INTRODUCTION

Chronic renal failure is the progressive reduction of the homeostatic functions of the kidney for a period longer than 3 months. It alters the internal balance in such a way as to be incompatible with life ***(Lagomarsimo et al., 1999)***. The development of renal replacement therapy has greatly improved the prognosis of these patients. Life expectancies of thousands of patients with end stage renal disease have been prolonged and their quality of life has improved ***(Esbjorner et al., 1997)***.

Cardiovascular diseases are the cause of death of 25 to 60% of patients with end stage renal disease and are a major cause of chronic morbidity among them ***(Bostom et al., 1997)***. In dialysis patients, left ventricular hypertrophy is strongly associated with dialysis-induced hypotension, arrhythmia and premature death ***(Huting et al., 1991)***.

C-reactive protein (CRP) and low serum albumin have been found to be significant predictors of mortality in hemodialysis patients ***(Fernandez-Reyes et al., 2002)***. Chronic inflammation characterized by increased CRP levels strongly predicts cardiovascular death in both non renal and renal patients. Elevated CRP concentrations associated with hemodialysis was found to be positively correlated with ventricular hypertrophy. So, it may be a simple, cheap and available useful tool for prediction and monitoring of proatherogenic reactivity and cardiac affection in hemodialysis patients ***(Park et al., 2002)***.

AIM OF THE WORK

The aim of this work is to evaluate the possible link between CRP and cardiac abnormalities among pediatric patients on regular hemodialysis treatment.

CHRONIC RENAL FAILURE (CRF)

I. Definition of CRF:

CRF is a functional diagnosis which occurs when sufficient nephrons have been destroyed, so that the glomerular filtration rate (GFR) is depressed with subsequent irreversible progression to end stage renal disease (ESRD) ***(Alfrey and Chan, 1992)***.

It can be defined as the chronic renal damage that causes more than 50% loss of renal function ***(Dawborn et al., 1994)***.

Table (1): The etiology of CRF in children in USA.

Aetiology of CRF	Percentage
Glomerulonephritis (Good pasture's syndrome, focal membranous …)	31.8%
Hereditary and Congenital (Renal dysgenesis, cystic kidney and alport's syndrome)	21.7%
Idiopathic	10.5%
Collagen vascular (Systemic lupus erythermatosus and Henoch Shonlein purpura)	7.6%
Interstitial nephritis(analgesic and other nephropathies)	4.6%
Hypertension	3.6%
Haemolytic uraemic syndrome	2.1%
Diabetic nephropathies	1.6%
Metabolic disease (systinosis, oxalate and amyloidosis)	1.1%
Sikle cell disease	0.5%
Malignancies (renal and urinary tract neoplasms)	0.3%
Others	0.6%

(Wassner, 1994).

II. Causes of CRF in Egyptian Children:

22%	nephritis
16%	reflux
13%	posterior urethral valve (PUV)
15%	congenital anomalies
5%	stones
29%	unknown

(Safouh, 1996).

Table (2): Summarizes the stages of chronic renal failure:

Stage	GFR	Clinical symptoms and signs
Impaired renal function	80-50% of normal	* Free of symptoms and signs except slight proteinuria. * Change of plasma concentration.
Chronic renal insufficiency	50-30% of normal	* Impaired calcium absorption. * Retarded growth rate. * Major stress as dehydration can lead to acute renal F.
Chronic R.F.	< 30% of normal	
- Early CRF	15-30% of normal	* Osteodystrophy. * Metabolic abnormalities.
- Late CRF	5-15% of normal	* Anaemia, hypertension.
Terminal CRF or end stage renal dis. (ESRD)	< 5% of normal	* Uremia and death unless renal replacement therapy.

(Purkerson and Cole, 1990).

When GFR decreases to less than 30% of normal, renal failure is severe and clinically evident. Acidosis, growth failure, renal osteodystrophy, hypertension and anemia are common. In the absence of therapy, the combination of anemia, acidosis and azotemia lead to increasing clinical disability. The multi-system complex known as uremia is characterized by anorexia, nausea, somnolence and malaise then progresses to vomiting, convulsions, coma and gastrointestinal bleeding. Cardiac failure and arrhythmias are common. Patients who are being treated don't progress to this stage unless an intercurrent illness induces a catabolic response to precipitate these symptoms ***(Wassner, 1994)***.

GFR below 5% of normal for age generally cannot sustain life in the absence of dialysis therapy. Clinical symptoms progress from lethargy, somnolence, anorexia and nausea to coma and death. However, individual vary in the development of symptoms relative to residual function. So institution of appropriate therapy depends upon clinical presentation rather than an arbitrary staging of renal impairment or a specific s-creatinine ***(Wassner, 1994)***.

III. The Pathophysiology of CRF:

Table (3): Summarizes the pathophysiology of CRF:

Manifestation	Mechanisms
Accumulation of nitrogenous waste products (azotemia)	Decline in glomerular filtration rate.
Acidosis	Urinary bicarbonate wasting, decreased ammonia excretion, decreased acid excretion.
Sodium wasting	Soluble diuresis. Tubular damage. Functional tubular adaptation for sodium excretion
Sodium retention	Nephritic syndrome. Congestive heart failure. Anuria. Excessive salt intake.
Urinary concentration defect	Nephron loss. Solute dieresis. Increased modularly blood flow.
Hyper kalemia	Decline in GFR. Acidosis. Excessive potassium intake. Hypoaldosteronism.
Renal osteodystrophy	Decreased intestinal calcium absorption. Impaired production of 1-25 dihydroxychol. Vitamin D by the kidneys. Hypocalcemia. Hyper parathyroidism. Secondary hyper parathyroidism.
Growth retardation	Proteincaloric deficiency. Renal osteodystrophy. Acidosis. Anemia. Inhibitors.
Anemia	Decreased erythropoietin production. Low grade hemolysis. Bleeding. Decreasing erythrocyte survival. Inadequate iron intake. Inadequate folic acid intake. Inhibitors of erythropoiesis.

Table (3): Cont.

Manifestation	Mechanisms
Bleeding tendency	Thrombocytopenia. Defective platelet function.
Infection	Defective granulocyte function. Impaired cellular immune function.
Neurologic (fatigue, poor concent, headache, drowsiness, loss of memory, slurred speech, muscule weakness and cramps, seizures, coma, peripheral neuropathy, asterixis).	Uremic factors. Aluminum toxicity.
Gastrointestinal ulceration	Gastric acid hypersecration, gastritis, reflux.
Hypertension	Sodium and water overload . Excessive rennin production.
Hypertriglyceridemia	Diminished plasma lipoprotein lipase activity.
Pericarditis and cardiomyopathy	Unknown.
Glucose intolerance	Tissue insulin resistance.

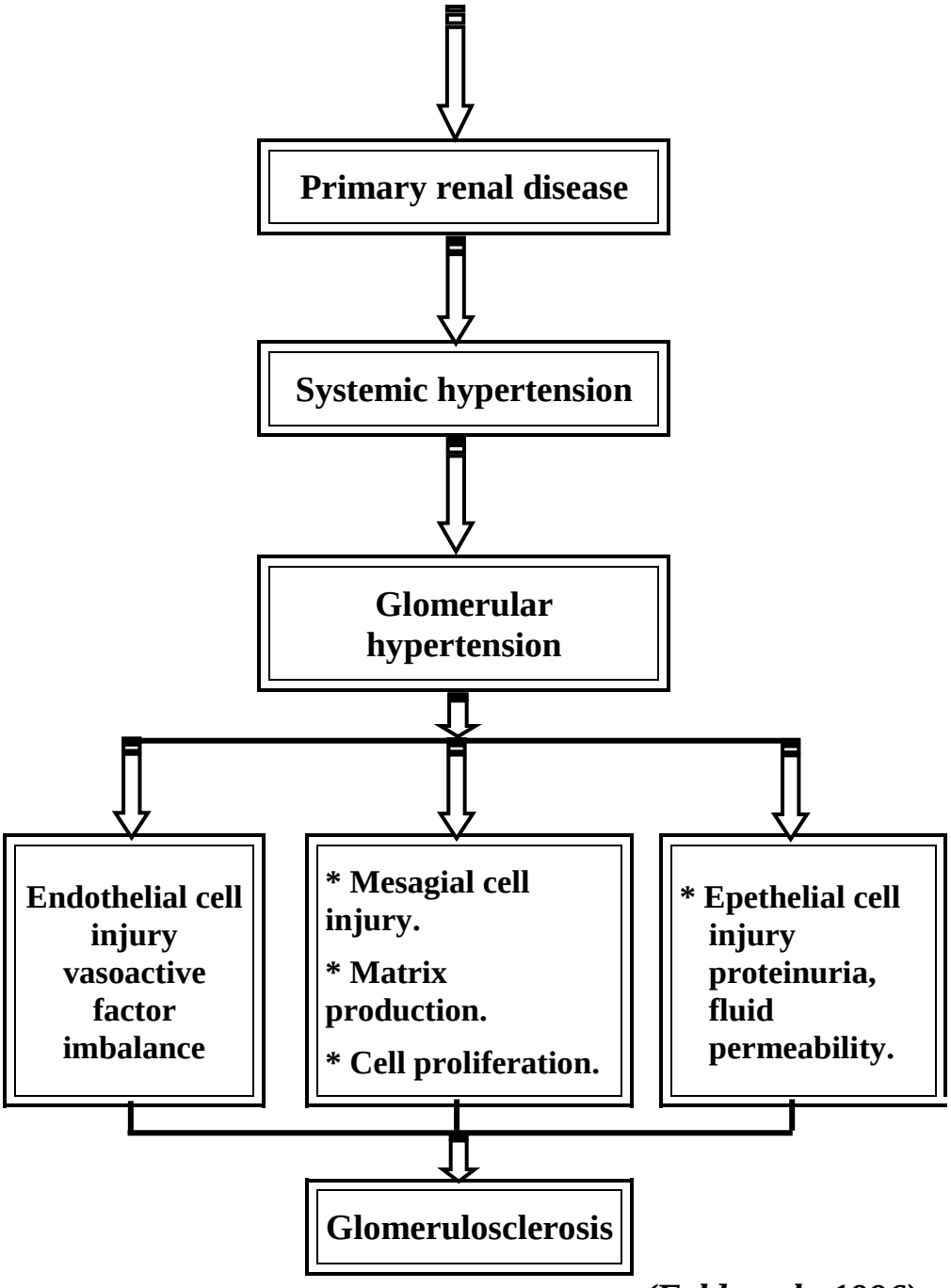
(Bergstein, 2000).

IV. Factors Affecting progression of CRF:

- Dietary protein.
- Dietary phosphorus.
- Caloric intake.
- Abnormal glomerular hemodynamics.
- Hypertension.
- Hyperlipidemia.
- Hormones (glucocorticoids, thyroxin, arginine, vasopressin, parathormone "PTH").
- Free radicals.
- Ammoniagenesis.
- Proteinuria.
- Prostaglandins.
- Coagulation (platelets derived growth factor "PDGF") and growth factors (transforming growth factor-B_1 [TGF-B_1]) .

(England and Mitch, 1995).

Fig. (1): The possible mechanisms by which glomerular hypertension causes glomerulosclerosis.



(Feld et al., 1996).

Cardiovascular events and abnormalities with CRF

Children with end stage renal disease have significant cardiac abnormalities that likely contribute to the high cardiovascular morbidity and mortality. Anemia and hypertension or their treatment probably contributes to these changes.

Children provide an ideal group to study this syndrome as they are free of potentially confounding factors such as atherosclerosis, diabetes mellitus and smoking ***(Morris et al., 1993)***.

Cardiovascular complication may occur in patients with ESRD who don't have any cardiac abnormalities before starting dialysis ***(London et al., 1993)***.

Cardiovascular complications in uremia are most commonly due to hypertension or extracellular volume expansion. Control of these, plays a vital role in conservative management and is associated with a significantly better prognosis ***(Dawborn et al., 1995)***.

Cardiac abnormalities in children with CRF can be summarized into the following:

1. Hypertension.
2. Anemia related cardiovascular manifestations.
3. Left ventricular hypertrophy and structure abnormalities of the heart.
4. Uremic endocarditis.
5. Uremic cardiomyopathy.

6. Uremic pericarditis and pericardial effusion.
7. Valvular heart disease.
8. Arrhythmias.
9. Heart failure.

I. Hypertension:

Hypertension is one of the high risk factors, which alter the cardiovascular dynamics in renal failure ***(Morris et al., 1993)***.

Anemia and hypertension are commonly associated with increased cardiac output ***(London et al., 1993)***.

Hypertension is present in approximately 80% of patients who have end stage renal failure. In recent years, it has been recognized that an increased blood pressure is a very early sign of renal dysfunction, which is observed even before glomerular filteration rate is decreased ***(Stefanski et al., 1996)***.

Systemic hypertension is present in the majority of patients with CRF but it is more common in primary glomerular diseases and in renal vascular accidents and is very late in the course of those presented with tubulo-interstitial disease or congenital malformations ***(Shuler et al., 1994)***.

A. Pathogenesis of hypertension:

Hypertension in CRF is due to chronic intravascular volume overload from impaired salt and water excretion. Moreover, decreased renal perfusion results in stimulation of renin release with subsequent increase in the circulating angiotensin II and aldosterone levels. Thus the

hypertension of CRF is either volume dependent or renin dependent or both, although other vasoconstrictors as norepinephrine, vasopressin, endothelin and others may act as a co-factor that impact on blood pressure regulation. Thus, the pressure is determined by a complex interplay of factors that modulate cardiac output and total peripheral resistance ***(Ingelfinger, 1990)***.

Besides that hypertension in chronic renal disease can be explained by the renal effects of sodium retension and inappropriate activity of renin, angiotensin system. Recent experimental and clinical data provide strong evidence that the increase in blood pressure is to a large part due to sympathetic overactivity which is triggered by afferent signals from the kidney and resetting sympathetic tone by stimulation of hypothalamic centers. The sequalae of sympathetic overactivity extend beyond their effects on blood pressure and include accelerated progression of renal failure and presumably increased cardiac arrhythemia ***(Orth et al., 2001)***.

On the other hand, hypertension of renal failure is characteristically sodium dependent. It is exacerbated by increased intake of sodium chloride and conversely responds to restriction of sodium intake or diuretic therapy ***(Davison et al., 1998)***.

Altered calcium metabolism could alter vascular reactivity and increase blood pressure through direct alterations in concentrations of ionized calcium or indirectly through effects on parathyroid hormone (PTH) or calcitriol ***(Shuler et al., 1994)***.

Extracellular volume expansion is important in pathophysiology of hypertension but it is also a

compensatory mechanism which depresses proximal tubular solute reabsorption. A primary objective in treatment is to maintain sodium balance by adjusting sodium intake and excretion and by avoiding sudden change in extracellular volume, which may compromise renal function ***(Dawborn et al., 1995)***.

B. Factors that impact on blood pressure regulation:

- Extracellular fluid volume.
- Vaso constrictors:
  - Angiotensin II
  - Norepinephrine
  - Vasopressin
  - Endothelin
- Vasodepressors:
  - PGE2, PGI2
  - Kinins
  - Atrial natriuretic peptide (ANP).
- Calcium-parathyroid axis.

(Shuler et al., 1994).

Hypertension in CRF may lead to cardiac decompensation and hypertensive encephalopathy with headache, blindness and seizures ***(Alfrey and Chan, 1992)***.

Regardless of the cause of CRF, hypertension accelerates the rate of decline in renal function. Appropriately prescribed antihypertensive therapy is a therapeutic intervention to preserve renal function. Besides the nephroprotective effect of antihypertensive therapy, cardiovascular morbidity and mortality in adulthood may

be reduced with appropriate intervention in childhood. Also, hypertension is an added risk factor in patients with progressive renal failure, proteinuria and hyperlipidemia ***(Feld et al., 1996)***.

Once patients have been started on dialysis, blood pressure is usually easier to control due to better correction of hypervolemia ***(Charra et al., 1992)***.

II. Anemia related cardiovascular manifestation:

The principle cause of anemia in CRF is the inadequate erythropoietin (a glycoprotein produced in the kidney) production by the failing kidneys. Iatrogenic blood loss during hemodialysis or frequent blood sampling also contributes to anemia ***(Kher, 1992)***.

Anemia of severe degree is common in chronic R.F. and has an important role in contributing to cardiac failure. When hemoglobin level is markedly reduced reduction in blood oxygen carrying capacity promotes an increased cardiac output to provide an adequate oxygen supply to the tissues. The work of cardiac ventricles is thus increased and when hypertension is also present, failure is likely to occur. Anemia also results in decrease in myocardial oxygen supply and this may seriously interfere with myocardial performance ***(Edlemann et al., 1992)***.

So, correction of anemia leads to fall in cardiac output, but peripheral resistance increases. So that the blood pressure remains constant in the majority of patients ***(Morris et al., 1993)***.

Left ventricular function as showed by fractional shortening was improved and the thickness of inter

ventricular septum and left ventricular hypertrophy were reduced by long-term correction of renal anemia with recombinant human erythropoietin (rhuEPo) therapy ***(Seracini et al., 1994)***.

So correction of anemia with administration of rhuEPo could reduce left ventricular dimensions and improve systolic function. However, diastolic function, an index of preload, does not change significantly ***(Fellner et al., 1993)***.

III. Left ventricular hypertrophy and structure abnormalities of the heart:

Left ventricular hypertrophy is the most frequent cardiac abnormality in patients with end stage renal disease with the prevalence ranging from 30 to 80 percent ***(Parfrey et al., 1996)***.

Left ventricular hypertrophy is clearly an important contributor to cardiovascular morbidity in all populations, and in those with renal failure, the institution of dialysis therapy does not improve preexisting left ventricular hypertrophy (LVH) ***(Levin et al., 1996)***.

The severity of hypertrophy is linked to hypertension, anemia, circulating catecholamines and myocardial calcium content ***(Canella et al., 1990)***.

Left ventricular hypertrophy is a complex phenomenon related to pressure and volume overload, and characterized by two principle echocardiographic alternations :

1. Increased internal dimension (dilatation) of cardiac cavities.