International Journal of Scientific and Innovative Research 2016; 4(2) : 9-15
P-ISSN 2347-2189, E- ISSN 2347-4971

PREVALENCE AND STUDY OF DIFFERENT STAGES OF CHRONIC KIDNEY DISEASES (CKD) IN PATIENTS.

Shailza Verma[1], Dheeraj Upadhyay[1],Rahul Singh[1],Neha Pandey[1], Saurabh Singh[1],Vishwajeet Pandey[1],*Sulabh Kharbanda[2]

[1]Graduate Student,Department of Biotechnology, Saroj Institute of Technology and Management, Lucknow, Uttar Pradesh, India,[2]Assistant Professor, Department of Biotechnology, Saroj Institute of Technology and Management, Lucknow,Uttar Pradesh, India.

*Address for correspondence: Dr. Sulabh Kharbanda,Assistant Professor, Department of Biotechnology, Saroj Institute of Technology and Management, Lucknow, India.
Email ID: sulabhchandra2000@gmail.com

ABSTRACT

Chronic kidney diseases are quite prevalent in USA and western countries due to hypertension and diabetes. Majority of the population in USA and western countries is affected by chronic kidney diseases leading to increased levels of creatinine and albumin in blood due to increase in filtration pressure inside the juxtaglomerular apparatus of kidney. In India also the rate of disease affliction has increased tremendously to 7%, with a range varying from 5%-13% in various regions like Jharkhand and Chandigarh.The symptoms of kidney disease include changes in the color of urine to darker in appearance with froth due to the presence of albumins as a result of increase in porosity of basement cell membrane cells and podocytes with changes in pressure affecting the levels of antidiuretic hormone, angiotensinogen and renin in kidney along with cirrhosis and the appearance of blood in urine. In addition to this there is retention of fluid in legs, feet, face, hand and ankles of patients suffering from chronic kidney diseases.

Keywords:CKD; Nephritis; Nephropathy; Anemia; GFR; Biomarker; Cell Signaling; Transplant.

INTRODUCTION

Chronic kidney disease (CKD) is prevalent in many countries of the world like USA, India etc.The major causes of chronic kidney diseases include lack of iron in diet which causes anemia[22], hypertension, diabetes and stress[1].Patients were divided into groups in which one group was given oral dose of iron(ferritin) and second group was given intravenous dose of iron. The levels of albumin, hemoglobin, proteinuria, transferrin,and glomerular filtration rate(GFR) were unchanged in both the groups of patient samples analysed by plasma iothalamatemeglumine method but the levels of serum ferritin and logarithmic-ratio of concentration of protein in urine andcreatinine were changed and increased and decreased for oral group and intravenous administered iron group respectively. Various infected samples from skin, bone, lung, sepsis, urinary tract infections (UTI), cardiovascular diseases, angina, stroke, and cancer related patient samples. The rate values for the ratio of intravenous iron to oral dose of iron and p-values were reported to be as follows for each sample (depending on the number of samples in each group which were adjusted accordingly like skin-3.79, and p value-0.013, lung value-4.53,and p-value-0.022, bone value-0.59, and p-value 0.2 (values adjusted further), urinary tract infections value(less number of samples)-2.37, and p-value-0.2 (samples-less and less harmful effects), sepsis (sample-more and more harmful effects) value-2.59, p value-0.056, cardiovascular-value-2.51,p-value-is equal to-0.001,arrhythmias value-1.29, p-value-0.2,angina-value-1.03,p(statistical)-value-0.2, hyperkalemia- value-0.69, p-value-0.2, cancer related samples value-2.07, p-value-0.2[1]. A comparative study was done for the analysis of CKD in patient samples from 48 hospitals and consisting of 4712 testing specimens. The samples were analysed for different types of diseases associated with kidney damage as mentioned in Table 1 below[2].

SNo.	Disease name	Percentage (%)
1.	Diabetes	41%
2	Hypertension	22%
3	Chronic glomerular nephritis	16%
4	Chronic interstitial disease	5.4%
5	Ischaemic nephropathy	5.4%
6	Obstructive uropathy	2.7%

Table 1: The percentage of occurrence of different diseases associated along with kidney damage in patient samples in A.I.I.M.S, New Delhi, India [2].

REVIEW OF LITERATURE

Diagnosis of Chronic Kidney Diseases

The diagnosis of chronic kidney diseases includesimbalances in the concentrations of ions, metabolites and hormones in the blood, and the kidney and changes in the glomerular filtration pressure (GFR). A decrease in the concentration of iron causes anemia and damage to the kidney along with decrease in the secretion of erythropoietin. There is increase in the levels of phosphate in kidney leading to a condition of hyperphosphatemia and less secretion of phosphate in blood, changes in the concentration of calcium, parathyroid hormone due to alteration in the levels of parathyroid hormone leading to bone mineral metabolism imbalance. Further hypertension is observed in patients with CKD which further leads to cardiovascular disease with altered blood pressure. Diabetes also leads to the development of this disease[3].The high levels of glucose metabolite in blood leads to changes in the glomerular filtration pressure in juxtaglomerular apparatus of kidney, loop of henle, distal convoluted tubule and proximal convoluted tubule. The alterations in the levels of ions like sodium, potassium in the blood and kidney due to the impaired transport in the aquaporin membrane channel in kidney cells also leads to the development of kidney diseases due to the impaired osmolality concentration gradient. The levels of urea,creatinine and albumin are also altered in kidney diseases.The renin-angiotensin-aldosterone system regulates the blood pressure in the arteries and filtration pressure in the kidney which gets altered in kidney diseases[4]. Angiotensin converting enzyme (ACE-1) converts the angiotensin-I to angiotensin-II which constricts the blood vessels in the kidney leading to changes in the filtration rate of different metabolites like glucose, maltose, sucrose, albumin, urea, uric acid, hippuric acid and creatinine. ACE-1 inhibitor drugs and angiotensin receptor blockers have been used to treat hypertension due to altered blood pressure [4].The flow chart depicted in figure no.1 gives the detailed analysis of the changes in filtration pressure in kidney cells(nephrons).The secretion of angiotensin and aldosterone in the renal cells leads to the constriction of blood cells which alters the filtration pressure in kidney juxtaglomerular apparatus cells. This mechanism leads to an alteration in the balance of sodium, potassium ions across the membrane channels of nephrons and increase in the absorption of sodium ions and excretion of potassium ionsbetween blood, interstitial fluid and tubules of kidney cells[5]. There is absorption, assimilation and excretion of different ions and metabolites in different parts of kidney namely, loop of henle, proximal convoluted tubule, distal convoluted tubule and the collecting duct before they are excreted in the form of urine from the urinary bladder.

Secretion of angiotensin by kidney cells and endothelin-1 by blood vessels.

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Vasoconstriction of blood vessels in kidney due to renin-angiotensin and lack of proper functioning of endothelial cells lining blood vessels due to generation of free radicals.

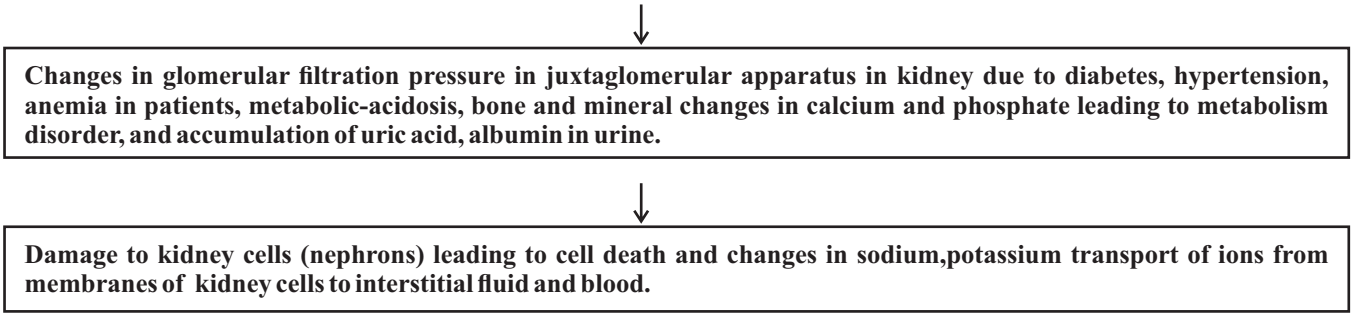

Figure 1: The flow-chart depicting the changes in the filtration pressure in kidney cells (nephrons).

Different stages in the development of chronic kidney diseases.

The different stages of progression of kidney disease are mentioned in table no.2 below along with decrease in the glomerular filtration rate[3].

SNo.	Stage of kidney disease	Glomerular filtration rate volume
1.	Stage 1	90ml/min per 1.73m^2 and albuminuria
2.	Stage 2	60ml/min-80ml/min per 1.73m^2
3.	Stage 3	30ml/min-59ml/min per 1.73m^2
4.	Stage 4	15ml/min-29ml/min per 1.73m^2
5.	Stage 5	Less than 15ml/min per 1.73m^2 with end stage renal disease

Table 2: The stages of progression of kidney disease along with glomerular filtration rate. Major types of Kidney diseases leading to chronic destruction of nephrons.

Granulointerstitialnephritis (GIN)

In this condition**,** there is inflammation at the site of infection inside the nephrons which leads to the aggregation of giant cells with multinucleated condition. There is formation of granuloma inside the nephrons with accumulation of eosinophils at that site. Prednisolone drug is used for the treatment of this nephritis condition[6].

Acuteinterstitialnephritis (AIN)

In this disease condition, the interstitial cells of kidney develop edema, which is the accumulation of fluid along with inflammation of these cells. The skin develops rashes, fever and destruction of nephrons by bacteria. Mycophenolate mofetil drug is used for the treatment of this disease[7].

Chronic tubulointerstitial nephritis.

In this condition, there is destruction of glomerulus cells of the kidney leading to apoptosis of these cells. They are caused by bacteria,fungi,virus or protozoan infection in kidney cells.It is identified by observing inflammation, interstitial fibrosis, and apoptosis, atrophy and degradation of proximal and distal tubular cells. Skin rashes, fever develops in patients with increase in eosinophils count in blood. It is also caused by heavy metal toxicity[8,21].

IgA nephropathy

In this condition, there is deposition of IgA antibody and C3 protein in the mesangial cells of the kidney and along the walls of glomerulus cells. In this there is a defect in the O-glycosylation of IgA antibody during post-translational modification of IgA chain and IgA-IgG aggregates are formed by the recognition of these epitopic regions on IgA by the immune system of the body leading to the generation of IgG antibodies complexed with IgA in the kidney cells leading to destruction and apoptosis of kidney cells. Galactosyltransfease enzyme is responsible for the modification and addition of O-linked carbohydrate groups to the IgA antibody. The complement system C3-C4-C5-C9 gets activated along with the release of tumor necrosis factor (TNF-alpha),TGF-beta, monocyte chemokine factor-1, macrophage migration inhibitory factor, interleukin(IL-6) which promotes inflammation at the site of injury. There are clusters of CD71-IgA complex, CD89-IgA complexes formed in the mesangial cells in the kidney[9]. Drugs used for treatment of this disease include cyclosporins[10,20].

Lupus nephritis

It is caused by an auto-immune disease called as systemic lupus erythematosus which causes damage to the kidney cells. The symptoms include blood in the urine, frothy appearance and bubbling in urine and pain and swelling in the hands and legs of the body.

Focal segmental glomerulonephritis.

In this disease, lesions are formed which leads to the destruction of podocytes in kidney cells. Further crescent shaped pauci-immune glomerular immune complexes are formed after infection in kidney cells. The levesl of urokinase plasminogen activator protein(uPAR) increases after inflammation in podocytes. Rituximab, a monoclonal antibody binds to the CD20 receptor of B-cells and is used for the treatment of focal segmental glomerulonephritis[17]. Further HIV virus infection also causes glomerulonephritis.

Diabetic Nephropathy

In this condition, there is increase in the amount of urinary albumin concentration from a stage of less albumin concentration called as microalbuminuria (20µg/min) to a stage of increase in albumin concentration and the condition is called as macroalbuminuria- (200µg/min).There is also an increase in the amount of blood glucose due to diabetes and the condition is called as hyperglycemia. Drugs used for the treatment of diabetic nephropathy include repaglinide and nateglinide. There is a chance of developing anemia and levels of low density lipoprotein go down (less than 70mg/dl). Sulodexide and pimagedine drugs reduce the excretion of proteins and albumin during diabetic nephropathy[18].

Drug-induced nephrotoxicity and chronic kidney diseases

There are various side-effects and harmful effects of drugs or medicines taken during infection caused to the body. The side-effects or harmful effects caused by drugs in kidney are listed in table no.3 given below[11].

SNo.	Type of Drug	Disease caused in kidney
1	Aminoglycosides	Chronic tubule- interstitial nephritis
2	vancomycin	Tubular destruction
3	acyclovir	Crystal formation
4	AmphotericinB	Renal tubular acidosis, necrosis
5	ciprofloxacin	Needle crystals
6	Pencillins and cephalosporins	Toxic tubular injury
7	Antiretroviral drugs	Crystalline deposition
8	cetuximab	Renal magnesium wasting and hypomagnesia
9	pamidronate	Focal segmental glomerulosclerosis

Table 3: Drug induced nephrotoxicity and chronic kidney disease

Cell signaling in chronic kidney diseases (CKD)

There are various cell signaling pathways which are activated during chronic kidney disease diagnosis in nephrons. The cell signaling molecule cluster is mentioned in table no.4 as mentioned below [12].It depicts the name of cell signaling molecule and the receptor signaling pathway activated during the infection in kidney.

SNo.	Name of cell signaling molecule	Signaling pathway
1	clusterin	Tumour growth factor-beta
2	Epidermal growth factor pathway	Hypoxia inducing factor(Hif - 1)
3	Lipocalin	Hif-1, Lcn2, EGF
4	Hepatocyte growth factor pathway	Nuclear factor -kappa B, tumour necrosis factor alpha (less CKD progression), and apoptotic proteins like Bcl-2(more CKD progression)

Table 4: Cell signaling molecules in chronic kidney diseases

Biomarkers of chronic kidney disease (CKD)

There are various markers used for the analysis of chronic kidney diseases as mentioned in table no.5 below[13,14,19].

S.No.	Name of biomarker molecule in kidney disease
1	Podocin
2	nephrin
3	podocalyxin
4	Cystatin
5	lipocalin
6	Kidney injury molecule-1
7	N-acetyl glucosaminidase
8	Beta-microglobulin
9	Albumin, transferrin, Liver FABP(liver type fatty acid binding protein)
10	Tenascin,TIMP-1
11	Asymmetric dimethyl arginine

Table 5: Biomarkers involved in chronic kidney disease

Treatment of kidney diseases

The treatment for end-stage kidney disease involves continuous renal replacement therapy (CRRT), peritoneal dialysis, and intermittent hemodialysis. Peritoneal dialysis method involves the use of catheter to remove solutes in circulation in blood from kidney. Intermittent hemodialysis involves the movement of solutes and ions across the membrane by means of concentration gradient in blood and kidney cells. This method involves hemodialysis, hemofiltration, and combination of two methods. Various salts like saline, anti-coagulants like heparin, buffer like citrate, and anti-coagulant drugs like danaparoid, argatobran and nafomostatmesilate is used for renal dialysis[15].

Various immunosuppressive drugs like tacrolimus is used during kidney transplantation to prevent organ rejection and auto-immune response in patients[16].

CONCLUSIONS

1. CKD leads to the development of anemia[1,20] in patients which was further studied by administering iron-sucrose in patients and measuring the glomerular filtration rates(GFR)[1,20].
2. A population survey was conducted in patients from A.I.I.M.S, New delhi which indicated the percentage of factors responsible for prevalence of chronic kidney diseases in the statistical study and predominant factor for CKD was found out to be diabetes[2].
3. Various others diseases associated with CKD include parathyroidism, bone-mineral associated disorder, decreased erythropoetin synthesis, anemia due to iron deficiency, calcification of skull, and cardiovascular diseases after statistical study in patients[3].
4. Various biomarkers indicate the diagnosis of chronic kidney disease[13,14,19] in patient samples.
5. The chronic kidney diseases are characterized as of various types as discussed [6,7,8,9,17,18].
6. Many different types of immunosuppressive drugs are used for kidney dialysis, replacement and transplantation[10,11,15,16].

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