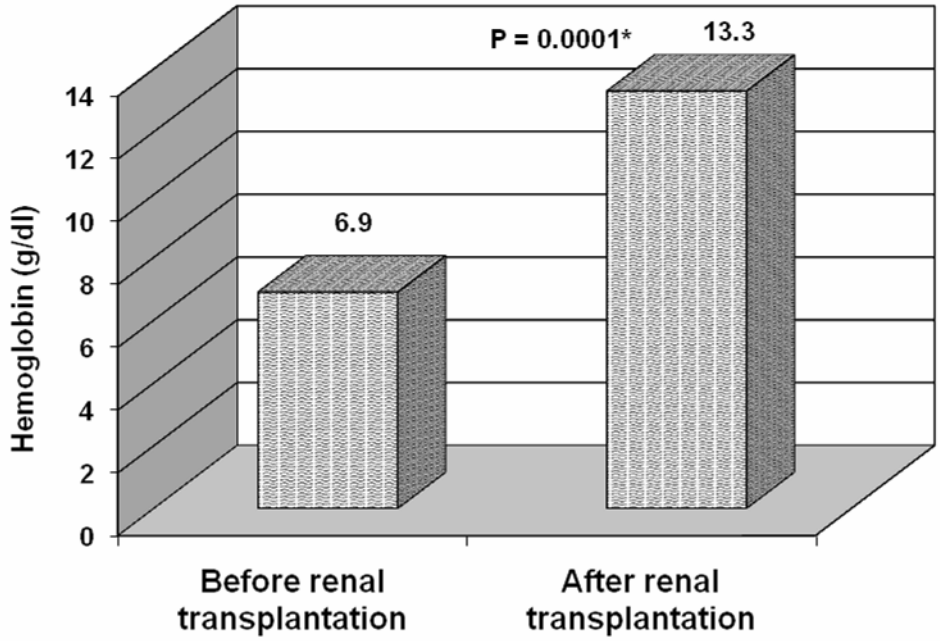


Fig 2 : Comparison between LVED of children before and after renal transplantation

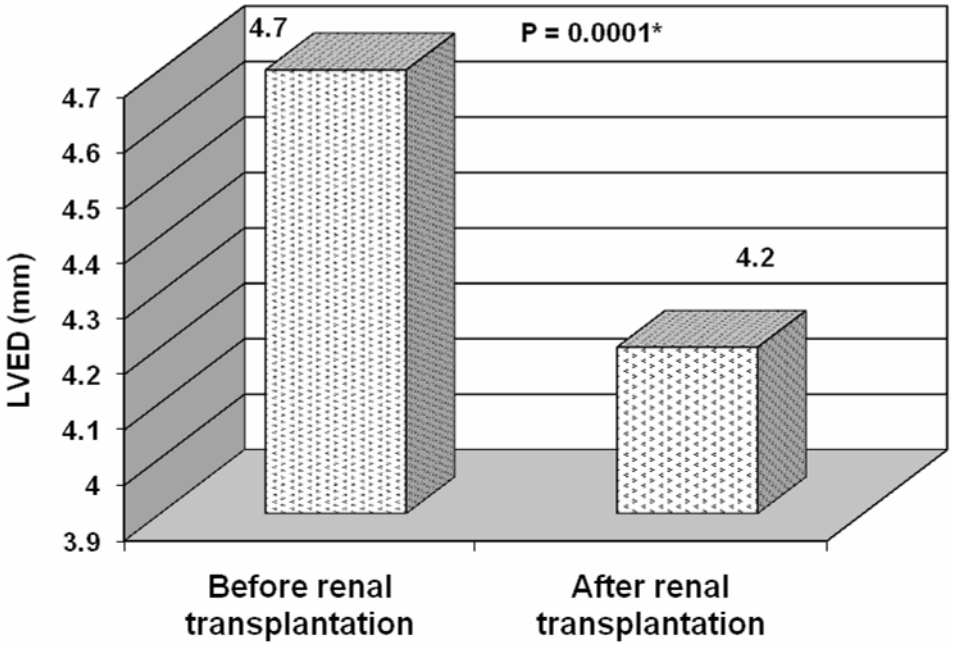


Fig 3 : Comparison between LVES of children before and after renal transplantation

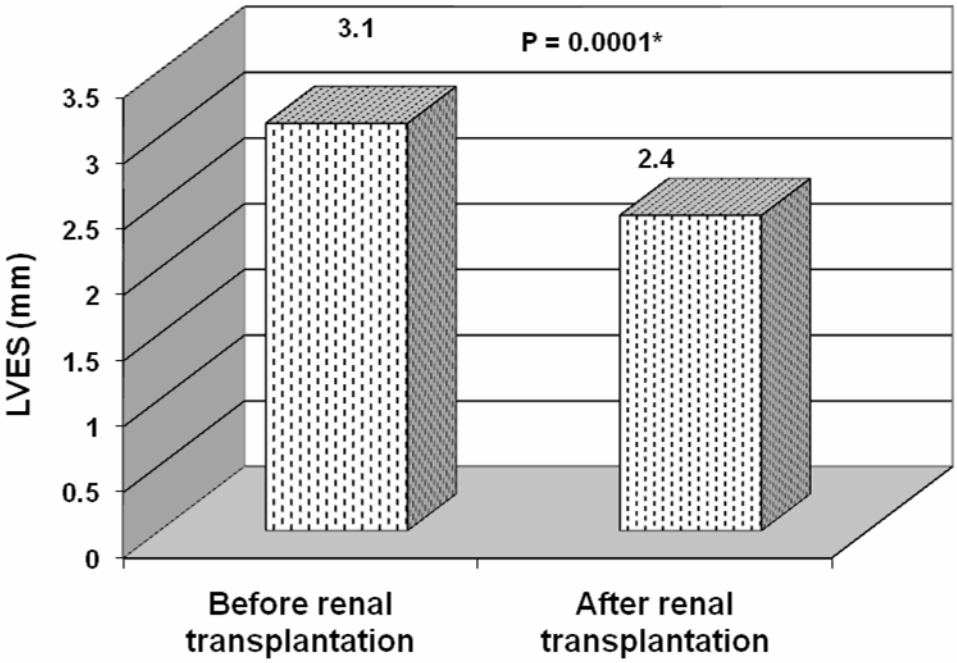


Fig 4 : Comparison between FS of children before and after renal transplantation

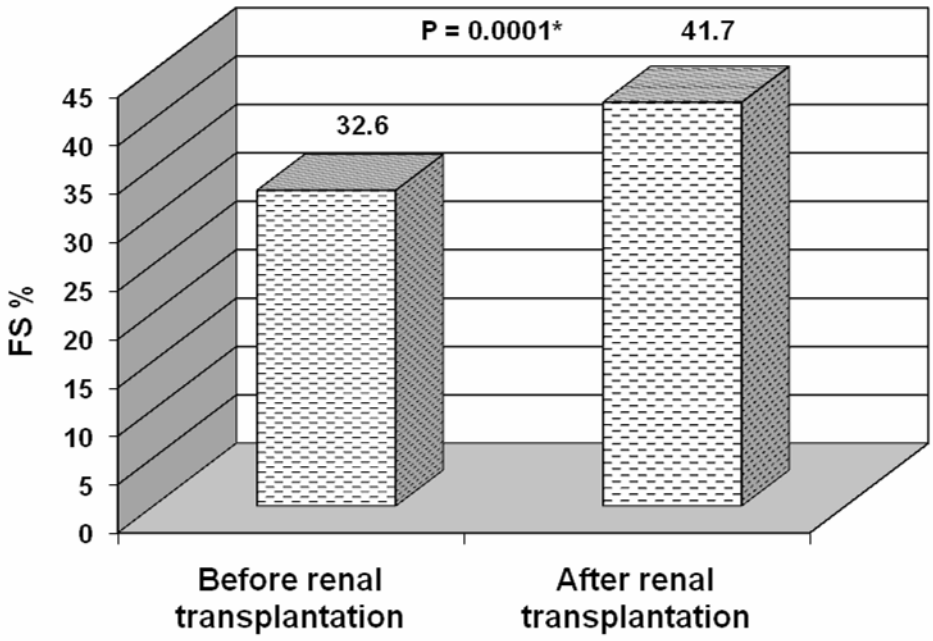


Fig 5: Comparison between EF of children before and after renal transplantation

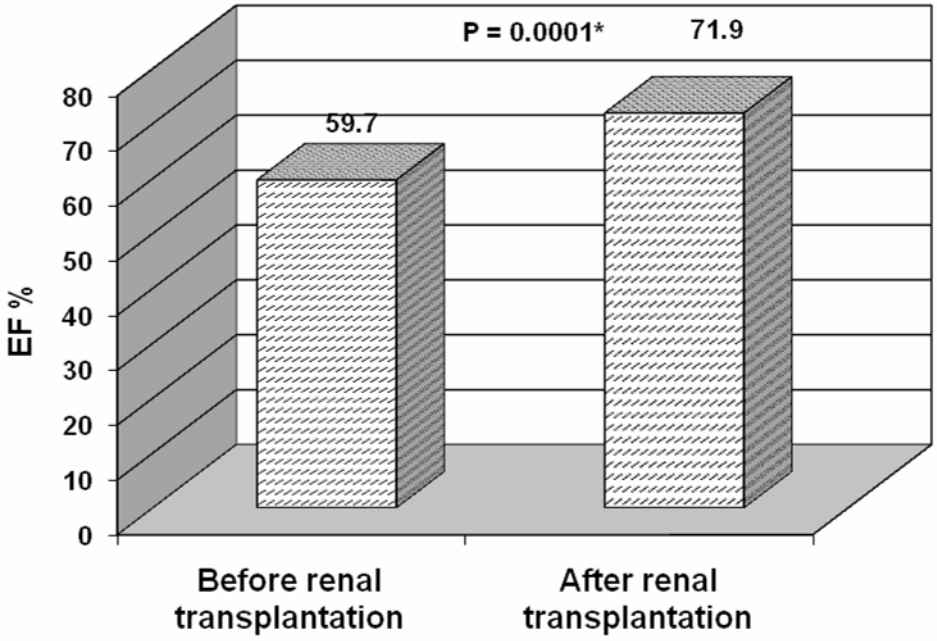


Fig 6 : Comparison between hemoglobin of adult before and after renal transplantation

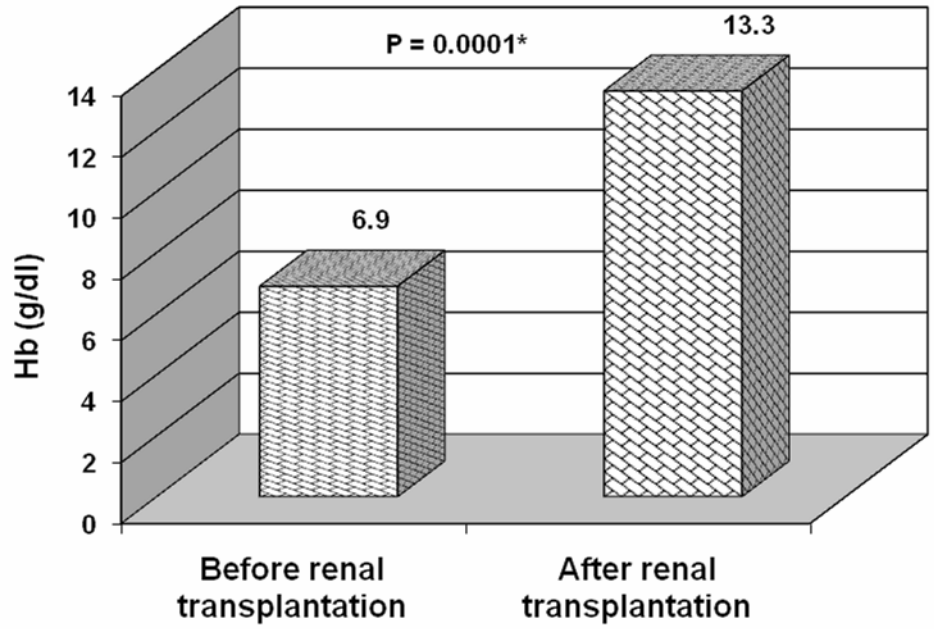


Fig 7 : Comparison between LVED of adult before and after renal transplantation

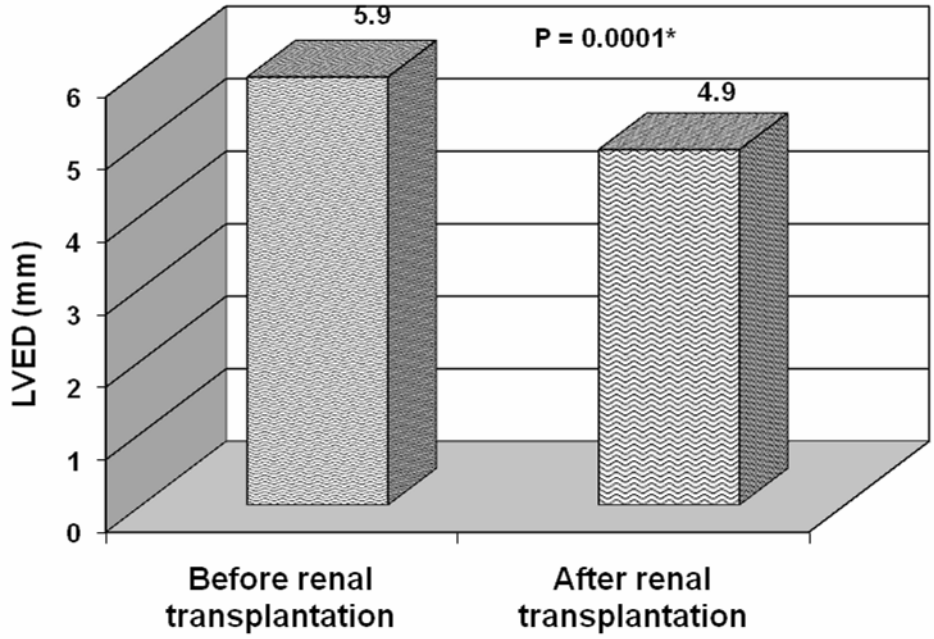


Fig 8: Comparison betweenLVES of adult before and after renal transplantation

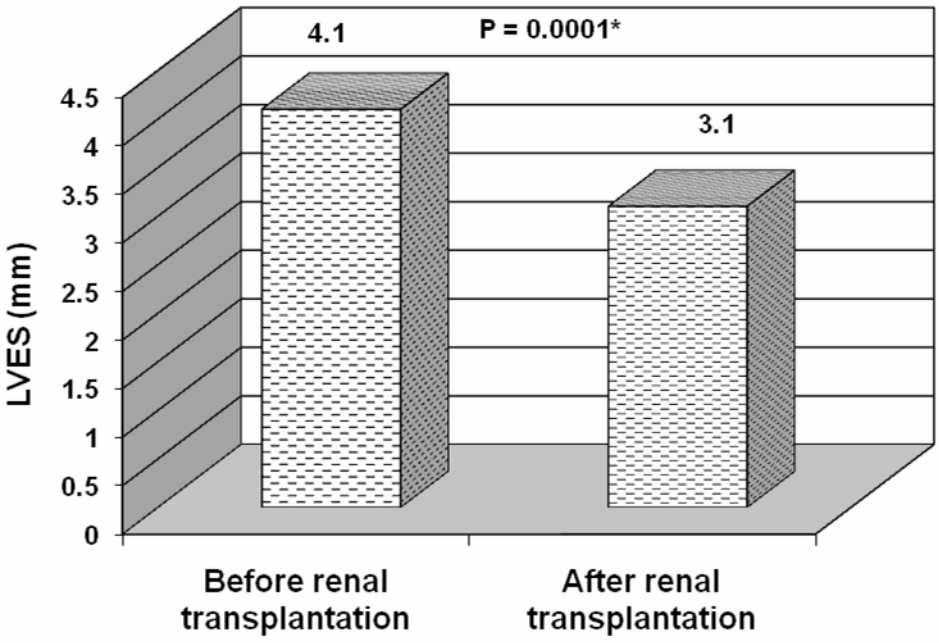


Fig 9 : Comparison between FS of adult before and after renal transplantation

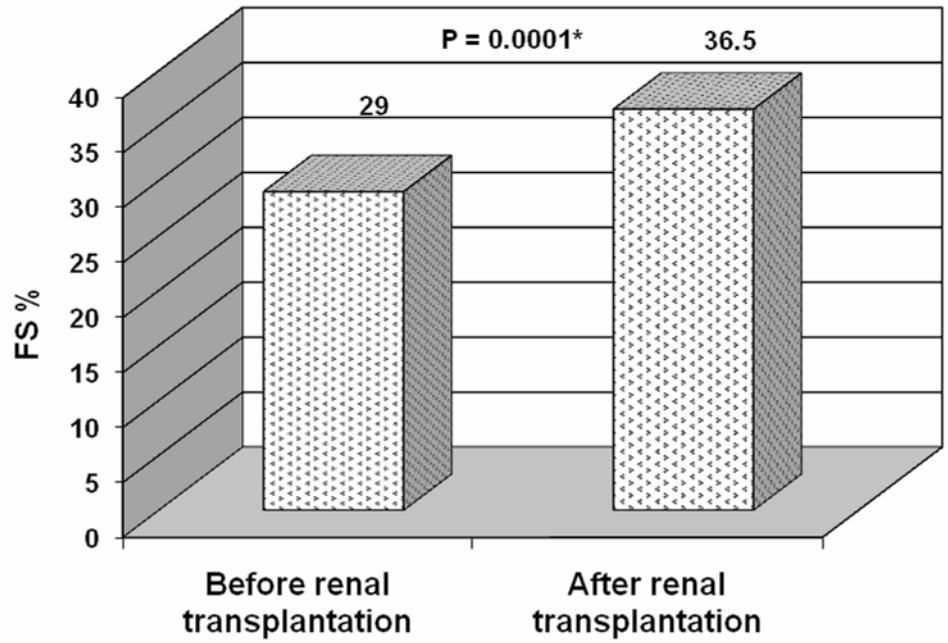


Fig 10 : Comparison between EF of adult before and after renal transplantation

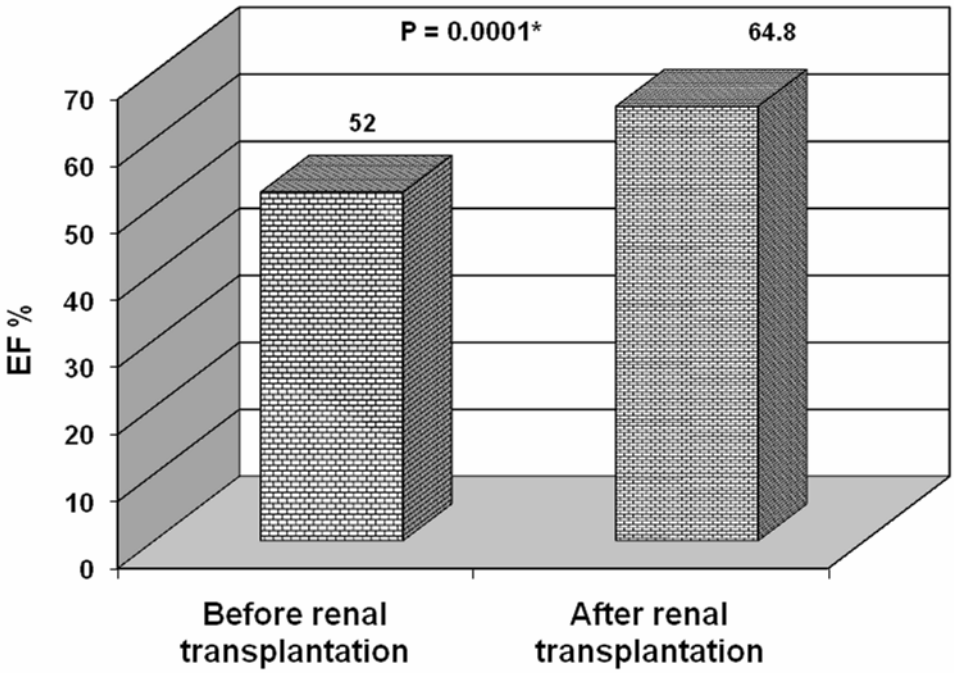


Fig 11 : Comparison between EF pre transplantation in children and adult

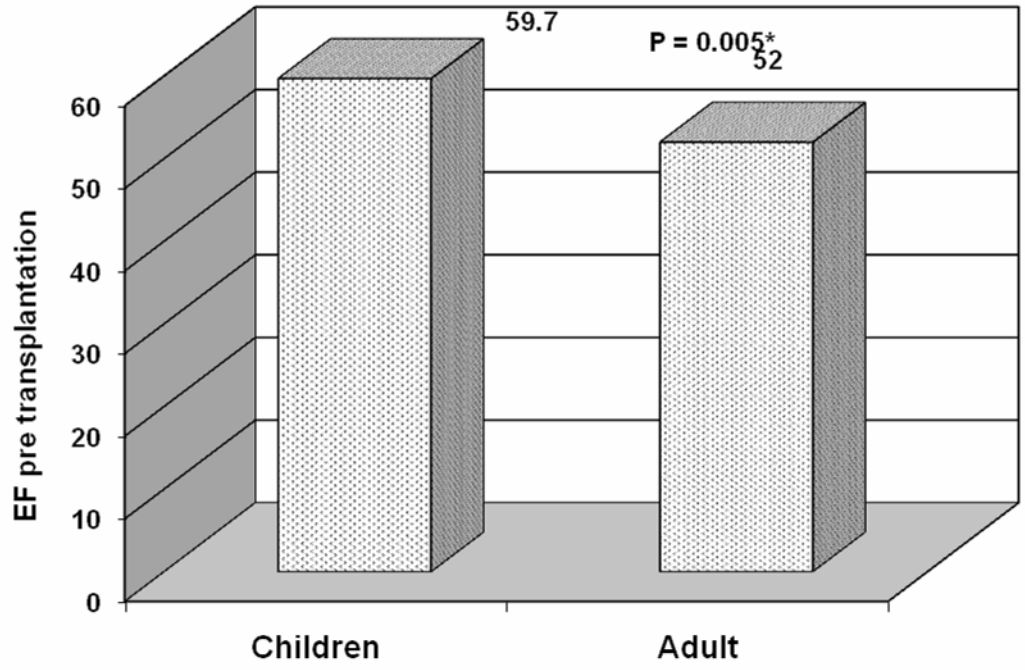
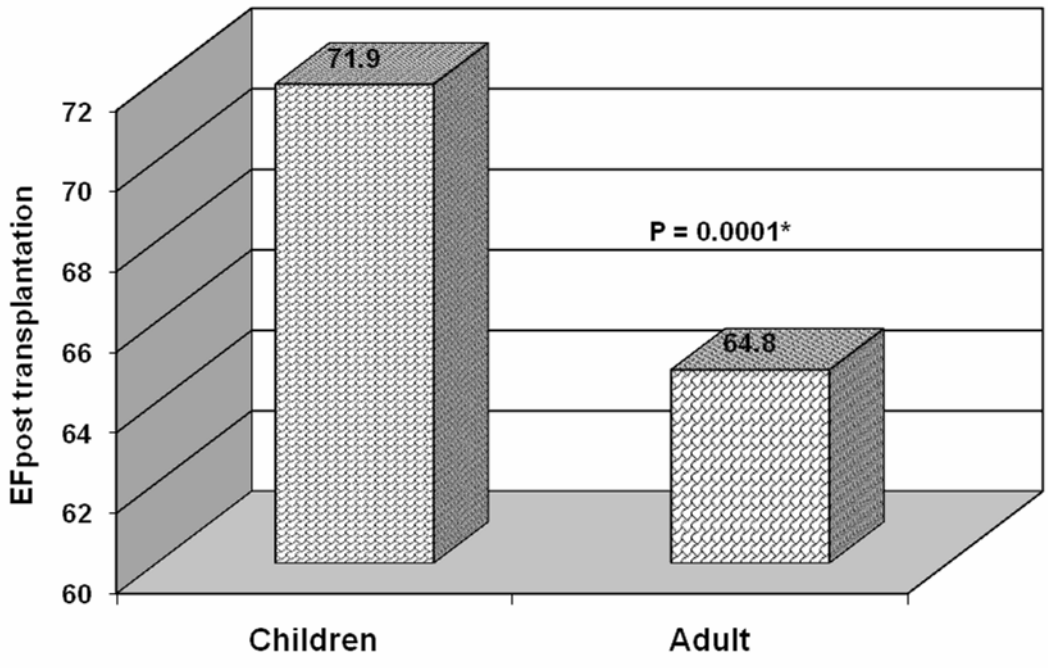


Fig 12 : Comparison between EF post transplantation in children and adult



Analysis of the results

The study population consisted of 6 groups in a total number of 110 patients

Group I: as shown in table 1

This group consisted of 30 patients who are CRF on regular hemodialysis who undergone renal transplantation. The mean age of this group was 9.8 ± 3.7 years. Eighteen of them were males while twelve of them are females. The mean of duration of dialysis before transplantation 0.6 ± 0.2 years. The mean hemoglobin before transplantation 6.9 ± 1.0 g/dl. The mean body weight 30.6 ± 12.5 kg. The mean height 107.9 ± 28.4 cm. The mean BMI 25.8 ± 4.4 (kg/m^2). The mean LVED pre transplantation 4.7 ± 0.8 (mm). The mean LVES pre transplantation 3.1 ± 0.6 (mm).The mean FS pre transplantation 32.6 ± 5.3 %. The mean EF pre transplantation 59.7 ± 7.0 %. The mean Creatinine post transplantation 0.9 ± 0.3 (mg/dl). The mean hemoglobin post transplantation 13.9 ± 0.9 (g/dl). The mean LVED post transplantation 4.2 ± 0.5 (mm).The mean LVES post transplantation 2.4 ± 0.4 (mm) .The mean FS post transplantation41.7 ± 7.6 %. The mean EF post transplantation 71.9 ± 6.1.

Group II: as shown in table 2

This group consisted of 30 patients who are CRF on regular hemodialysis who undergone renal transplantation. The mean age of this group was 26.8 ± 5.6 years. Twenty-five of them were males while five of them are females. The mean of duration of dialysis before transplantation 0.9 ± 0.4 years. The mean hemoglobin before transplantation 6.9 ± 1.2 g/dl. The mean body weight 68.7 ± 11.4 kg. The mean height 166.3 ± 7.3 cm. The mean BMI 24.7 ± 3.1 (kg/m^2). The mean LVED pre transplantation 5.9 ± 0.7 (mm). The mean LVES pre transplantation 4.1 ± 0.9 (mm).The mean FS pre transplantation 29.0 ± 6.6%. The mean EF pre transplantation 52.0 ± 12.5 %. The mean Creatinine post transplantation 1.2 ± 0.2 (mg/dl). The mean hemoglobin post transplantation 13.3 ± 1.9 (g/dl). The mean LVED post transplantation 4.9 ± 0.6 (mm).The mean LVES post transplantation 3.1 ± 0.5 (mm). The mean FS 36.5 ± 4.1% post transplantation . The mean EF post transplantation 64.8 ± 5.9 % .

Group III: as shown in table 3

This group consisted of 20 patients who are CRF on regular hemodialysis. The mean age of this group was 10.7 ± 2.4 years.Twelve of them were males while eight of them are females. The mean of duration of dialysis 3.3 ± 1.2years. The mean hemoglobin 8.7 ± 1.5 g/dl. The mean body weight 34.1 ± 8.0 kg. The mean height 112.6 ± 21.3 cm. The mean BMI 28.2 ± 9.0 (kg/m^2). The mean LVED 4.7 ± 0.8 (mm). The mean LVES 3.2 ± 0.6 (mm).The mean FS 30.9 ± 5.0 %. The mean EF 56.5 ± 6.3 %.

Group IV: as shown in table 4

This group consisted of 20 patients who are CRF on regular hemodialysis. The mean age of this group was 43.9 ± 14.1 years. Eight of them were males while twelve of them are females. The mean of duration of dialysis 8.5 ± 4.7 years. The mean hemoglobin 9.7 ± 1.9 g/dl. The mean body weight 59.4 ± 19.2 kg. The mean height 160.2 ± 12.7 cm. The mean BMI 22.7 ± 5.2 (kg/m^2). The mean LVED 5.6 ± 0.8 (mm). The mean LVES 4.0 ± 1.0 (mm).The mean FS 29.2 ± 4.3 %. The mean EF 50.2 ± 7.4 %.

GroupV: as shown in table 5

This group consisted of 5 patients who are normal kidney function. The mean age of this group was 12.0 ± 1.5 years. Five of them were males. The mean hemoglobin 14.2 ± 0.8g/dl. The mean body weight 36.0 ± 3.9 kg. The mean height 141.0 ± 6.1 cm. The mean BMI18.0 ± 1.5 (kg/m^2). The mean LVED 4.2 ± 0.4(mm). The mean LVES3.0 ± 0.5 (mm).The mean FS41.9 ± 2.3 %. The mean EF 71.6 ± 4.0 %. The mean Creatinine 0.6 ± 0.1 (mg/dl).

GroupVI: as shown in table 6

This group consisted of 5 patients who are normal kidney function. The mean age of this group was30.2 ± 3.7 years. Five of them were males. The mean hemoglobin13.2 ± 1.3 g/dl. The mean body weight 80.0 ± 13.5 kg. The mean height 172.2 ± 5.7 cm. The mean BMI 25.7 ± 3.8 (kg/m^2). The mean LVED 5.0 ± 0.3 (mm). The mean LVES 3.1 ± 0.6 (mm).The mean FS 38.0 ± 1.9 %. The mean EF 64.8 ± 3.4 %. The mean Creatinine 0.9 ± 0.09(mg/dl).

Comparison between the means of different items of children before and after renal transplantation as shown in table 7, figure (1 to 5) Group I

By comparing data of children pre and post renal transplantation regarding Hemoglobin (g/dl) There were statistically significant differences P-value (0.0001*) , LVED (mm) There were statistically significant differences P-value (0.0001*) , LVES (mm) There were statistically significant differences P-value (0.0001*) , FS % There were statistically significant differences P-value (0.0001*) , EF% There were statistically significant differences P-value (0.0001*) .

Comparison between the means of different items of adult before and after renal transplantation as shown in table 8,figure (6to10) Group II

By comparing data of adults pre and post renal transplantation regarding Hemoglobin (g/dl) There were statistically significant differences P-value (0.0001*) , LVED (mm) There were statistically significant differences P-value (0.0001*) , LVES (mm) There were statistically significant differences P-value (0.0001*) , FS % There were statistically significant differences P-value (0.0001*) , EF% There were statistically significant differences P-value (0.0001*) .

Comparison between the means of different items of children after renal transplantation, chronic renal failure and controls as shown in table 12

By comparing data of children post renal transplantation (group I) to data of children on regular hemodialysis (group III) to children with normal kidney function (groupV) regarding Hemoglobin (g/dl) There were statistically significant differences P-value (0.0001*) , LVED (mm) There were statistically significant differences P-value (0.02*) , LVES (mm) There were statistically significant differences P-value (0.0001*) , FS % There were statistically significant differences P-value (0.0001*) , EF% There were statistically significant differences P-value (0.0001*) .

Comparison between the means of different items of adult after renal transplantation, chronic renal failure and controls as shown in table 13

By comparing data of adults post renal transplantation (group II) to data of adults on regular hemodialysis (groupIV) to adults with normal kidney function (groupVI) regarding Hemoglobin (g/dl) There were statistically significant differences P-value (0.0001*) , LVED (mm) There were statistically significant differences P-value (0.001*) , LVES (mm) There were statistically significant differences P-value (0.0001*) , FS % There were statistically significant differences P-value (0.0001*) , EF% There were statistically significant differences P-value (0.0001*) .

Correlation between EF (post transplantation) and improved EF in children with other parameters as shown in table 9

Comparison of the effect of improved EF after transplantation to other parameters they show **no** statistically significant differences as Hemoglobin (g/dl) P- value (0.4) , Age (yrs) P- value (0.5) , Duration of dialysis (yrs) P- value (0.3) , BMI (kg/m^2) P- value (0.8) .

Correlation between EF (post transplantation) and improved EF in adults with other parameters as shown in table 10

Comparison of the effect of improved EF after transplantation to other parameters they show **no** statistically significant differences as Hemoglobin (g/dl) P- value (0.1) , Age (yrs) P- value (0.1) , Duration of dialysis (yrs) P- value (0.4) , BMI (kg/m^2) P- value (0.7) .

Comparison between EF(pre & post transplantation) and improved EF in children and adult as shown in table 11 (Figure 11,12)

Comparing of EF before renal transplantation in children to adults there was a statistically significant differences P- value (0.005*), comparing of EF after renal transplantation in children to adults there was a statistically significant differences P- value (0.0001*) . While comparing improved EF in children to adults there was **no** statistically significant differences P- value (0.8).

Discussion

Discussion

Chronic kidney disease (CKD) refers to the myriad problems that follow loss of kidney function.

Chronic kidney disease (CKD) is associated with cardiovascular (CV) disease and mortality.
It is not known whether cardiac rhythm disturbances are more prevalent among individuals with CKD or whether resting electrocardiogram findings predict future CV events in the CKD setting.**(Johnston et al, 2006)**

Kidney transplantation (KTX) is the preferred form of renal replacement therapy. **(John and Olwyn ,2007).**

Kidney transplantation has dramatically evolved from a life-saving yet unproven therapy for patients with renal failure to a mature field that is the preferred treatment for those suffering from ESRD.**(Todd ,2009)**

It is now well established that early kidney transplantation is associated with optimal outcomes in terms of patient and graft survival. **(Innocenti et al, 2007)**

Kidney transplantation reduces mortality and cardiovascular deaths, more so than dialysis, although survival for both remains worse than in non renal disease populations.

Compared with the general population, renal transplant recipients (RTR) are at higher risk for morbidity and mortality, largely as a result of cardiovascular disease (CVD). **(Anushree et al,2008)**

Significant improvements in cardiac parameters occur after renal transplantation. The alterations are evident in the early posttransplant period and continued over time, depending on BP control and renal function status. **(Peteiro et al,2006)**

The aim of our study is evaluation of the impact of renal transplantation on the cardiac morphological and functional characteristics.

Also, our aim is to evaluate the improvement of cardiac morphological and functional characteristics in children and adults who had renal transplantation and compare the degree of improvement in children to that of adults.

This study was conducted on 110 subjects who were admitted at Kasr Alaini hospital and King Fahd unit.

Renal transplant patients had transthoracic echocardiography before renal transplantation and 6 months after transplantation.

The key and novel finding in the present study is the relation between renal transplantation and degree of improvement of ejection fraction (EF)% after transplantation in children and adults.

Also, we compare the degree of improvement of ejection fraction% in children in comparison tothe degree of improvement of ejection fraction in adults after transplantation.

We also compare the degree of improvement of hemoglobin , left ventricular end-diastolic volume (LVED), left ventricular end-systolic volume (LVES) , fraction systolic % (FS) before and after renal transplantation in children and adults.

We also compare the degree of improvement of cardiac morphological and functional characteristics in renal transplant recipient to those of chronic renal failure patients on regular hemodialysis in children and adults.

In our study we found a statistically significant differences in hemoglobin which is markedly increased after transplantation in both children and adults but there was no statistically significant differences in the effect of improvement of hemoglobin on improvement of ejection fraction after transplantation.
This was in contrast to **M.M. Iqbal et al,2008** that shown the reductions in blood pressure with correction of anemia and decreased creatinine levels also influenced the improvements in LV parameters, where increased hemoglobin and low serum creatinine negatively correlated with abnormal cardiac factors.

In our study, we showed a statistically significant differences in improvement of LVED, LVES and FS 6 months after renal transplantation in children. This was in agreement with **El-Husseini et al,2004** whereThey reported that the degree of improvement in LV contractility after transplantation was 56% increase in fractional shortening and it was larger than that expected for correction of anemia.
In our study**,**we also found a statistically significant differences in improvement of EF 6 months after renal transplantation in children. We did not find a previous study used EF to reflect improvement of cardiac morphological and functional characteristics after renal transplantation.

But many studies used left ventricular hypertrophy (LVH) and left ventricular mass index (LVMI).

Foley et al in 1995 reported that correction of uremia by renal transplantation was associated with 17% improvement in LVMI, similar to the degree of regression of hypertrophy observed on partial correction of anemia with erythropoietin. The degree of regression of LVH may have been limited by hypertension, as a significant association was observed between fall in blood pressure and fall in LVMI.

In our study ,we found statistically significant differences in Hemoglobin in children which is improved in transplant recepients. This was in agreement with **Ferreira et al,2002**
We also found statistically significant differences in LVED, LVES and FS in children which is improved in transplant recepients .

These parameters reflects improvement in degree of left ventricular dilatation and systolic dysfunction in RTR than those on hemodialysis. This was agreed with **Marcello Chinali et al, 2007**

Also there was statistically significant differences in EF between two groups **(I and III)** showing improvement of EF in RTR.

In children with CRF, a single report by **Colan *et al, 2001*** found a significantly reduced ejection fraction in children who were undergoing dialysis, that was agreement with our findings.

Whereas most other previous studies which done by **Johnstone et al,1996 and Palcoux et al,1982** predialysis or dialysis-dependent CRF showed a normal or even supranormal ejection fraction at rest. This difference may be attributed to the small number of patients in our study correlated to the duration of dialysis.

Our subjects in group I who had renal transplantation had marked improvement in hemoglobin, LVED,LVES,FS and EF due to correction of anemia, control of blood pressure, normal kidney function, decrease of volume overload with satisfactory urine output. All of these factors helped to improve cardiac morphological and functional characteristics after renal transplantation.

Most of our patients in group I had hemodialysis for less than one year before transplantation , most of them were dialyzing through a double lumen catheter not through A-V fistula.

All of these factors contribute in that significant prognosis in cardiac morphological and functional characteristics after renal transplantation.

In our study, **group II** shows a statistically significant differences in improvement of LVED, LVES and FS 6 months after renal transplantation in adults.

We also found in **group II** a statistically significant differences in improvement of EF 6 months after renal transplantation in adults.

Montanaro et al,2005 observed a significant decrease in left ventricular mass and left ventricular mass index compared to the pre transplantation period.

In renal transplant recipients, the prevalence of left ventricular hypertrophy significantly decreased (78% versus 44%, P < .03). Systolic 24-hour blood pressure was the only predictor of left ventricular mass and of left ventricular mass index at 2 years after transplantation. In conclusion, successful renal transplantation produces a regression of left ventricular hypertrophy. This beneficial effect depends on a decrease in systolic pressure levels.

In our study we used LVED, LVES, EF and FS in order to assess effect of renal transplantation on cardiac morphological and functional characteristics this was in difference to the study done by **Montanaro et al in 2005** .

In our study we found statistically significant differences in Hemoglobin which is improved in transplant recepients. Correction of anemia in CRF patients and renal transplant patients is very important issue as shown by**Alexander et al, 2006** who reported that patients with anemia and patients with chronic renal failure have elevated risks for cardiovascular disease.

This also was evident in study showed that The risk for hospitalization with myocardial infarction was two to five times higher in anemic (Hb <12 g/dl) patients than in people with Hb from 12.0 to 12.9 g/dl**.(Al-Ahmad et al ,2001)**

A similar but less dramatic pattern of higher incidence of coronary revascularization was observed with lower Hb levels. Risks for hospitalization with congestive heart failure declined regularly with increasing Hb levels from a doubling of risk at Hb <10 g/dl to a 61% decrease at 15 g/dl, both relative to 12.0 to 12.9 g/dl. **(Pereira and Sarnak , 2003)**

In our study we found statistically significant differences in LVED, LVES and FS in aduls which is improved in transplant recepients .

Also there was statistically significant differences in EF in adults showing improvement of EF in RTR.

Schrier , 2007 reported that in chronic renal failure patients the most prevalent cardiovascular abnormalities are LVH (up to 93%), systolic dysfunction (30%–60%), LV dilatation (27%), and diastolic dysfunction (17%).

Iqbal MM et al, 2006 concluded that significant beneficial changes in cardiac function and morphology become evident by 3 months post transplantation. The alterations, mainly due to reduction in diameters, are further influenced by correction of anemia and BP control.These changes are maintained over longer periods among subjects with functioning allografts.

Systolic or diastolic HTN is an important risk factor for patient and graft survival after renal transplantation.

The effect of high blood pressure on kidney grafts has been attributed to amplification of vascular injury**.(Schwenger et al,2001)**

Proteinuria is also a significant marker of poor long-term allograft function, representing an independent risk factor for total and cardiovascular mortality in the renal transplant population**.(Fernandez-Fresnedo et al,2004)**

Our subjects in group II who had renal transplantation had marked improvement in hemoglobin, LVED,LVES,FS and EF due to correction of anemia, control of blood pressure, normal kidney function, decrease of volume overload with satisfactory urine output. All of these factors helped to improve cardiac morphological and functional characteristics after renal transplantation.Most of our patients in group II had hemodialysis for less than one year before transplantation , most of them were dialyzing through a double lumen catheter not through A-V fistula.All of these factors contribute in that

significant prognosis in cardiac morphological and functional characteristics after renal transplantation.

In our study we made comparison between EF% (pre & post renal transplantation) and improved EF5 in children and adult.

We reported that comparing of EF% before renal transplantation in children to adults there was a statistically significant differences P- value (0.005*) which shows that ejection fraction in children with renal failure is much better than ejection fraction in adults with renal failure.

Comparing of EF% after renal transplantation in children to adults there was a statistically significant differences P- value (0.0001*) which shows that improvement of ejection fraction in children after renal transplantation is much better than improvement of ejection fraction in adults after renal transplantation .

A successful kidney transplant remains the most effective renal replacement therapy for children with end-stage renal failure. **(Salvatierra et al, 2002).**

Pediatric renal transplantation presents a number of challenges, especially in the younger age group. Graft and patient survival were often reported to be not so good in young recipients compared with older children and adults, but the results have been improved **(Ettenger , 2004).**

Alfrey et al in 2004 reported that in chronic uremia, cardiomyopathy manifests itself as systolic dysfunction, concentric left ventricular hypertrophy (LVH) or left ventricular dilatation. The correction of uremic state by renal transplantation leads to normalization of left ventricular contractility, regression of LVH and improvement of cavity volume and so dialysis patients with uremic cardiomyopathy would benefit from renal transplantation.

Our study agreed with **Alfrey et al, 2004** that renal transplantation improve LVED volume, LVES volume ,FS % and EF %

Parekh et al, 2002 reported that cardiovascular morbidity and mortality in renal transplant recipients are much lower than in dialysis patients but they still remain unacceptably high.

The aim of our study was to prove that transplantation in children is preferred to be as early as possible to decrease duration of dialysis before transplantation, hemodynamic effects of A-V fistula, correction of anemia, decrease volume overload and control of blood pressure all of these factors will improve risks of morbidity and mortality of these population and make their lives easier.

Conclusion

Kidney transplantation is the renal replacement therapy of choice for most patients with ESRD, not only improving quality of life but also offering extended life expectancy compared with dialysis.

Kidney transplantation reduces mortality and cardiovascular deaths, more so than dialysis, although survival for both remains worse than in non renal disease populations.

In our study we concluded that renal transplantation is treatment of choice for chronic renal failure especially in children and adolescence as it improves cardiac morphological and functional characteristics as it improves EF% after transplantation.

We need more number of patients to be studied, more follow up of patients after one year to five years after transplantation with frequent cardio logical assessment through echocardiography every 6 months, ECG, control of anemia, control of BP, control of lipid profile and detection of new onset diabetes.

Summary and conclusion

Summary and conclusion

Morbidities related to the cardiovascular system (CVS) are responsible for 90% of deaths in chronic kidney disease (CKD), even before reaching end-stage renal failure (ESRD).

Renal transplant recipients are also at much greater risk of deteriorating renal function than the general population . Renal transplant recipients have many conventional risk factors for acute cardiovascular disease, including hypertension, hyperlipidemia, and posttransplant diabetes mellitus.

Pediatric patients post-kidney transplant are at continuous risk for developing cardiovascular disease**.** Cardiovascular events are among the most frequent causes for long-term morbidity and mortality in children after renal transplantation.

Kidney transplantation is the renal replacement therapy of choice for most patients with ESRD, not only improving quality of life but also offering extended life expectancy compared with dialysis. Kidney transplantation reduces mortality and cardiovascular deaths more so than dialysis, although survival for both remains worse than in non renal disease populations.

In this study we discussed the effect of renal transplantation on the cardiac morphological and functional characteristics through making echocardiography before renal transplantation and six-months after transplantation.

In our study we have four groups:

Group I consists of 30 patients below age of 18years who had renal transplantation more than 6 months and less than one year duration.

Group II consists of 30 patients above age of 18years who had renal transplantation more than 6 months and less than one year duration.

Group III consists of 20 patients below age of 18years who were chronic renal failure patients on regular hemodialysis.

Group IV consists of 20 patients above age of 18years who were chronic renal failure patients on regular hemodialysis.

In our study we used echocardiography to study cardiac morphological and functional characteristics before and after transplantation.

We aimed to report improvement of LVED,LVES,FS and EF% after transplantation especially in children more than adults but we did not find statistically significant differences.

The aim of our study was to prove that transplantation in children is preferred to be as early as possible to decrease duration of dialysis before transplantation, hemodynamics effects of A-V fistula, correction of anemia, decrease volume overload and control of blood pressure all of these factors will improve risks of morbidity and mortality of these population and make their lives easier.

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مقارنة تغيرات القلب و الأوعية الدموية بين الأطفال و البالغين قبل و بعد زراعة الكلى

البحث

توطئة للحصول على درجة الماجستير فى الأمراض الباطنة العامة

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الملخص العربى

إن الأمراض المتعلقة بالقلب و الأوعية الدموية مسئولة عن ٩٠% من أسباب الوفاة فى مرضى القصور الكلوى و حتى قبل الوصول إلى مرحلة الفشل الكلوى .

إن مرضى زراعة الكلي معرضين إلى حدوث تدهور فى وظائف الكلى أكثر من الأشخاص الطبيعين .

إن مرضى زراعة الكلي معرضين إلى حدوث أمراض حادة بالقلب و الأوعية الدموية تتضمن إرتفاع بضغط الدم و إرتفاع مستوى الكوليسترول بالدم و إرتفاع مستوى السكر بالدم.

الأطفال الذين قاموا بزراعة الكلي معرضين إلى حدوث أمراض حادة بالقلب و الأوعية الدموية.

إن أمراض القلب و الأوعية الدموية تعتبر واحدة من أكثر أسباب الوفاة فى الأطفال الذين قاموا بزراعة الكلي.

إن زراعة الكلى تعتبرمن أفضل وسائل علاج الفشل الكلوى ليس فقط لأنه يحسن مستوي معيشة المرضى و لكنه أيضا يزيد من متوسط عمرالمريض عن مريض الغسيل الكلوى.

رغم أن زراعة الكلى تحد من التعرض لأمراض القلب و الأوعية الدموية و تقلل من أسباب الوفاة إلا أن معدلات الوفاة مازالت أعلى من الأفراد غير المصابين بالقصور بوظائف الكلى.

فى هذه الرسالة تم بحث تأثير زراعة الكلى على كفاءة عضلة القلب بعمل موجات صوتية على القلب قبل و بعد زراعة الكلى بستة أشهر.

فى هذه الرسالة تم دراسة أربع مجموعات:

المجموعة الأولى : تألفت من ثلاثون مريضا أقل من ١٨ عاما يعانون من فشل كلوى مزمن قاموا بزراعة الكلي منذ أكثر من ستة أشهر و أقل من عام.

المجموعة الثانية : تتكون من ثلاثون مريضا أكثر من ١٨ عاما يعانون من فشل كلوى مزمن قاموا بزراعة الكلي منذ أكثر من ستة أشهر و أقل من عام.

المجموعة الثالثة: : تتكون من عشرون مريضا أقل من ١٨ عاما يعانون من فشل كلوى مزمن

المجموعة الرابعة : تتكون من عشرون مريضا أكثر من ١٨ عاما يعانون من فشل كلوى مزمن

فى هذه الرسالة تم ملاحظة تحسن واضح فى كفاءة عضلة القلب من حيث الشكل و قوة و كفاءة الضخ.

و تم ملاحظة هذا التحسن فى كفاءة عضلة القلب فى الأطفال أكثر من البالغين.

إن من أهداف هذه الرسالة هو إثبات أن التعجيل فى زراعة الكلى فى الأطفال يحسن من مستوى معيشة هؤلاء الأطفال من حيث تقليل مدة الغسيل الدموى و البعد عن عمل وصلة شريانية وتحسن نسبة الأنبميا بالدم و ضبط ضغط الدم كل هذه العوامل تحسن من مستوى معيشة هؤلاء الأطفال.