TESI DI DOTTORATO XIX CICLO

TRAPIANTI D'ORGANO

CATTEDRA DI CHIRURGIA UNIVERSITA'

DEGLI STUDI DI ROMA TOR VERGATA

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UOC CHIRURGIA UROLOGICA

UOS CHIRURGIA DEI TRAPIANTI RENALI

TITOLO

ARTERIAL CHANGES IN PEDIATRIC PATIENTS WITH CHRONIC RENAL FAILURE UNDERGOING RENAL TRANSPLANTATION

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Abstract

Premessa: Dai dati della letteratura è noto che nel paziente uremico adulto sono presenti diverse alterazioni cardiovascolari legate allo stato uremico, alla durata e al tipo di dialisi. Recenti studi hanno evidenziato alterazioni cardiovascolari anche nel paziente uremico pediatrico.
Materiali e Metodi: Dal 2004 al 2006, 26 pazienti sono stati sottoposti a trapianto renale presso il nostro Istituto. 15 maschi e 11 femmine età media 13.12 anni (range 3-27 anni). 8 pazienti si trovavano in dialisi peritoneale da 14,85 mesi, 17 pazienti in emodialisi da 25,16 mesi, 1 paziente non aveva ricevuto nessun trattamento dialitico, poiché era stato sottoposto a trapiantato renale 5 anni prima con successivo rigetto . Tutti i pazienti sono stati divisi in due gruppi A e B a seconda della malattia di base. Nel gruppo A risultavano 18 pazienti età media 12,27 anni, 12 con malformazioni della via urinaria e displasia renale, 4 con valvole congenite dell'uretra, 1 con reflusso vescico-ureterale, 1 con vescica neurogena. La durata media della dialisi in questo gruppo è stata di 17,33 mesi. Nel gruppo B risultavano 8 pazienti età media 12,57 anni con malattia glomerulare acquisita; la durata media della dialisi in questi pazienti è stata di 30,62 mesi. In tutti i pazienti sono stati analizzati il valore del PTH, colesterolo, trigliceridi, calcio, fosforo, creatininemia, uremia, glicemia. 8 pazienti presentavano ipertensione in trattamento farmacologico con ACE inibitori. Tutti i pazienti sono stati trattati con dosi giornaliere di vitamina D da 0,5 a 1,5 µg/dl per prevenire l'iperparatiroidismo. Nei pazienti in emodialisi è stato usato il calcio carbonato per prevenire l'iperfosfatemia. Durante il trapianto è stato prelevato un campione di arteria del donatore e successivamente un campione di arteria iliaca del ricevente e conservati in formalina. Le sezioni (3-4 µ) sono state analizzate con microscopia ottica, con colorazioni ematossilina eosina per valutare l'ispessimento dell'intima, Geison-Weigert tricromo per lo studio delle fibre elastiche, Alcian-Pas per valutare la presenza di mucopolisaccaridi
Analisi Statistica: sono stati usati il *t*-test, il test di Mann-Whitney e il test di Fischer per l'analisi statistica, considerando il valore di $P<0,05$ significativo.
Risultati: Nel gruppo A e B non sono state trovate differenze significative riguardanti età, sesso, durata emodialisi e dialisi peritoneale, pressione arteriosa, valori del PTH, fosforo, calcio, colesterolo, trigliceridi, creatinina, urea, glucosio. La microscopia ottica ha evidenziato modificazioni patologiche in 12 su 26 pazienti riceventi: 9 pazienti presentavano frammentazione della parete elastica, 2 una severa frammentazione delle fibre elastiche, 1 frammentazione di fibre elastiche e deposito di mucopolisaccaridi . In nessuno erano presenti alterazioni ateromasiche. Tra i due gruppi non vi sono state differenze statisticamente significative ($p>0.05$). Un dato interessante è stata l'incidenza di alterazioni nei pazienti in dialisi peritoneale 6 su 8. Questo dato non risulta statisticamente significativo sicuramente per l'esiguità del campione. Altro dato da sottolineare è che in 11 campioni di arteria del donatore sono state riscontrate lievi frammentazioni delle fibre elastiche ma anche questo dato non risulta statisticamente significativo se comparato con i due gruppi A e B ($P<0.05$)
Conclusioni: Le alterazioni riscontrate nel nostro studio sono caratterizzate da lievi modificazioni della parete arteriosa e riscontrate soprattutto nei pazienti con uropatia. Si tratta, inoltre, di alterazioni verosimilmente aspecifiche in quanto analoghe a quelle delle arterie di donatori di rene di pari età, considerati come gruppo di controllo normale. E' possibile che tale dato dipenda dai ridotti tempi che intercorrono tra la dialisi e il momento del trapianto.

Abstract

Introduction: cardiovascular modifications are common in adults with chronic renal failure and are frequently cause of death. Pathological changes of large arterial wall and heart were described in the literature. This modifications are described also in children with chronic renal failure. Aim of the study was to verify the incidence of arterial changes in our series of patients with end stage renal disease undergoing transplantation.

Patients and methods

Since 2004 to 2006 twenty-six patients underwent kidney transplantation in our department. There were 15 boys and 11 girls with a mean age of 13.12 years (range 3-27 years). Twenty-five patients were submitted to dialysis treatment: peritoneal dialysis treatment was done in 8 cases, with mean duration of 14.85 months, whereas haemodialysis treatment was needed in 17, with mean duration of 25.16 months. One patient did not have any dialysis treatment, because received a previously kidney transplantation five years before in another hospital with successive rejection.

All patients were divided in two groups "A" and "B" according to primary renal disease. In the group "A" there were 18 patients (mean age 12.27 years) with congenital urinary malformations, renal displasia (12 patients), congenital urethral valve (4 pts), vesicoureteral reflux (1 pt), neurogenic bladder (1 pt); the mean duration of dialysis treatment in this group was 17.33 months. In the group "B" there were 8 patients (mean age 12.57 years) with acquired glomerular diseases; the mean duration of dialysis treatment in this group was 30.62 months.

The biochemical analyses (PTH, cholesterol, triglycerides, calcium, phosphorus, serum creatinine level, serum urea and glucose level) were performed before of kidney transplantation using routine laboratory methods and were compared between groups "A" and "B".

Eight patients were suffering from arterial hypertension in responsive pharmacologic treatment (ACE inhibitor). In all patients was administered 1-25 vitamin D in doses of 0.5 to 1.5 µg/day to prevent activity of parathyroid hormone. In patients, all treated with same haemodialysis, calcium carbonate was used to maintain predialysis phosphataemia at no pathological level.

In each case , a sample of artery from both donor (aortic patch of kidney) and receiver (iliac patch of graft allocation) was obtained during the renal transplantation Samples were formalin-fixed and paraffin embedded. Three µm sections (3-4µm) were stained with haematoxylin-eosin (HE), with Van Gieson-Weigert (VGFE) Trichrome to study pattern distribution of elastic fibres and with Alcian PAS to valuate mucopolysaccharide allocation.

Statistics: The two-sample *t*-test, Mann-Whitney test and Fisher's exact tests were used for statistical analysis; values of $P < 0.05$ were considered as statistically significant.

Results:The groups "A" and "B" are compared in Table 1. There were no differences about age, sex, duration of hemodialysis, blood pressure, PTH, cholesterol, triglycerides, calcium, phosphorus, serum creatinine level, serum urea and glucose level.

Light microscopy showed pathological changes in 12 out of 26 donor arteries: nine arteries showed light fragmentation of the internal elastic lamina; two had more severe fragmentations; one case showed fragmentation of the internal elastic lamina associated with mucopolysaccharide deposits, In our samples, no atheromatous features was observed. Pathological changes were more evident in group "A" than "B", but the difference was not statistically significant ($P > 0.05$).

Interestingly, these findings were common in six of the eight patients treated with peritoneal dialysis (75%). In the donor's group 11 patients had light fragmentation of the internal elastic lamina, but there were not statistically significant with group A and B ($P< 0,05$). This patients had any pathological disease and their death was due by cerebral accident or traumatic.

Conclusions: in our group of patients we found only slight modifications of the arterial wall, mainly in children with congenital anomalies of the lower urinary tract. Moreover, these changes are aspecific, similar to those found in the control group (donors matched for age). A possible explanation of these findings may depend on the short time of hemodialysis before transplantation.

Keywords: hemodialysis,arterial changes,children chronic renal failure, uremia, arterial wall.

Chronic Renal Failure: Manifestations and Pathogenesis

Chronic renal failure is characterized by a decrease in glomerular filtration rate (GFR) and histologic evidence of a reduction in nephron population. The clinical course is typically one of a progressive and unrelenting loss of nephron function ultimately leading to end-stage renal disease (ESRD). However, the time between the initial onset of disease and ultimate development of terminal renal failure may vary considerably not only between different disease but also in different patients with similar disease processes. The incidence of ESRD shows marked geographic variation as determined by the population base in regard to age, race, and sex. The reported incidence of ESRD in the United states in 1991 was 198 per million population [1]. In 1993, there were 171, 479 patients being treated for end-stage renal failure with dialysis. An additional 10,934 patients received a renal transplant. In addition, approximately 50,000 patients were added to the ESRD program in this country in 1993 [1]. The incidence of ESRD in the United States is increasing by approximately 8.7 percent annually. A similar increase in incidence is occurring in most other industrialized countries as well; the reason for this increase in frequency of ESRD is unclear. The distribution of patients by race most recently reported shows that 67.9 percent were white, 28.8 percent were black, with the remaining 3.3 percent being Asian/Pacific islanders and Native Americans. In the U.S. population, it is clear that chronic renal failure is more prevalent in the black population and Native

Americans than in the white population. Although life for chronic renal failure patients can be sustained by chronic dialysis and kidney transplantation, neither form of therapy is totally satisfactory. The current yearly mortality rate in the U.S. dialysis population is 23.6 percent. With the advent of improved immunosuppressive therapy with cyclosporine, results with renal transplantation have improved considerably [1]. The adjusted and averaged 1-year graft survival was approximately 90 percent for living related donor and 77 percent for cadaveric donor transplants in 1991 [1]. With improved transplant outcomes, growth in the number of patients wanting or needing a transplant has outpaced the supply of available organs. Although kidney transplant has become the preferred method of treatment for many ESRD patients, fewer than 25 percent of patients entering ESRD programs receive renal transplantation because of age, associated disease, anatomic abnormalities of the urinary tract, the presence of preformed cytotoxic antibodies, or lack of availability of a suitable donor. The rehabilitation rate of patients on chronic dialysis has been disappointing, and the cost of this treatment has been of increasing concern [1].

Causes of Chronic Renal Failure

The causes of renal failure should be established, if possible, since some conditions if corrected may result in partial or full functional recovery. The major causes of chronic renal failure found in adult patients entering the ESRD program in 1991 are:

Diabetes mellitus (30.6%), Hypertension (26,5%), glomerulonephritis (13,6%), Cystic disease (3.4%), Other urologic (5.4%), other or unknown (20,5%). In children the major cause of chronic renal failure are congenital malformations (65%).

Glomerular Diseases

Diabetes mellitus has become the most common cause of chronic renal failure in adults. It is estimated that 40 percent of patients who have had type I diabetes mellitus for over 20 years will have renal disease. Although the incidence of renal failure in patients with type II diabetes is only about 10 percent of that found in type I diabetes, because of the larger number of patients with type II diabetes it is a more frequent cause of ESRD than type I diabetes [2].

Glomerulonephritis represents the third most common cause of ESRD. The most common glomerular disease are focal glomerulosclerosis and membranoproliferative and lupus glomerulonephritis. However, it should be noted that the majority of glomerular disease are unclassified. Since IgA nephropathy is the most common glomerular disease responsible for ESRD in most other developed countries, it is possible that this disease accounts for a relatively large fraction of the unclassified glomerular diseases.

Vascular Disease

Hypertension is the second leading reported cause of ESRD. A 15-year follow-up study of 361,659 men with hypertension found that 924 developed ESRD [3]. This

represented an incidence of 17.12 per 100,000 person years. The relative risk for development of ESRD for diastolic blood pressure above 120 mmHg versus below 70 mm Hg was 30.9. For systolic blood pressure above 200 mmHg versus below 120 mmHg, the relative risk was 48.2. Across the entire range, blood pressure represented an independent risk factor. The relative risk for blacks was 1.99 [4]. This increased risk could not be explained by difference in levels of systolic or diastolic pressure or other known risk factors. In general, ESRD from hypertension occurs in black patients with a history of malignant or accelerated hypertension [5-7]. Although the incidence of renal failure from hypertension can be markedly attenuated by treatment of accelerated or malignant hypertension [5-8], adequate chronic treatment of milder hypertensive states, especially in the black population, may not prevent progression of renal failure [4-6]. Other less common vascular causes of chronic renal failure are atheroembolic disease and bilateral renal artery stenosis. Atheroembolic disease should be suspected in any individual who develops progressive renal failure following a vascular diagnostic procedure or surgery. In contrast to other vascular renal disease, atheroembolic disease may include high-grade proteinuria, eosinophiluria, and decreased serum complement. Diagnostic of atheroembolic disease largely depends on renal biopsy in which the cholesterol clefts are observed. There is no specific treatment for atheroembolic disease. Bilateral renal artery stenosis , as a cause of renal failure, is suggested by a further reversible reduction in renal function produced by converting enzyme inhibitors. Arteriography is usually required for the diagnosis of renal artery stenosis. As of this time, there is no good

evidence that renal function can predictably be improved in patients with bilateral renal artery stenosis by either angioplasty or surgical correction of the lesions. Uncontrolled studies have, however, suggested that these procedures can improve renal function in some rare instances.

Interstitial Nephritis

Interstitial nephritis is a descriptive term implying and an inflammatory response in the interstitium of the kidney. The glomeruli are involved only secondarily as a result of the fibrosis and vascular changes. Because of the potential reversibility or prevention of this group of renal disease, it is important to differentiate interstitial nephritis from glomerulonephritis. A number of clinical and biochemical features, listed in table-1 tend to separate these two forms of renal disease.

Feature differentiating glomerulonephritis and interstitial nephritis

Feature	Glomerulonephritis	Interstitial nephritis
Proteinuria	>3g	<1,5g
Sediment	Numerous cells and red blood cell casts	Few cells and casts
Sodium handling	Normal until late	Sodium wasting
Anemia	Moderate severity until late	Disproportionately severe for degree of renal failure
Hypertension	Common	Less common
Acidosis	Normochloremic	Hyperchloremic
Uric Acid	Slightly elevated	Markedly elevated
Urine volume	Normal	Increased

Table 1

Characteristically, patients with interstitial nephritis complain of polyuria and nocturia. Their urine volume is unusually large (3-5 L/day) because the kidneys' ability to concentrate urine is lost early in the course of renal failure. The diluting capability in interstitial nephritis is maintained even late in the course of renal failure; thus, the urine osmolality and specific gravity may be low when determined on a random collection of urine. A feature of advanced glomerular diseases is high-grade proteinuria, which usually is in excess of 2.5 g/day. Even with advanced interstitial nephritis, the 24-hour urinary protein excretion is usually less than 1 to 2 g. Furthermore, the urinary protein may be predominantly an alfa2 or beta-globulin instead of albumin. This finding is characteristic of the so-called tubular type of proteinuria. In the majority of chronic renal diseases, serum uric acid increases only slightly, and clinical gout is uncommon [9]. However, in interstitial nephritis, serum uric acid is commonly elevated, and in one type of interstitial nephritis, lead nephropathy, clinical gout has been recognized in approximately 50 percent of the patients [10]. The urinary sediment in interstitial nephritis may be totally unremarkable, or there may be a few white blood cells and hyaline casts. Renal salt wasting appears to be more common on patients with interstitial nephritis than in other forms of renal disease, and salt supplementation must sometimes be given to maintain extracellular fluid (ECF) volume. Finally, hypertension is less common in interstitial nephritis than in chronic glomerulonephritis, and anemia may be disproportionately more severe for the degree of compromised renal function. As is apparent in Table 2, a variety of drugs and toxins can be the etiologic agent

responsible for causing interstitial nephritis. In general, with the exception of analgesics, drugs cause an acute interstitial nephritis that is reversible when were the drugs are discontinued. The severity and chronicity of other forms of interstitial nephritis are largely related to the amount and duration of exposure to the various nephrotoxins. Interstitial nephritis accounts for 3 percent of the patients in this country being treated for ESRD. In this group, currently analgesic nephropathy accounts for 0.8 percent of patients being treated for ESRD. Analgesic nephropathy used to account for up 20 percent of ESRD in a number of countries [11]. However, following the removal of analgesics containing the combination of aspirin and phenacetin, the incidence of this disease has markedly decreased worldwide. The typical patient with this disease is a depressed, middle-aged woman who gives a history of years of daily ingestion of analgesics containing caffeine, aspirin, and phenacetin. Usually, the total consumption of analgesics amount to several kilograms. Patients frequently complain of headaches, backache, or other type of chronic pain and state that the analgesic are consumed to relieve this pain. Uric acid and oxalate nephropathy and cystinosis represent less than 0.1 percent each of the ESRD population [1]. Renal failure is uncommon in patients with primary gout, and when it does occur, it is slowly progressive and only becomes clinically important late in life [12]. However, in some hematologic disorders, particularly in association with the use of chemotherapeutic agents, there may be marked overproduction of uric acid, which may cause acute renal failure due to deposition of urate crystals in the tubules. Another compound capable of inducing a severe interstitial nephritis is oxalate. Two

enzymatic defects have been described that can result in the accumulation of glyoxylic acid and hyperoxaluria. In the first type, urinary excretion of oxalic acid, glyoxylic acid, and glycolic acid is increased as a result of deficiency of 2-oxoglutarate-glyoxylate carboligase [13]. In the second defect, urinary excretion of glycolic acid is normal, but the excretion of L-glyceric acid and oxalate is increased. This condition is due to a deficiency of D-glyceric dehydrogenase. [13]. Both disease are characterized by nephrolithiasis, nephrocalcinosis, and renal failure, with few patients living beyond the age of 40 years.

Various etiologies of interstitial nephritis

Analgesic	**Uric acid**
Other Drugs	Gouty nephropaty
Sulfonamide	Hematologic disorders
Penicillin and homologues	Oxalate deposition
Furosemide, thiazides	Associated with small-bowel disease
Phenindione	Hereditary
Phenytoin	Anesthetic agents: methoxyflurane
Cimetidine	Ethylene glycol
Nonsteroidal anti-inflammatory	Heavy metals
Calcium disorders	Lead
Hyperparathyroidism	Cadmium
Milk-alkali syndrome	Uranium
Sarcoid	Copper
Neoplasm	Miscellaneous Infection Idiopathic
Multiple myeloma	

Table 2

Recently, a number of acquired forms of hyperoxaluria and renal failure have been described. Methoxyflurane anesthesia can cause hyperoxaluria and renal failure [14].

In addition, it has been recognized that patients with distal small-bowel disease may have hyperoxaluria [15]. In this group of patients, calcium oxalate stones are common, however, marked oxalate deposition occasionally may occur in the kidney, resulting in interstitial nephritis and loss of renal function. The mechanism responsible for the hyperoxaluria has been shown to be a consequence of increased absorption of dietary oxalate [15]. It is felt that this results from calcium and possibly magnesium (which normally binds oxalate in the gut, rendering it insoluble and nonabsorbable) being bound to fatty acids in steatorreheic states, allowing the oxalate to be absorbed. Similarly, this condition has been successfully treated by giving supplemental calcium. Furthermore, cholestyramine has also been showed to be effective in decreasing oxalate absorption from the bowel and thus in decreasing urinary excretion of this compound [15]. All other causes of interstitial nephritis are even less prevalent. Condition that cause hypercalcemia, hypercalciuria, or both can lead to the deposition of calcium in the kidney, with a resulting interstitial nephritis. Radiographic evidence of nephrocalcinosis is frequently a late finding and even then may be observed only by using the technique of nephrotomography. Thus, radiographic evidence of nephrocalcinosis cannot be relied on to establish the diagnosis even when renal function is severely impaired. In this condition, too, if the underlying cause responsible for the disturbance of calcium metabolism such as primary hyperparathyroidism, sarcoid, milk-alkali syndrome is corrected or treated, further progression of renal failure can be either slowed or prevented [16, 17]. A

final group of agents that can produce a chronic interstitial nephritis are some of the heavy metals, including copper, lead, cadmium, and uranium [10,18,20].

Reflux Nephropathy

Reflux nephropathy is the second most common renal disease in children [21]. According to the European Dialysis and Transplantation Association, it accounts for 30 percent of advanced renal failure in children under 16 years and 15 to 20 percent of severe renal disease in adults below 50 years of age. The infant kidney is especially susceptible to intrarenal reflux. Most evidence would suggest that scarring usually occurs by 2 years of age [22] and that new scarring is unusual after age 5 [22-24]. Increasing evidence suggests that severe congenital renal damage may already be present at birth [23]. This may be represent a disorder in kidney embryogenesis as a result of an abnormal development of ureteral bud. Prognosis is largely determined by the extent to which the kidney is scarred and contracted when the patient is initially seen. It has also been shown that the severity of the reflux can be correlated with the degree of renal damage and that surgical correction of reflux is associated with eradication of upper urinary tract infection and improvement of renal growth and function. However, a study in children would suggest that surgical correction of reflux offers no advantage over good medical management [24]. Although there are no control trials in adults regarding surgical correction of reflux, most studies would suggest that it does not influence the course of renal failure.

Hereditary Renal Disease

Approximately 5 to 8 percent of patients with chronic renal failure have a hereditary form of renal disease such as polycystic kidney disease, Alport's syndrome, Fabry's disease, congenital nephritic syndrome, medullary cystic disease, cystonosis, of familial amyloidosis. This is another group of renal disease for which no specific treatment is available [25]. Through genetic counselling, however, a number of these diseases are potentially preventable. The physician therefore has an obligation to advise potential parents of the risk of having children with renal disease and to determine when possible which family members are at risk or have diagnosable renal disease. In adult polycystic kidney disease, which is inherited as an autosomal dominant disorder with complete penetrance, a DNA probe has localized the majority of the cases (> 90%) to a mutation to the short arm of human chromosome 16. This technique has been used to diagnose the disease in utero in 9-Week fetus [26]. The potential success of genetic counseling is demonstrated by a study carried out at the genetic clinic at the Hospital for Sick Children in London. Approximately two-third of the families who were informed that the chances were greater than 10 percent that their children would develop hereditary disease decided to have no more children, whereas three-fourths of the families informed that the chances were 10 percent or less elected to have more children [27].

Symptomatology of Chronic Uraemia

Early in chronic renal failure, when the GFR is greater than 25 ml/min, that is, approximately 25 percent of normal, the majority of patients have few symptoms, and the biochemical abnormalities are equally unremarkable. Although arise in serum uric acid has been reported to occur early in renal, failure, the increment is usually less than 1 mg/dl [9]. Therefore, with the exception of some patients with interstitial nephritis, secondary gout is common in renal failure. Proteinuria is common at this stage, and in some glomerular disease the nephritic syndrome may be present. In association with high-grade proteinuria, the patient may also lose antithrombin III, with resulting antithrombin III deficiency, a hypercoagulable state, and a predisposition to thromboemboling complication [28]. The third major finding in the early stage of renal failure is **hypertension.** If the hypertension is not treated, arteriolar nephrosclerosis as well as focal glomerulosclerosis may develop and accelerate the loss of renal function. Since it is extremely difficult to determine whether the progressive loss of renal function is consequence of underling renal disease or hypertensive state, it is imperative that blood pressure be well controlled.

Fluid and Electrolyte Disturbance

As the GFR falls below 25 ml/min, disturbances of fluid and electrolytes may occur. The interesting aspect is that on a normal diet, even with a GFR of 3 to 5 ml/min, there may be only minimal disturbances of plasma electrolytes and the body water content. This is a result of the fact that as GFR falls there is increased fractional

clearance of electrolytes, as well as water. This has been termed the magnification phenomenon [29]. This implies that the diseased kidney continues to be under the control of a variety of biologic system that regulate the excretion of the various electrolytes, and the excretory response per nephron evoked by these systems varies inversely with the number of surviving nephron. Because of this, the individual with advanced renal failure is able to excrete the elements and waste products obtained from a normal dietary intake, maintaining reasonable water and electrolyte balance. However, the range over which the individual can maintain balance is limited. Because of the inability to dilute or concentrate urine, if water intake is restricted, the patient will develop increasing dehydration and hypernatremia, and the degree of azotemia may increase secondary to further impaired excretion of nitrogenous waste products. Conversely, if water intake is excessive, hyponatremia may occur. When placed on a low-sodium diet, the majority of patients with advanced chronic renal failure are either unable to reduce urinary sodium excretion to the level of their sodium intake or else it takes three to four times longer to do so than in a normal person. In a few patients, usually with medullary cystic disease, autosomal dominant polycystic kidney disease, or interstitial nephritis, an excess sodium intake may be necessary to maintain sodium balance [30]. A rare patient may require as much as 10 to 20 g of salt supplementation daily to maintain ECF volume and maximum renal function. In general, such severe renal salt wasting is very infrequent and occurs in the presence of far-advanced renal failure. In the absence of an endogenous or exogenous potassium load, hyperkalemia rarely occurs in patients who have a GFR

above 5 ml/min. Potassium balance is maintained in the majority of patients by a combination of increased tubular secretion of potassium, which is mediated in part by aldosterone [31-32] and the increased fecal potassium loss [32]. Since these mechanism must work to the maximum in advanced renal failure, there are several circumstances in which hyperkalemia may develop. Competitive inhibition of aldosterone with spironolactone, or inhibitors of distal potassium secretion, such as amiloride or triamterene, may induce severe hyperkalemia. A second cause of hyperkalemia is an increased intake of potassium, and third is acute acidosis that caused intracellular potassium to be released into the extracellular pool. A rough clinical estimate of the effect of acidosis on serum potassium concentration is as follows: For every decrease of 0.1 pH unit, serum potassium will increase by approximately 0.6 mEq/L. An additional cause for the spontaneous occurrence of hyperkalemia in patients with renal failure was described by Schambelan and associates [33]. Although all their patients had hyperkalemia in association with chronic renal failure, the degree of renal impairment often was not severe. The majority of their patients had either diabetes mellitus or interstitial nephritis [33]. The highlight of the findings in these patients was diminished plasma levels of rennin and aldosterone. It has been suggested that the hyperkalemia is a result of hypoaldosteronism, which is attributable to hyporeninemia. The diminished plasma rennin activity may in turn be due to an autonomic neuropathy or sclerosis of the iuxtaglomerular apparatus in the diabetic patients. Sickle cell disease, renal transplantation, and lupus nephritis have also been associated with hyperkalemia,

probably secondary to diminished tubular secretory capacity. Another cause of hyperkalemia occurs in some patients with chronic obstructive uropathy [34]. In contrast to the hyporeninemic-hypoaldosterone patients, these individuals appear to have a tubular resistance to aldosterone. Thus, when hyperkalemia is noted in patients with chronic renal failure, and other causes have been excluded, these conditions should be considered. Hypokalemia may also occur in patients with chronic renal insufficiency. A number of factors may be responsible for this findings, including poor dietary intake of potassium, diuretic therapy, hyperaldosteronism secondary to volume depletion or malignant hypertension, or specific renal tubular defect such as those found in association with the Fanconi's syndrome. The fractional clearance of phosphorus, magnesium, and calcium all increase as GFR progressively falls. As a result, plasma magnesium and phosphorus are not elevated until GFR falls below 25 ml/min [35]. Even then, plasma values rarely increase more than 1 to 2 mg/dl until GFR falls below 5 ml/min. The serum magnesium concentration may be slightly elevated when the patients is ingesting a normal magnesium intake. Since such patients have difficulty in excreting large magnesium loads, magnesium-containing antacids and laxatives should be avoided [36]. Although fractional clearance of calcium is increased in renal failure, absolute excretion is actually decreased. In contrast to other elemental disturbances, there may be major consequences as a result of the altered calcium metabolism associated with the uremic state. Parathyroid hormone levels are found to increase when GFR falls to 70 to 80 percent of normal, and 1,25-dihydroxy vitamin D3 levels fall when GFR is 40

percent or less than normal. Hypocalcemia is also a common finding in patients with advanced renal failure. Hypocalcemia probably results from a combination of factors including low 1,25(OH)2D3 with decreased gastrointestinal absorption of calcium, hyperphosphatemia , and bone resistance to the calcium effect of parathyroid hormone. Acidosis is a common disturbance at a more advanced stage of chronic renal failure. Normally, the kidneys are responsible for excreting 60 to 70 mEq of hydrogen ions daily. Although in a majority of patients with chronic renal failure the urine can be acidified normally [37], these patients have a reduced ability to produce ammonia. With advanced renal failure, total daily acid excretion is usually reduced to 30 to 40 mEq; thus, throughout the reimander of their course of chronic renal failure, many patients may be in a positive hydrogen ion balance of 20 to 40 mEq/day. The retained hydrogen ions probably are buffered by bone salts, although this has not yet been unequivocally proven. On occasion, in the early stage of renal failure, hypercloremic renal tubular acidosis with a normal anion gap may occur. With more advanced renal failure, the plasma chloride concentration becomes normal, and a fairly large anion gap may develop. In most patients with renal failure, the metabolic acidosis is mild, and the pH is rarely less than 7.35. As with other abnormalities in chronic renal failure, the primary symptomatic manifestations of the acid-base disturbances occur when the patient receives an excessive endogenous or exogenous acid load or loses excessive alkali (e.g., with diarrhea). The final stage of chronic renal failure occurs when the GFR falls below 5 ml/min. The deranged metabolic

functions present at this stage of renal failure are responsible for the striking clinical features of uremia.

Anemia

Anemia is extremely common at the advanced stage of renal failure and is of the normocytic, normochromic type. The hematocrit is usually first noted to be reduced when the BUN increases to 60 to 80 mg/dl [38]. The hematocrit progressively falls with further deterioration of renal function but only rarely is lower than 18 to 20 percent. The anemia of uremia has been felt to result from a combination of factors, including reduced erythropoietin activity, circulating factors that appear to inhibit the bone marrow response to erythropoietin, and shortened erythrocyte life span. With the recent availability of recombinant erythropoietin, it would appear that the major cause of anemia has been a failure of erythropoietin production by the diseased kidney, since uremic patients typically respond so well to exogenously administered erythropoietin [39].

Other Disorders

Disturbance in the coagulation system also occur with an advanced stage of chronic renal failure. Approximately 20 percent of uremic patients have a modest degree of thrombocytopenia, but it is rare to find a platelet count of less than 50.000. Severe thrombocytopenia may occur in patients with the haemolytic-uremic syndrome as a consequence of disseminated intravascular coagulation. However, this is not a common cause of chronic renal failure in adults. Platelet factor 3 is reduced and

platelet aggregation is decreased [40] in advanced renal failure. Another complication noted with some frequency in patients with far-advanced renal failure is involvement of the serous membranes as manifested by pericarditis and pleuritis. The involved membrane is markedly thickened, extremely vascular, and infiltrated with plasma cells and histiocytes [41]. Most patients with far-advanced renal failure have gastrointestinal symptoms that are a major part of their clinical picture [42]. Specifically, nausea, vomiting, and anorexia are extremely common. Uremic stomatitis, characterized by dry mucous membranes and multiple, bright-red, small, ulcerative lesions, may occur with advanced uremia. The neuromuscular disturbances occurring in patients with advanced renal failure were some of the earliest clinical symptoms described in uremia [43]. The initial symptoms are mild and consist of emotional lability, insomnia, and a lack of facility in abstract thinking. If the uremic state is allowed to progress, more striking changes are noted, consisting of increased deep tendon reflex, clonus, asterixis, and stupor, which progress to coma, convulsions, and death.

Skeletal Abnormalities (Renal Osteodystrophy)

Other major causes of disability in chronic renal failure, especially in children, are the abnormalities in the skeletal system. Growth is markedly retarded in children with chronic renal failure. The reason are not well understood, but there is evidence that dialysis, especially chronic cyclic peritoneal dialysis, will improve the growth rate. A high caloric and protein intake may also be helpful. Even with these measures,

however, children on dialysis rarely grow normally. The use of corticosteroids after kidney transplantation is also associated with growth retardation. More recently, recombinant human growth hormone has been used with considerable success to increase height velocity in uremic children and children who have received transplant [44]. Severe rickets with resulting deformities and disability can develop in children with advanced chronic renal failure. The typical radiographic feature of rickets is an irregular and fragmented line that separates the metaphysic from the growth cartilage. The space separating the metaphyseal line and the epiphyseal nucleus is widened, and the epiphyseal center appears late. Although this radiographic finding is classic of vitamin D-deficient rickets, uremic children with this findings characteristically show histologic changes of hyperparathyroidism rather than osteomalacia. Vitamin D and calcium therapy may be effective in correcting this abnormality. The most common skeletal disturbance found in adults with advanced chronic renal failure is hyperparathyroid bone disease, which is characterized by increased osteoclastic bone resorption. Bone histomorphometry performed in 60 nondialyzed uremic patients revealed that over 80 percent showed evidence of hyperparathyroid bone disease [45]. Only one patient in this series had histologic evidence of osteomalacia, and this patient was an alcoholic chronic pancreatitis, suggesting an etiology other than uremia. The parathyroid glands may be markedly hyperplastic, and parathyroid hormone levels are increased. Characteristically, there are few symptoms, and the diagnosis is made by finding the typical radiographic features of subperiostal resorption. The hyperparathyroid state usually resolves following renal

transplantation [46]. On occasion, however, persistent hypercalcemia that is endangering the integrity of the kidney graft may necessitate parathyroidectomy. With the advent of chronic hemodialysis, osteomalacia has been noted with increased frequency in uremic patients. This disease is characterized by bone pain, fracturing bone disease, and proximal myopathy. Unlike other types of bone disease, osteomalacia is unresponsive to any vitamin D analogues.

Metastatic Calcification

A serious complication associated with chronic renal failure is metastatic calcification. Three distinct types of metastatic calcium phosphate deposits have been described in uremic patients. The specific mechanism responsible for the development of these deposit have not been well delineated, and it is possible all three have different pathogenic mechanisms. One of the most potentially devastating forms of metastatic calcification is vascular calcification. An example of diffuse calcification is the arterial vessels of the hand of patients with advanced renal failure. This vascular calcification can affect virtually any medium-size artery in the body and rarely can cause severe vascular insufficiency with the production of gangrene of the extremities [47] and ischemic ulceration of the skin and gastrointestinal tract. Although improvement is occasionally observed following renal transplantation, in general this vascular calcification persist after renal transplantation or parathyroidectomy. Histologic evidence of vascular calcification occurs even in young individuals with uremia, and by age 50 years, radiographic evidence of

vascular calcification is present in almost 100 percent of uremic patients [48]. It is felt that vascular calcification results from an accelerated aging process of the vessels in the uremic state. The second variety of calcium phosphate deposit is felt to result from hyperphosphatemia. This is based on the fact that these deposits can be rapidly mobilized by reducing the serum phosphorus and thus the calcium phosphate product by dialysis, the use of phosphate-binding antacids, or transplantation [46]. These deposits occur in three forms. Conjunctival calcification cause redness and gritty feeling in the eyes. The major symptoms associated with these deposits is a limitation of joint movement because of the size of the deposits. The third type of deposit resulting from hyperphosphatemia is acute arthritic episodes secondary to hydroxyapatite crystal deposit in the synovium and joint fluid. The final type of calcification found in uremic patients is visceral calcification, which occurs in the lung, skeletal muscle, and myocardium. This is an amorphous calcium phosphate deposit that markedly different chemical and thermochemical properties from the other two types of calcium phosphate deposits. The vascular and hyperphosphatemic-induced calcifications appear to consist of hydroxyapatite, while visceral calcifications have the thermochemical properties of whitlockite.

Cardiovascular anomalies in adults with chronic renal failure

In adults with chronic renal failure, cardiovascular disease is responsive for 7.5 to 26% of deaths [49-50]. In a previous study, Ibels et al [51] demonstrated that in vitro arteries from uraemic patients had fibroelastic intimal thickening, calcification of elastic lamellae, and ground substance deposition. Clyne et al [52] evaluated 94 autopsies cases of chronic renal failure and concluded that most deaths among patients with end-stage renal failure were due to cardiovascular disease. The results of the present study show that pathological changes can be seen even in the arteries of uraemic paediatric patients. Recent studies in adults [53], epidemiological and clinical have shown that cardiovascular disease in patients with end-stage renal disease is frequently related to damage of large conduit arteries. Arterial disease is responsible for the high incidence of ischemic heart disease, peripheral artery diseases, left ventricular hypertrophy and congestive heart failure. The vascular complication in end stage renal disease are due to two different but associated mechanisms, namely atherosclerosis and arteriosclerosis. Whereas the former principally affects the conduct function with primarily disturbs the cushioning function of large arteries. Arteriosclerosis in cronical renal failure patients is characterized by diffuse dilation and hypertrophy of large conduit arteries and stiffening of arterial walls, and represents a clinical form of an accelerated aging

process. The main clinical characteristics of arterial stiffening are changes in blood pressure with isolated increase in systolic pressure and normal or lower diastolic pressure. The consequences of these alterations are: an increased left ventricular afterload with development of left ventricular hypertrophy and increased myocardial oxygen demand, and altered coronary perfusion and subendocardial blood flow distribution. Epidemiological studies have identified arterial remodelling and stiffening as independent predictors of overall and cardiac mortality in end stage renal failure patients. Reynolds JL et al [54] described that patients with chronic renal failure have a high circulating calcium (Ca) x phosphate (P) product and develop extensive vascular calcification that may contribute to their high cardiovascular morbidity. However, the cellular mechanisms underlying vascular calcification in this context are poorly understood. In an in vitro model, elevated Ca or P induced human vascular smooth muscle cell calcification independently and synergistically, a process that was potently inhibited by serum. Calcification was initiated by release from living vascular smooth muscle cell calcification of membrane-bound matrix vesicles and also by apoptotic bodies from dying cells. Vesicles released by vascular smooth muscle cell calcification after prolonged exposure to Ca and P contained preformed basic calcium phosphate and calcified extensively. However, vesicles released in the presence of serum did not contain basic calcium phosphate, co-purified with the mineralization inhibitor fetuin-A and calcified minimally. Importantly matrix vesicles released under normal physiologic conditions did not calcify, and vascular smooth muscle cell were also able to inhibit

the spontaneous precipitation of Ca and P in solution. The potent mineralization inhibitor matrix Gla protein was found to be present in muscular vesicles, and pre-treatment of vascular smooth muscle cell with warfarin markedly enhanced vesicle calcification. These data suggest that in the context of raised Ca and P. vascular calcification is a modifiable, cell-mediated process regulated by vesicles release. These vesicles contain mineralization inhibitor derived from vascular smooth muscle cell and serum, and perturbation of the production or function of these inhibitor would lead to accelerated vascular calcification. London GM et all. [55] described that arterial calcification is similar to bone formation, involving differentiation of vascular smooth muscle cells into phenotypically distinct osteoblast-like cells. Elevated phosphate and/or calcium trigger a concentration-dependent increase of calcium precipitates in vascular smooth muscle cell in vitro. The calcification is initiated by vascular smooth muscle cell release of membrane-bound matrix vesicles and formation of apoptotic bodies. The presences of serum prevents these changes, indicating the presence of calcification inhibitors. Arterial calcification occurs in two sites: the tunica intima and tunica media. Intimal calcification is a marker of atherosclerotic disease and is associated arterial stenotic lesions. Medial calcification influences outcome by promoting arterial stiffening whose principal consequences are left-ventricular hypertrophy and altered coronary perfusion. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in chronic kidney disease patients. Age, duration of dialysis, smoking and diabetes are risk factors for the development of arterial calcification in end-stage renal disease. Oversuppression

of parathyroid hormone and low bone turnover potentiate the development of arterial calcification in and stage renal disease. Ketteler M et all [56] report that vascular calcification are highly prevalent in end-stage renal disease. Vascular calcifications manifest as both medial and intimal calcification of arteries and are a hallmark of the accelered atherosclerosis observed in uremia. The nature of vascular calcification is progressive, and is associated with arterial stiffness and increased cardiovascular mortality. Age, duration of dialysis, and diabetes mellitus are clear determinants of the severity of vascular calcification; however, more recently novel insights into the pathomechanisms of unwanted calcification processes have been gained. Disturbances of mineral metabolism such as hyperphosphatemia and hypercalcemia appear to contribute to progressive calcification, not only by passive precipitation but by actively inducing changes in vascular smooth muscle cell behaviour toward an osteoblast-like phenotype. Specific calcium-regulatory proteins may act locally or systemically as calcification inhibitors. Dysregulations of calcification inhibitors, including fetuine-A matrix Gla protein, osteoprotegerin, and pyrophosphates may also be pathophysiologically relevant factors in the context of uremic extraosseous calcification. In the context, low serum fetuin-A levels were recently found to be associated with increased mortality in cohorts of dialysis patients. This overview intends to summarize current knowledge of the scientific concepts involved in the pathogenesis of extraosseus calcification in end stage renal disease. Others authors [57] described that significant contribution to formation of risk factors of cardiovascular complications in chronic renal failure on programmed hemodialysis is

made by disturbed phosphorus-calcium metabolism resulting in higher rigidity and diameter of the arteries (carotid and femoral arteries) studied with ultrasonic dopplerography. The above changes lead to a rise in systolic pressure and fall in diastolic one. Increased pulse pressure is an independent predictor of the risk to develop acute coronary syndrome. S. Prichard et all [58] described also cardiovascular disease in peritoneal dialysis. Lipid abnormalities in peritoneal dialysis may be more important than in hemodialysis. Vessel calcification may have a role in atherosclerotic heart disease, but this is only an inference from several clinical observations, and it remains to be defined more clearly as a risk factor. Left ventricular hypertrophy is frequent in this patient population, and is associated with specific clinical patterns and an increased risk of death. Erythropoietin treatment of anemia and tight blood pressure controls have proved to help in reversing severe left ventricular hypertrophy. Finally, is described a syndrome of the hypertrophic, high cardiac output hemodialysis heart, which is characterized by a high cardiac output in hemodialysis patients. It is associated with left ventricular hypertrophy and eventually right ventricular hypertrophy with tricuspid insufficiency. This may require fistula revision and even a switch peritoneal dialysis.

Cardiovascular anomalies in children with chronic renal failure

Left ventricular geometric and functional changes and arterial structural alterations have been well documented in adult with end stage renal disease; however, little is known about the relationship between ventricular and arterial remodelling in children with this disease [59-60-61]. However, it has been demonstrated that left ventricular hypertrophy in end stage renal patients generally starts at an early age. [62-63-64]. In other study is revealed that metabolic and hormonal factors likely play important roles in left ventricular hypertrophy.[62-65]

Hyperparathyroidism and elevated serum alkaline phosphates were associated with increased posterior wall end-diastolic thickness. [66-62]

Changes in arterial structure are known to be associated with hypertension in end stage renal disease patients. [64-67-68]. Thus, the increased intima media thickness that was observed was due to increased pressure load and systemic vascular resistance [62-69-70]. In the end stage renal disease group, they noted statistically significant correlations between cardiac and vascular parameters. The common carotid artery intima media thickness was significantly greater in end stage renal disease patients than in controls, and there was also a significant correlation between common carotid artery intima media thickness and left ventricular mass in this group [67-64-61]. The increased resistive index and pulsatility index that they observed in the common carotid artery of their end stage renal disease patients reflect increased systemic vascular resistance, which, along with hypertension causes left ventricular

hypertrophy. Other studies in adult end stage renal disease patients have noted the same changes [69-71]. Previous research indicates that these relationships between left ventricular wall thickness and intima media thickness reflect hypertensive complications in end stage renal disease [67-64-68-71].This study shows that parallel cardiac and vascular adaptation occur in children with end stage renal disease. They observed both left ventricular structural changes and increased carotid artery intima media thickness in these patients. Their findings also demonstrate cardiovascular changes that occur due to arterial alterations associated with left ventricular hypertrophy. The results suggest that evaluation of early cardiac and intima media thickness changes with echocardiography and Doppler ultrasonography is valuable for preventing cardiac complications in children with end stage renal disease [72-73].

Cardiovascular complications-the main cause of death in end stage renal disease adults-are present in a disproportionately large incidence and prevalence in children with chronic kidney disease, comparated with normal controls [74]. This increase in cardiovascular morbidity and even mortality in children and adolescents with end stage renal disease, has been attributed to classical cardiovascular risk factors (hypertensions, dyslipidemia), as well as to the presence of hyperhomocysteinaemia, inflammation, and NO-synthetase inhibitors-causing endothelial dysfunction and vascular damage. Clinical and epidemiological studies have shown that structural and functional changes in large arteries are major contributing factor to the high mortality recorded in adult uraemic patients [75]. Recognised hallmarks of chronic renal disease are: a dramatic increase in arterial stiffness, a high prevalence of surrogate,

early markers of athero-/arteriosclerosis (increased carotid intima-media thickness) and of sub-clinical (carotid plaques) or clinically overt atheromatous disease [76]. Currently, surrogate markers of increased arterial stiffness (such as pulse wave velocity), increased peripheral arterial reflectivity (such as augmentation index) or atheromatous disease (carotid intima-media thickness) are amongst the most powerful predictors of morbidity and mortality in pre-dialysis, dialysis and even renal transplant subjects [74-77-80]. Post-mortem findings suggest that atherosclerosis starts early in children and adolescents with end stage renal disease; furthermore very recent findings demonstrated that chronic kidney disease is associated with morphologic alterations of the large arteries as early as in the **second** decade of life [81-82]. Although well described in adults, comparably few data exist in children, assessing arterial stiffness and intima media thickness, to demonstrate that the prevailing metabolic milieu in (moderate-to-severe) chronic renal failure favours an increased rate of vascular damage. Groothof et al [83] analysing in 2002, 130 young adult Dutch patients with onset of end stage renal disease between age 0 to 14 described a significantly reduced arterial wall distensibility and increased stiffness, but similar intima- media thickness, compared with controls. More recently, arterial distensibility was found to be comparable with controls in paediatric renal transplant recipients [84-85]. In addition, only two other studies in children with renal impairment describe a significant increase of carotid intima-media thickness, proving also information regarding possible determinants and consequences on left ventricular changes [81-82]. In a study of Adrian Covic et al. [86] they found that,

comparated with controls, children on dialysis (14 patients in haemodialysis and 4 patients in peritoneal; dialysis duration between 1 month and 6 years) have already significant arterial wall structural abnormalities, and as a consequence, stiffer large arteries (as reflected by a aortic pulse wave velocity 225 greater than in controls) and increased reflective properties of the peripheral arterial sites (as reflected by an augmentation index 257% greater than in controls). These result suggest that even at this age, uraemia has a profound impact on arterial structure and function, and these children are at risk for accelerated atherosclerosis and arteriosclerosis. In adults, two highly reproducible markers of arterial stiffness-aortic pulse wave velocity and augmentation index have been shown to be the strongest predictors of cardiovascular mortality in haemodialysis patients: for each increase of 1 m/s in pulse vave velocity the all-cause mortality-adjusted odds ratio was 1.39; similarly, for each 10% increase in augmentation index, the risk ratio was 1.51 for all- cause mortality [78-79]. Shoji et al. demonstrated that increased arterial stiffness is the most important contributor to the excessive cardiovascular mortality rate see in diabetic end stage renal patients [87]. In a review of Querfeld [88] is described that mortality statistic of young adults with childhood-onset end-stage renal disease show that cardiovascular disease is responsible for most deaths on dialysis and after transplantation. This is most likely explained by the presence of a multitude of traditional and non-traditional risk factors in uraemia, promoting the combination of classical atherosclerosis, uremic vasculopathy, and uremic cardiomiopathy. Vascular (arterial) calcifications occur with a high prevalence in young adults and their presence correlates with non-

traditional risk factors, markers of inflammation, intake of calcium-containing phosphate binders, and the calcium-phosphorus product in serum. This might be explained by a high positive calcium and phosphorus balance in end-stage renal disease patients, which may be comparatively higher in the young. In addition, treatment with active vitamin D preparations may enhance the positive calcium and phosphorus balance and have a direct calcifying effect on the arterial wall. The biological process of vascular calcification resembles osteogenesis. These data indicate that vascular calcifications are related to non-traditional risk factors, inflammatory mechanisms, and disturbances in calcium and phosphorus metabolism in uraemia. They provide strong evidence for a change in the current management of renal disease. In a retrospectively review of Milliner et al. [89] he described soft tissue calcification in paediatric patients with end-stage renal disease. Soft tissue calcification is a recognized complication of uraemia in adult patients and has been implicated as a cause of ischemic necrosis, cardiac arrhythmias, and respiratory failure. However, soft tissue calcification has been regarded as rare in paediatric renal patients. Following a sudden death due to pulmonary calcinosis in an adolescent after renal transplantation, he retrospectively reviewed clinical, biochemical and autopsy data of 120 patients with uraemia, on dialysis, or following renal transplantation cared for at Childrens Hospital of Los Angeles from 1960 to 1983. Soft tissue calcification was found in 72 of 120 patients (60%). Forty-three patients (36%) had systemic calcinosis (Group A): the most frequent sites of mineral deposition were blood vessels, lung, kidney, myocardium, coronary artery, central nervous systemic,

and gastric mucosa. Vascular calcification was uniformly accompanied by deposit in other organs. Twenty-nine patients had small amounts of focal calcification (group B) and 48 patients had no soft tissue calcification (Group C). By multiple logistic regression analysis, the use of vitamin D or its analogues, the form of vitamin D medication prescribed, the peak calcium x phosphorus product, the age at onset of renal failure, and male sex were jointly associated with calcinosis (Group A). Vitamin D therapy showed the strongest independent association with calcinosis and the probability of calcinosis was greater in patients receiving calcitriol when comparated with dihydrotachysterol and vitamin D2 or D3. The duration of renal failure, peak serum calcium, serum calcium at death, serum phosphorus at death, and primary renal diagnosis, were not statistically associated with calcinosis. Sheth et al. [90] in their review described that cardiovascular disease is a major cause of morbidity and mortality in adult patients with end stage renal disease receiving maintenance dialysis. Coronary artery calcifications contribute to the high prevalence of cardiac disease and are associated with hyperphosphatemia, an elevated calcium-phosphorus product (CaxP), and prolonged time of dialysis. Chronic inflammation and malnutrition are also associated with an increased risk for development of cardiac calcifications. Young adults receiving maintenance dialysis develop cardiac calcifications at degree out of proportion to healthy adults of the same age and gender. Many of these young adults initiated dialysis as children or teenagers. Risk factors associated with the development of coronary artery calcification are also seen in the paediatric dialysis population. In this review they present two paediatric

patients with ANCA-positive vasculitis diagnosed with cardiac calcifications while receiving maintenance dialysis. Hyperphosphatemia and elevated CaxP product were seen in both patients and probably contributed to the development of extraskeletal calcifications. In addition, both patients had an underlying systemic inflammatory disease and significant weight loss/malnutrition that may have contributed to the early and rapid onset of cardiac calcification. Finally a study of Ahmet et al. demonstrated that pathological changes are common in the arteries of uremic pediatric patients, and that calcification and atherosclerosis are integral to this disease process. In their study, these alterations were common in the patients with uropathy. They speculate that the patients with uropathy are more prone to these alterations due to slower progression and longer duration of renal insufficiency. In this study to explain the difference between the group of uropathy and the group of nephropathy, the most important factors that promote atherogenesis in chronical renal failure (blood pressure, glucose metabolism, lipid metabolism, and fibrinogen, calcium, phosphorus and PTH levels) were comparated [91].

OUR Experience

Patients and methods

Since 2004 to 2006 twenty-six patients underwent kidney transplantation in our department. There were 15 boys and 11 girls with a mean age of 13.12 years (range 3-27 years). Twenty-five patients were submitted to dialysis treatment: peritoneal dialysis treatment was done in 8 cases, with mean duration of 14.85 months, whereas haemodialysis treatment was needed in 17, with mean duration of 25.16 months. One patient did not have any dialysis treatment, because received a previously kidney transplantation five years before in another hospital with successive rejection.

All patients were divided in two groups “A” and “B” according to primary renal disease. In the group “A” there were 18 patients (mean age 12.27 years) with congenital urinary malformations, renal displasia (12 patients), congenital urethral valve (4 pts), vesicoureteral reflux (1 pt), neurogenic bladder (1 pt); the mean duration of dialysis treatment in this group was 17.33 months. In the group “B” there were 8 patients (mean age 12.57 years) with acquired glomerular diseases; the mean duration of dialysis treatment in this group was 30.62 months.

The biochemical analyses (PTH, cholesterol, triglycerides, calcium, phosphorus, serum creatinine level, serum urea and glucose level) were performed before of kidney transplantation using routine laboratory methods and were compared between groups “A” and “B”.

Eight patients were suffering from arterial hypertension in responsive pharmacologic treatment (ACE inhibitor). In all patients was administered 1-25 vitamin D in doses

of 0.5 to 1.5 µg/day to prevent activity of parathyroid hormone. In patients, all treated with same haemodialysis, calcium carbonate was used to maintain predialysis phosphataemia at no pathological level.

In each case , a sample of artery from both donor (aortic patch of kidney) and receiver (iliac patch of graft allocation) Fig 1 (a,b) was obtained during the renal transplantation Samples were formalin-fixed and paraffin embedded. Three µm sections (3-4µm) were stained with haematoxylin-eosin (HE), with Van Gieson-Weigert (VGFE) Trichrome to study pattern distribution of elastic fibres and with Alcian PAS to valuate mucopolysaccharide allocation.

Statistics

The two-sample *t*-test, Mann-Whitney test and Fisher's exact tests were used for statistical analysis; values of $P < 0.05$ were considered as statistically significant.

Results

The groups "A" and "B" are compared in Table 1. There were no differences about age, sex, duration of haemodialysis, blood pressure, PTH, cholesterol, triglycerides, calcium, phosphorus, serum creatinine level, serum urea and glucose level.

Light microscopy showed pathological changes in 12 out of 26 receiver arteries: nine arteries showed light fragmentation of the internal elastic lamina; two had more

severe fragmentations; one case showed fragmentation of the internal elastic lamina associated with mucopolysaccharide deposits, Fig 2 (a,b,c) In our samples, no atheromatous features was observed. Pathological changes were more evident in group ”A” than “B”, but the difference was not statistically significant (P > 0.05).

Interestingly, these findings were common in six of the eight patients treated with peritoneal dialysis (75%). In the donor’s group 11 patients had light fragmentation of the internal elastic lamina, but there were not statistically significant with group A and B (P< 0,05). This patients had any pathological disease and their death was due by cerebral accident or traumatic.

Table 1

Patient number	Age *years*	Sex	Primary Disease *Group* *	duration haemo-dialysis *months*	Type of dialysis **	Arterial Changes in receiver	Arterial changes in donor group	hypertension	PTH *mg/ml*	Calcium *mg/dl*	Phosphorus *mg/dl*	Creatinine *mg/dl*	Urea *mg/dl*	Glucose *mg/dl*
1	16	F	A	16	H	No	No	No	200	9.09	8.01	8.00	51	97
2	16	F	A	7	H	No	No	No	16	9.00	6.04	5.07	84	108
3	18	F	A	30	H	No	Yes	Yes	62	8.06	2.08	9.00	**34**	**69**
4	15	F	B	29	H	No	Yes	Yes	496	10.00	5.05	6.05	57	103
5	17	F	B	10	H	Yes	No	No	11	9.09	5.03	10.00	74	72
6	10	M	B	23	H	No	No	No	117	9.03	3.07	7.05	**31**	**72**
7	10	M	B	106	H	No	No	No	568	9.09	5.04	7.80	45	67
8	16	M	B	3	H	No	Yes	Yes	287	9.04	5.03	12.06	**33**	**80**
9	16	F	A	30	H	Yes	Yes	No	175	9.03	2.05	7.00	20	**79**
10	16	M	A	13	H	No	Yes	No	33	**9.00**	4.08	7.09	37	**69**
11	12	M	A	12	H	Yes	Yes	Yes	21	**9.02**	**5.03**	6.00	56	**78**
12	14	F	A	5	H	No	Yes	No	200	**8.00**	**2.05**	5.09	50	**72**
13	5	M	A	5	P	No	Yes	No	209	10.00	5.08	9.06	67	60
14	16	M	A	0	/	No	Yes	No	18	**8.09**	4.08	4.06	53	99
15	7	M	A	6	H	Yes	No	No	267	8.00	4.01	6.00	52	**67**
16	3	M	A	4	P	Yes	No	No	180	7.00	5.02	5.09	43	**69**
17	16	F	A	30	P	Yes	No	No	20	7.03	3.03	7.00	23	**71**
18	19	M	B	24	P	No	No	Yes	400	9.00	4.03	6.05	52	**65**
19	14	M	A	25	P	Yes	No	Yes	265	7.00	5.05	10.00	35	**68**
20	5	M	A	1	P	Yes	No	No	60	8.00	5.03	6.00	45	**68**
21	17	M	A	1	P	Yes	No	No	114	9.00	3.07	7.00	37	**73**
22	3	F	B	38	P	Yes	No	No	85	9.00	3.05	6.00	23	**67**
23	27	M	B	12	H	Yes	No	Yes	21	7.00	7.05	6.05	21	**69**
24	18	F	A	80	H	Yes	Yes	No	94	8.00	7.00	9.00	51	**74**
25	6	F	A	35	H	No	No	No	36	7.00	8.00	8.00	27	**72**
26	6	M	A	12	H	No	Yes	Yes	23	7.00	7.00	7.00	50	**65**

* A = uropathy group; B = glomerulopathy group

** H = haemodialysis ; P = peritoneal dialysis

Fig 1 a: Small aortic patch of donor's kidney obtained during table preparation

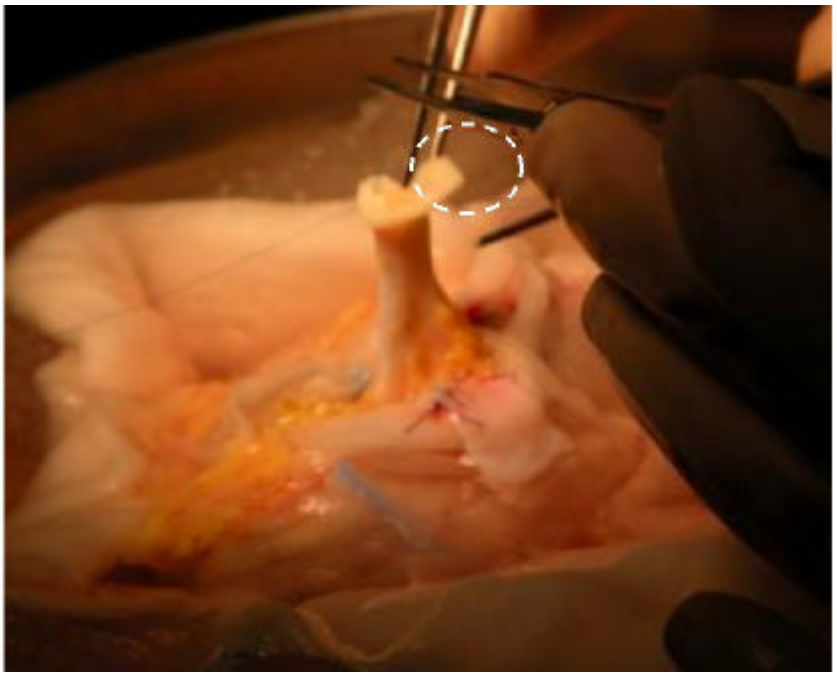


Fig 1 b: Iliac artery of receiver with allocated renal graft after removal of a small patch of wall.

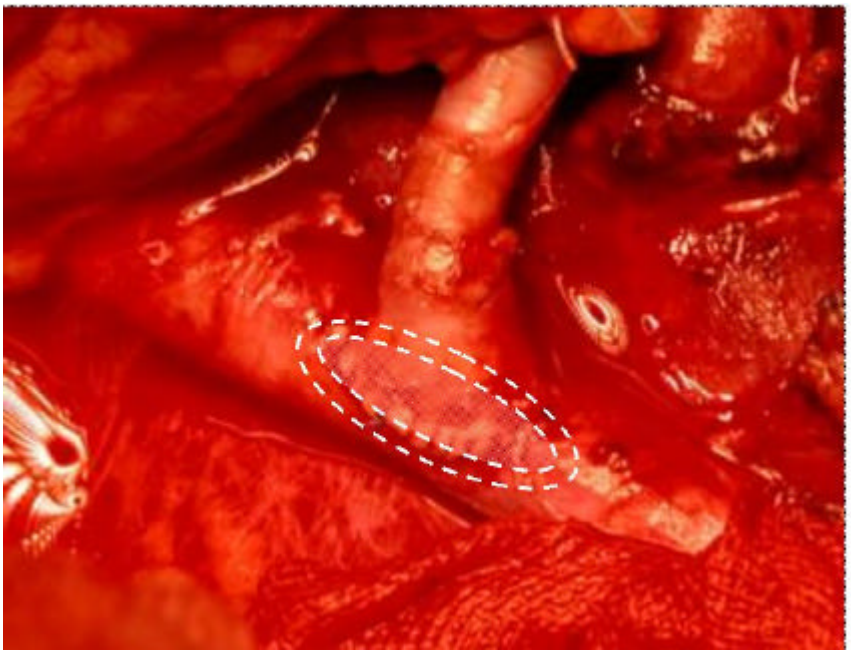


Fig. 2a Arterial wall taken from a 12-year old boy stained with Ematoxiline–Eosine, showing fragmentation of the elastic lamina

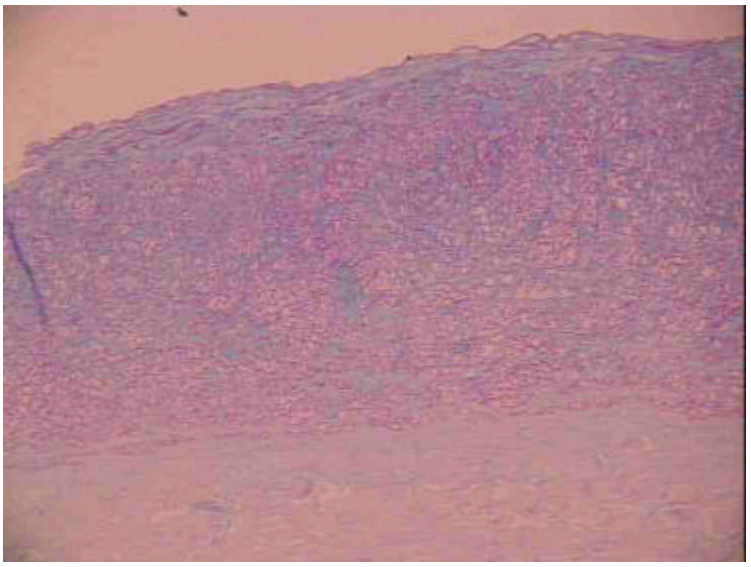


Fig 2b Arterial wall taken from a 11-year old boy stained with Alcian Pas, showing mucopolisaccharide

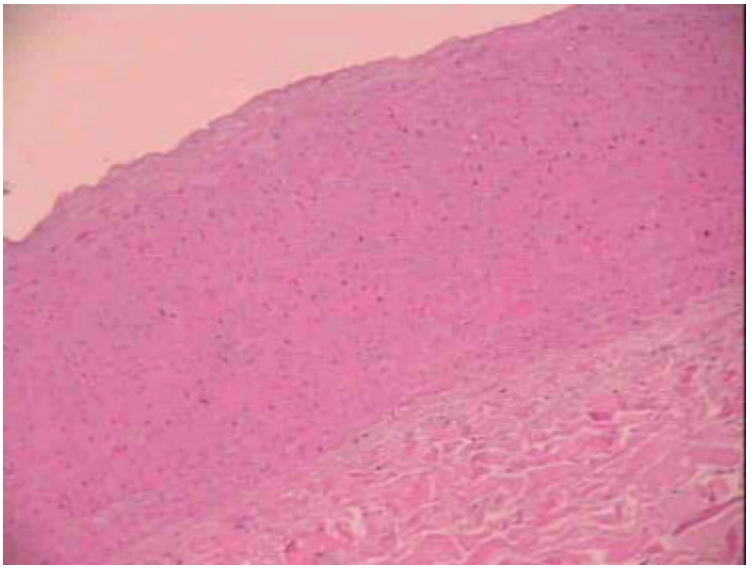
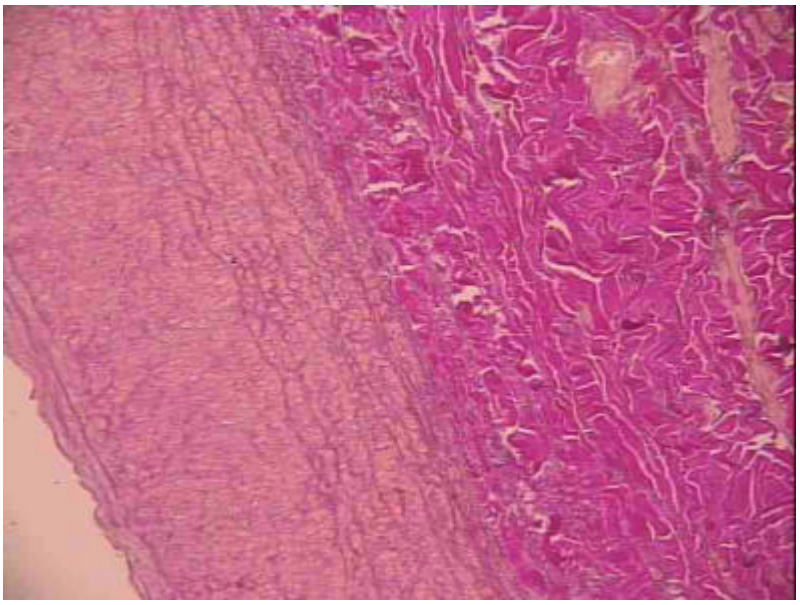


Fig 2c Arterial wall taken from a 12-year old boy stained with Van Geison-Weigert, showing severe fragmentation of the internal elastic lamina



Discussion

A review of literature shows that in adults and children with chronic renal failure there are cardiovascular modifications, particularly in the left ventricular wall, in small vessels and large arteries (iliac, aortic, carotid). In large arteries modifications are described as increased intima-media thickness and reduced arterial wall distensibility and increased stiffness [74-75-76]. Other severe modifications are represented by calcification, atherosclerosis and arteriosclerosis [80-81-82]. In some study regarding adults these modifications are due to causes that determine chronic renal failure, such as diabetes mellitus, hypertension and due to concomitant factors: hyperlipemia, smoke, age and alimentary [55]. Other causes are common with

children: hyperparathyroidism, alterated concentration of Ca/P, duration of dialysis. In children with chronic renal failure arterial modifications are due to uremic status [86], hyperparathyroidism, secondary hypertension, duration of hemodialysis and peritoneal dialysis. In our study arterial modifications are found in patients from group A with uropathy. This is consistent with the literature [91]. However these modifications are not so marked because they are represented only by alterations of elastic fibres and one case of mucopolisaccharide deposit. In our study there are no arterial calcifications, no increase of intima-media thickness, no atherosclerosis. Another interesting finding is the presence of slight modifications of elastic fibres also in the control group. This data is interesting because it demonstrates that there are arterial changes also in patients without renal failure and uremic status. These results could be explained by the fact that our patients had no pathologic alteration of parameters described in literature, such as hypertension, hyperlipemia, increased Ca/P product, prolonged hemodialysis. Our patients had normal values of blood pressure (some controlled by therapy), no hyperlipemia, normal Ca/P product. Finally, period of dialysis treatment was short compared to that described in literature. Another interesting data in our study is that in patients on peritoneal dialysis there are more arterial changes than in patients in hemodialysis ,according to the authors who attribute this to hyperlipemia associated with peritoneal dialisys [58].

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