Hepcidin and Anaemia in chronic haemodialysis patients

Thesis

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List of abbreviations

A -V: Arteriovenous
ACD: anemia of chronic disease
ACE: Angiotensin converting enzyme
ADMA: Asymmetric dimethylarginine
AIDS: Acquired immunodeficiency syndrome
AT: Angiotensin I
AUC: Area under curve
BFU-E: Erythroid burst- forming units
BHK: Baby hamster kidney cells
BP: Blood pressure
C max: Maximum Plasma concentration
CAD :coronary artery disease
CAN :chronic allograft rejection
CAPD: Continuous ambulatory peritoneal dialysis
c-DNA: Complementary DNA
CFU-E: Erythroid colony - forming unit
CHF: Congestive heart failure
CHO: Chinese hamster ovary cells
CHr: Reticulocyte Hb content
CKD: chronic kidney disease
COPD: Chronic obstructive pulmonary disease
CREAT: Cardiovascular reduction early anaemia treatment
CRF: Chronic renal failure
CRI: Chronic renal insufficiency
CRP :C-reactive protein
CVD: cardiovascular disease
DCT1:divalent cation transporter
DCytb: duodenal cytochrome b
DM: Diabetes Mellitus
DMT1:divalent metal transporter 1
DST: donor specific transfusion
DVT: Deep venous thrombosis
EBPGs: European Best Practice Guidelines
EPO: Recombinant human erythropoietin
ESA: Erythroid stimulating agents
ESRD: End stage renal disease
ET-1:endothelin-1
ETUs: The erythroid transferrin uptakes
Fe2+: ferrous state
Fe3+: ferric state
FPN :ferroportin
gaEPO: Gene activated Epo
gDNA: Genomic DNA
GFR: Glomerular filtration rate
Hb : Haemoglobin
HCP1 :haem carrier protein 1.
Hct: Haematocrit
HD: Haemodialysis
Hepcidin:(*hep* atic bacteri *cid* al prote *in*).
Heph :hephaestin
HFE: haemochromatosis gene
HH hereditary hemochromatosis
HIF :hypoxia-inducible factor
HIV: Human immunodeficiency virus
HJV: haemojuvelin
HLA: Human Leucocyte antigen
HRC: Hypochromic red blood cells
I.P: Intraperitoneal
I.V. Intravenous
IDA :iron deficiency anaemia
IL: Interleukin
IL-6:interleukin-6
IREG 1:iron regulatory protein
JAK: Jamus kinase
KDOQI:National Kidney Foundation's Kidney Disease Outcomes Quality Initiative
LEAP-1:liver-expressed antimicrobial peptide-1
LPS :lipopolysaccharide
LVH: Left ventricular hypertrophy
LVMI: Left ventricular mass index,
MCH: Mean corpuscular haemoglobin
MCHC: Mean corpuscular haemoglobin concentration
MCV: Mean cell volume
MDS: Myelodysplastic syndrome
MI: Myocardial infarction
NESP: Novel Erythropoietin Stimulating protein
NKF/DOQI: The National Kidney Foundation's Dialysis Outcome
NO : nitric oxide
NRAMP2: natural resistance-associated macrophage protein
NSAID: Non steroidal anti-inflammatory drugs
NTBI :non-transferrin-bound iron
OSAS :Obstructive sleep apnea syndrome
PCKD: Polycystic kidney disease
PD: Peritoneal dialysis
PKD ;polycystic kidney disease
PRCA: Pure red cell aplasia
PTFE: Prosthetic Percutaneous Ethylene
PTH: Parathormone
QOL: Quality of Life
RBC :red blood cells or
RLS: restless legs syndrome
RR: Relative risk
RRF:Residual renal function
RRT renal replacement therapy
s.c: Subcutaneous
Slc11a2:Solute carrier family 11, member 2
SLE: Systemic Lupus erythematosis
Steap 3: six-transmembrane epithelial antigen of the prostate 3
s-TfR: soluble transferring receptor
SVR: sustained virological response
Tf :transferrin
TfR 1:Tf receptor 1
TGF β ;transforming growth factor
TIBC: Total iron binding capacity
TNFα :tumor necrosis factor-α
TSAT: Transferrin saturation
VHL :Von Hippel-Lindau
WBC:white blood cells).
WHO: The world health organization
ZPP: zinc protoporphyrin

Abstract

Background: Hepcidin has recently been recognized as a hormone essential to the negative regulation of iron. Synthesis of hepcidin is increased by iron overload or inflammation, and decreased by iron deficiency, anemia and erythropoietin. Dialysis patients frequently suffer the effects of both hepcidin increasing and decreasing factors. *(Tsuchihashi D;2007)*

Methods: In this study, we investigated pro-hepcidin in dialysis patients while minimizing or manipulating these factors. We measured the serum pro-hepcidin in 35 haemodialysis patients without inflammation (the HD group) and 10 age-matched healthy volunteers.
Iron status, complete blood count, creatinine were assessed using standard laboratory methods. Hepcidin and CRP were measured using commercially available kits.

Results: Serum iron, TIBC, TSAT, erythrocyte count, Hb, Ht, platelet count were lower, whereas ferritin and hepcidin were higher in haemodialyzed patients over controls.
Hepcidin correlated positively ferritin .CRP and erythropoietin dose and negatively with erythrocyte count, Hb, and Ht in haemodialyzed patients
hepcidin was lowest in the haemodialysis group with haemoglobin higher than 10. It was highest in the transplant group.

Conclusions: Elevated hepcidin levels in haemodialyzed patients may be due to functional iron deficiency and anemia. Liver plays an important role in the synthesis of hepcidin. Low-grade inflammation, frequently found in haemodialyzed patients, might also contribute to elevated hepcidin concentration. The hypothesis that hepcidin might link anemia, inflammation and liver function in kidney disease should be further evaluated.
Lowering hepcidin in CRF patients by antihepcidin therapy might decrease the need for iron therapy and erythropoietin therapy with all their potential hazards .Lowering hepcidin may be associated with a better control of anaemia.

Key Words: CRF, Dialysis, Transplantation, Anaemia, Erythropoietin, Iron, Iron metabolism, Hepcidin , Pro-hepcidin

Chronic renal failure

Definition

Chronic renal failure (CRF) is a functional diagnosis characterized by progressive and irreversible decline in glomerular filtration (GFR),*(David; 1996),*and an increasing inability of the kidney to maintain normal low levels of the products of protein metabolism ,normal blood pressure ,haematocrite, sodium, water, potassium and acid base balance*.(Bruce; 2000 and Remuzzi et al.; 1997)*

Epidemiology and aetiology

The incidence and prevalence of end-stage renal disease (ESRD) are rising in Europe, the USA, and Japan. Prevalence is rising more steeply than incidence, due mostly to improved efficiency of treatment, patients are surviving longer. Hypertension and diabetes, the main causes of progression from chronic kidney disease (CKD) to ESRD, are becoming more frequent in the general population and make a large contribution to the rising incidence of ESRD.More effective therapies for other conditions have introduced new complications for patients with CKD, thereby also increasing the incidence of ESRD. Increased survival in the general population is reflected in the greater number of elderly people requiring care for ESRD. ESRD is a great economic burden and one that will increase as the incidence and prevalence of the disease increase. This needs to be considered when planning treatment. Prevention and early treatment of hypertension and diabetes will have the greatest impact on the future prevalence of ESRD and the costs associated with its treatment.*(Bommer J; 2002)*

Tables 1 and 2 show that the origin of renal disease in new patients on haemodialysis (HD) differs markedly between countries. For example, glomerulonephritis accounts for about 15% of ESRD in Germany, but only 8.7% in the United States Renal Data System (USRDS) report.
One reason for the differences might be that diagnosing glomerulonephritis depends on kidney biopsies, which are performed at different rates in different centres. Countrywide studies of patients with glomerulonephritis, such as the UK Medical Research Council's Glomerulonephritis Registry, might help to optimize treatment and reduce progression of renal failure.
Different diagnostic procedures and techniques cannot fully explain the difference in frequency of cystic kidney disease between Germany and the USA. It can be assumed that ultrasonography is performed on all patients with CKD, so polycystic kidney disease (PKD) will rarely be missed. However,

cystic kidney disease was observed in 2.1% of patients on dialysis in the USRDS report compared with 5.5-6.4% in Germany. *(Frei U et al.; 2001)*

More intense education and genetic counseling of young people may have resulted in a reduced incidence of PKD in Germany from 1997 to 2000. Similarly, recent legal changes in the use of analgesia may have reduced the incidence of reported analgesic nephropathy in Germany. The incidence of interstitial nephritis may have decreased because the risk of its occurrence is better understood and therefore prevented in clinical practice, although the evidence for this is not clear. *(Bommer J.; 2002)*

Prevalence and socio-economic aspects of CKD

Table 1. CKD by cause in incident HD patients in Germany

	Patients (%)			
	1997	1998	1999	2000
Diabetes type 1	6.4	6.3	5.6	4.8
Diabetes type 2	24.6	26.6	29.0	31.4
Glomerulonephritis	16.3	17.0	14.5	15.2
Hereditary kidney disease	0.5	0.5	0.4	0.4
Cystinosis	0.06	0.03	0.03	0.05
Primary oxalosis	0.06	0.03	0.02	0.02
Fabry's disease	0.01	0	0	0.02
Interstitial nephritis (unknown origin)	5.5	4.6	3.8	3.3
Pyelonephritis of neurological causes	1.1	1.3	1.0	1.1
Obstructive kidney disease	2.1	2.0	2.1	1.8
Interstitial nephritis	0.9	0.8	1.0	1.4
Analgesic nephropathies	2.8	2.2	2.1	1.9
Toxic effects	0.6	0.8	0.7	0.6
Congenital	0.5	0.3	0.6	0.5
Systemic diseases (plasmocytoma)	1.4	1.1	1.2	1.6
Amyloidosis	0.9	0.8	1.1	0.8
Immunological diseases	1.5	1.3	1.3	1.2
Unknown	11.2	11.3	10.8	9.3
Vascular causes	12.6	12.9	14.6	14.4
Wegener's granulomatosis	0.9	0.8	0.7	0.8
Various	3.7	4.0	3.7	3.9
Cystic kidney disease	6.4	5.2	5.7	5.5

(Jürgen Bommer, 2002)

Table 2. Kidney disease in incident HD patients by cause: USA

	Patients (*n*)	Proportion of total (%)	Change/year 1991–1995 (%)	Change/year 1995–1999 (%)
Diabetes	32 016	44.8	9.6	9.8
Hypertension	19 683	27.6	2.3	7.8
Glomerulonephritis	6242	8.7	3.3	3.5
Cystic kidney disease	1490	2.1	3.2	3.9
Other urological diseases	1301	1.8	2.3	6.2
Total	71 421	100	6.3	7.3

Table 3 shows a marked influence of race on hypertensive ESRD. For example, between 1995 and 1999, a third of black patients but only 12% of Native Americans on dialysis had ESRD with underlying hypertensive kidney disease. *(Bommer J.; 2002)*

Table 3. Primary disease (%) in incident dialysis patients 1995–1999 ($n = 392\,847$)

	Patients (%)				
	White	Black	Native American	Asian	Hispan
Diabetes	42.8	41.6	68.2	46.0	59.6
Glomerulonephritis	10.3	8.2	8.4	15.6	9.1
Secondary glomerulonephritis/vasculitis	2.3	2.6	2.1	2.3	2.5
Interstitial nephritis	5.0	2.1	1.9	3.2	2.4
Hypertension of large vessels	24.1	32.8	12.0	23.3	16.6
Cystic/congenital kidney disease	4.0	1.5	1.3	2.2	2.6
Tumours	2.3	1.2	0.9	0.8	0.9
Miscellaneous	3.5	4.8	1.8	1.4	2.1
Uncertain	4.3	3.0	2.6	4.1	3.6
Missing	1.4	2.2	0.8	1.1	0.6

Aetiology of CRF in Egypt

In Egypt the causes are differently arranged according to their prevalence as shown in the results of the study done in 1996 by El-Sharkawi.**(Table 4)**

Table.4 Causes of CRF in Egypt

Causes	**1980-1987**	**1988- 1990**	**1991-1993**
Chronic pyelonephritis and obstructive uropathy	28.6%	26.6%	27.3%
Chronic glomerulonephritis	30.4%	22.8%	20.2%
Miscellaneous diseases	7.9%	9.4%	9.6%
Hypertensionand nephrosclerosis	5.7%	8.1%	8.6%
Diabetes mellitus	5.5%	8.5%	8.4%
Congenital diseases and polycystic kidney	2.5%	2.8%	2.6%
Unknown aetiology	17.6%	21.8%	23.3%

Chronic pyelonephritis in Egypt is the leading cause of CRF and Diabetes Mellitus (DM) comes late, though more recent studies indicate increased prevalence of DM. (It accounts for about 13.5% of the causes of CRF in Egypt).Also the unknown causes make up more of the Egyptian ESRD patients compared to USA study. *(Afifi et al.; 1999).*

Pathophysiology of renal failure

Irreversible and progressive destruction of nephron mass leads to increased glomerular capillary flow and pressure in the intact nephrons which undergo compensatory hypertrophy. However, as a result of persistent hyperfiltration the latter eventually suffer glomerulosclerosis. (**Fig.1)**
Regardless of the primary cause of nephron loss, some usually survive or are less severely damaged.These nephrons then adapt and enlarge, and clearance per nephron markedly increases. If the initiating process is diffuse, sudden, and severe such as in some patients with rapidly progressive glomerulonephritis), acute or subacute renal failure may esue with the rapid development of ESRD. In most patients progression is more gradual and nephron adaptation is possible. Glomerular hypertrophy, a marked increase in glomerular plasma flow and and single-nephron GFR, and increased capillary pressure occur. Focal glomerulosclerosis develops in these glomeruli and they eventually become nonfunctional. At the same time that glomerulosclerosis develops, proteinuria markedly increases and hypertension worsens.*(Luke R; 2003)*

Some antihypertensive ACE inhibitors slow this process and diminish proteinuria; even at the same level of blood pressure control, other drugs such as β-blockers, hydralazine, and dihydropyridine calcium channel blockers do not. Similar pathophysiology occurs in humans and ACE inhibitors and ARBs are also protective by mechanisms that include both a reduction in systemic blood pressure and a fall in intra glomerular pressure.*(Yu HT; 2003)*

Other mechanisms of progression that are probably important in the sclerosis of adapted glomeruli include glomerular coagulation, hyperlipidemic effects, and mesangial cell proliferation. The pathophysiology of focal glomerulosclerosis has been compared with that of atherosclerosis. It is likely that tubulointerstitial fibrosis and interstitial inflammation contribute to nephron failure in the process of nephron adaptation. This result is in part secondary to the potential of proteinuria to cause proximal tubule atrophy enhanced apoptosis); the release of transforming growth factor, angiotensin II secondary to tubular injury; and nephron ischemia secondary to arteriosclerosis.
This process of nephron adaptation has been termed the “final common path” The ability of nephrons to adapt by enlarging and increasing function has beneficial effects in maintaining whole-kidney GFR, as well as rates of sodium, potassium, phosphorus,acid , and solute excretion, especially the end products of protein metabolism that cause the uremic syndrome. Adapted nephrons enhance the ability of the kidney to postpone uremia, but ultimately

the adaptation process leads to the demise of these nephrons. Much of the present experimental work is aimed at maintaining adaptation but without deleterious effects on the nephron by blocking the release and effects of angotensin II and aldosterone, endothelin, and transforming growth factor **β** which promote mesangial proliferation, fibrogenesis, and vasculo- pathic changes. If these processes are, initially at least, important in postponing ESRD, it is clear that monitoring renal function only by changes in serum creatinine is, at the least, insensitive to nephron dropout because whole-kidney GFR can be maintained by increasing single–nephron GFR in surviving adapted nephrons. Quantitation of urinary protein excretion, the use of urinary microscopy, and, perhaps in the future measurement of potentially harmful urinary and blood cytokines may all be important. Whenever possible, primary continuing injury must also be treated.*(Luke R; 2003)*

Two other important concepts in understanding progression of CRF are the ***intact nephron hypothesis*** and ***the trade off hypothesis*****.**The first states that in general ,adapted nephrons behave like normal nephrons .Some of the failure to regulate sodium and water relates to increased solute excretion per nephron –in effect, an osmotic diuresis of the remaining nephrons that impairs sodium and water conservation, especially in states of extracellular fluid volume depletion. Thus ,renal concentrating ability is lost ,as well as the ability of the remaining nephrons to adjust to low and high intake of sodium , water , potassium ,and other dietary solutes ,because these nephrons are functioning at maximum capacity even with normal intake of these substances.
Renal handling off solute is influenced by hormonal effects e.g.as serum phosphate levels rise secondary to a fall in GFR, plasma calcium levels decrease and serum PTH increase , thereby decreasing tubular reabsorption of phosphate, and serum phosphate returns to normal .Elevation of PTH level occurs relatively early in progressive renal disease and contributes to the pathogenesis of renal osteodystrophy .***The trade off*** is increased renal excretion of phosphate with serum level maintained by at the expense of elevated PTH .Similarly normal serum potassium levels can be maintained at the expense of elevated aldosterone secretion.*(Yu HT; 2003)*

The progressive drop in GFR, osmotic diuresis of the remaining nephrons, and elevated hormone levels all contribute to restrict the flexibility of the kidney to adapt to low and high intake of various solutes. CRF is thus associated with progressive loss of the ability of the kidney to maintain a constant internal environment in the face of substantial changes in solute intake. Adapted nephrons have not only an enhanced GFR but also enhanced tubular functions. *(Hsu CY et al.; 2003)*

Finally, it is likely that the growth factors responsible for hypertrophy of nephrons also eventually lead, after chronic dialysis for some years , to acquired renal cyst formation; these cysts are believed to be premalignant.
As the GFR drops from normal levels (about 125 ml/ min in an average sized man and 10% lower in women) to 35-50% of normal, the overall renal function is sufficient to keep the patient symptom free and blood urea and serum creatinine within normal range or they may get only slightly elevated .As the GFR drops to 20-35 % of normal, manifestations of renal insufficiency appear. Further drop of GFR below 20% of normal results in overt renal failure.*(Luke R; 2003)*

The term uraemic syndrome refers to the constellation of symptoms, signs and altered body physiology and chemistry that arises from impairment of renal functions. It results mainly from toxic accumulation of urate products, but depletion of essential compounds and failure of the biosynthetic functions of the kidney also contribute.*(David; 1996),*

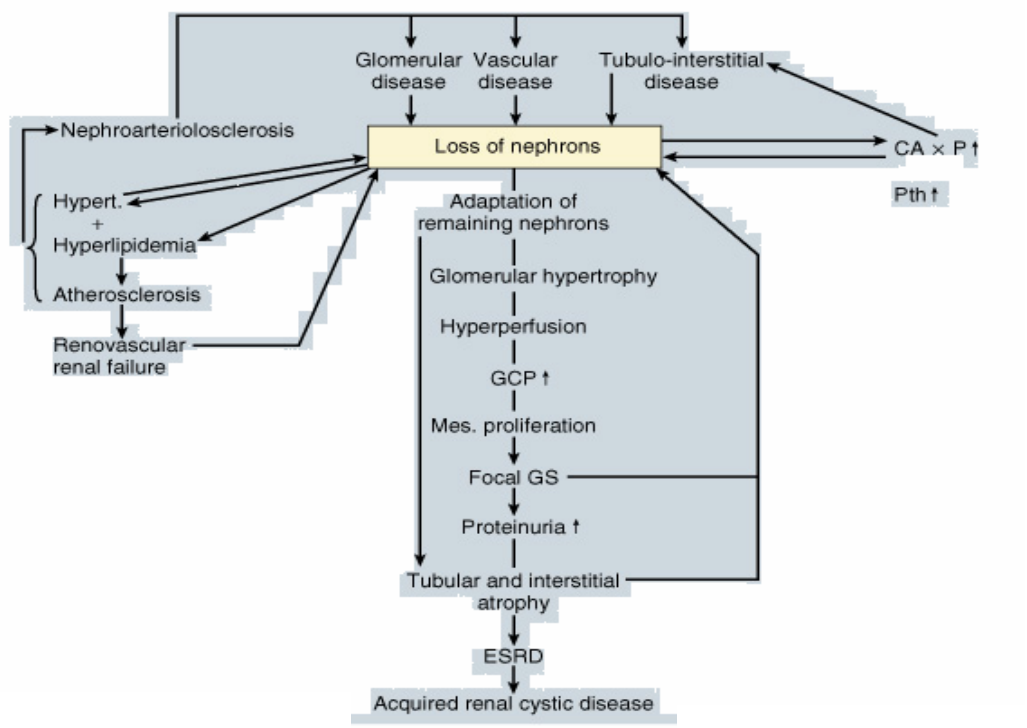
The most likely uraemic toxins are products of protein and amino acid metabolism since their metabolites depend mainly on the kidney for excretion. Urea retention probably contributes to only a few clinical abnormalities including malaise, anorexia, vomiting and headache. Creatinine may cause adverse effects after conversion to sarcosine and methylguandine. Nitrogenous products with a molecular weight of 500 to 12.000 daltons (so-called middle molecules), peptide hormones (PTH, gastrin glucagons, calcitonin) purine metabolites, aliphatic and aromatic amines, phenols and indoles may all be involved. *(Schreier ; 1997)*

Many of the manifestations of uremia are due to inhibition of active efflux of Na+ across the cell membrane leading to increased intracellular concentrations of Na + and decreased intracellular concentration of K+ with consequent reduction in the magnitude of transmembrane voltage. There is also inhibition of Ca2+flux across the cell membrane. The increased intracellular Na+ concentration leads to cellular overhydration. Despite the deficits of intracellular K+, serum K+ usually remains normal or high due to metabolic acidosis which induces efflux of K+ from cells. However, in late stages hyperkalaemia consistently occurs. The total body content of Na+ and water is increased modestly. Hyponatraemia may develop as a result of excessive water ingestion but hypernatraemia rarely occurs. As the GFR drops to about 30% of normal, metabolic acidosis develops as a result of decreased ammonia formation from glutamine by the renal tubules. The diversion of glutamine metabolism to the liver results in the formation of urea and hydrogen ion. The latter leads to depletion of plasma bicarbonate, and

consequent chloride retention by the kidney, resulting in hyperchloraemic metabolic acidosis. *(Yu HT; 2003)*

As the GFR drops further, retention of phosphate, sulfates and other unmeasured anions occurs further aggravating the metabolic acidosis.*(Schreier ; 1997).*The traditional view has been that anaemia becomes more common and severe with decreasing renal function. However, more recent data indicate that anaemia starts much earlier during the progression of CKD.*(Hsu CY et al.; 2003).* Although it varies, the degree of renal insufficiency at which the Hb concentration drops below 11 g/dl is typically when renal function falls below a GFR of 30 ml/min. Some patients, particularly diabetic patients, can develop anaemia earlier or more severely than other patients, at GFR levels of up to 45 ml/min *(Bosman DR et al.; 2001).*
In fact, anaemia has been found to be two to three times more prevalent in patients with diabetes compared with the general population at all levels of GFR. This may be due in poorly treated diabetic patients, or to reduced red cell deformability. *(Thomas MC et al.; 2003)*

Fig.1 Pathophysiology of CRF



Stages of renal failure

The presence and stage of chronic kidney disease should be established, based on presence of kidney damage and level of kidney function [GFR], irrespective of diagnosis .Table 5 shows the stages of CKD as classified in DOQI guidelines 2002

Table 5 Definition of the five stages of chronic kidney disease (CKD)

Stage	Description	GFR (ml/min/1.73 m^2)	Action
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment, treatment of co-morbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild decrease in GFR	60–89	Estimating progression
3	Moderate decrease in GFR	30–59	Evaluating and treating complications
4	Severe decrease in GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uraemia present)

1. Kidney damage for >3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either pathological abnormalities; or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m2 for >3 months, with or without kidney damage

Stage 1 CKD is recognized by the presence of kidney damage at a time when GFR is preserved and includes such patients as those with albuminuria or abnormal imaging studies.

Stage 2 CKD includes patients with evidence of kidney damage with decreased GFR (60 to 89 ml/min per 1.73 m2). The guidelines recognize the fact that decreased GFR can occur in the absence of overt signs of kidney damage. This would include infants and older adults, individuals on vegetarian diets, following unilateral nephrectomy, or with prerenal causes such as congestive heart failure and cirrhosis. Finally, all patients with GFR <60 ml/min per 1.73m2 are classified as having CKD irrespective of whether kidney damage is present

The staging of CKD is advantageous for many reasons. Having a common classification scheme will facilitate defining the epidemiology of CKD and its complications in the population. This classification will provide a common language for patients and the practitioners involved in the clinical care and research of CKD. The system also provides a framework action plan.

The identification and staging of CKD is not meant to minimize the need to diagnose the specific cause of the kidney disease and institute focus therapies if these are available.*(Rosenberg ME; 2003)*

Recommendations for the screening of CKD

To slow the progression of kidney failure, to prevent the consequences of CKD and to decrease cardiovascular mortality associated with CKD, it is crucial to detect patients with CKD early and to optimize their care. To assist physicians in patient management, several recommendations have been identified for the screening of patients at risk of CKD and for the management of patients with established CKD.
The recommendations on screening for CKD are intended to cover the majority of cases (but not the exceptions). The guidelines shown in table 6 focus on feasibility in daily practice but do not determine who should apply them. Above all, they should help raise awareness as to whether or not and when a patient should be referred to a nephrologist. *(Rossert J. and Wauters J.; 2002)*

Patients at risk for developing CKD.

The following factors contribute to the risk of developing CKD:

1. Arterial hypertension or cardiovascular disease
2. Diabetes mellitus
3. Age above 60 years
4. Family history of kidney disease
5. Recurrent urinary tract infections
6. Exposure to certain drugs [e.g, NSAIDs , antibiotics and contrast agents] or chemicals.

Screening methods

As a screening test, a urine dipstick analysis should be performed using an untlined spot urine sample to screen not only for the presence of protein, but also for red blood cells (RBC) or white blood cells (WBC
Who ,how and when to evaluate for CKD is summarized in table 6.

Table 6. Screening for chronic kidney disease

Who to screen for chronic kidney disease?

Patients at risk
Arterial hypertension cardiovascular disease
Diabetes mellitus, other systemic disease
Age > 60 years
Family history of' kidney disease
Recurrent urinary tract infections
Exposure to certain drugs or chemicals

How to screen for chronic kidney disease?

Dipstick (untimed spot urine sample) for proteinuria, WBC and RBC If *postitve for proteinuria*: measure total protein to creatinine ratio in an untimed spot urine sample
If *negative for proteinuria*:perform a specific search for microalbuminuria in patients with diabetes mellitus or hypertension If *positive for WBC or RBC*: perform a sediment analysis in an untimed spot urine sample Estimate creatinine clearance Use Cockcroft-Gault formula:

$$\frac{(140 - \text{age}) \times \text{weight}}{\text{serum creatinine (umol /l)}} \quad (\times 1.23 \text{ for men})$$

When to evaluate screening'?

If screening was negative:
Every 1-3 years, depending on risk factors
If abnormality is evidenced at screening:
Perform diagnostic and therapeutic work-up *(Rossert J. and Wauters J.;2002)*