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Sickle Cell Disease and Renal Disease

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1. Introduction

The kidney of patients with sickle cell disease (SCD) is affected by both haemodynamic changes of chronic anaemia and by the consequences of vaso-occlusion which are especially marked within the renal medulla. There are many abnormalities in renal structure and function as a result of these changes. Functional changes occur with increasing age in subjects with sickle cell disease. Proteinuria, severe anaemia and haematuria are reliable markers and predictors of chronic renal disease in patients with sickle cell disease (Emokpae et al., 2010a). Sickle cell disease is characterized by chronic haemolytic anaemia due to adverse effects of oxygen transport by the red blood cells. This often leads to a decrease in oxygen supply to peripheral tissues.

The substitution of valine for glutamic acid at the sixth position of the β -globin polypeptide chain made haemoglobin S (HbS) different from normal adult haemoglobin A (HbA) (Reid et al., 1984). The inheritance of HbS gene in the heterozygous state results in sickle cell trait while inheritance in the homozygous state results in sickle cell disease (SCD). The prevalence of Hb S gene in various parts of Africa varies between 20-40% (Arabs, 1970), while in Nigeria the prevalence is put at 20-25percent (Lindner et al., 1974; Ukoli et al., 1988). Sickling phenomenon occurs secondary to intra erythrocytic HbS polymerization because of low oxygen tension which becomes reversible with adequate re-oxygenation of the haemoglobin. But with repeated sickling and resultant deformation, the red cell membranes become fragile and haemolyse. Sickle cell disease often results in a severe disease, with profound anaemia and multiple organ involvement including cerebrovascular events, acute vaso-occlusive episodes, retinopathy, acute chest syndrome and renal damage (Guash et al., 2006). Haemoglobin S may coexist with other mutant beta globin chains (β^c or β^D) in a mixed heterozygous state leading to haemoglobin SC or SD disease. Haemoglobin SC disease is the most common mixed heterozygous form of sickle haemoglobinopathies occurring in one per 800 births in the African Americans (Guash et al., 2006). Sickle cell anaemia (SCA) affects the kidney, causing defects in tubulomedullary function (Allon, 1990); and also causes proteinuria, progressive renal insufficiency and end stage renal disease (Pham et al., 2000). The glomerulopathy is the cause of the proteinuria and progressive renal insufficiency (Guash et al., 1996).

2. Origin of sickle cell disease

The origin of sickle cell disease is not known but a substantial evidence that the sickle cell mutation occurred as several independent events was reported (Serjeant, 1992). Two

theories of evolution were postulated, namely- single mutation theory and multiple mutation theory. A single mutation occurring in Neolithic times in the then fertile Arabian Peninsula was favoured by Lehmann (1954), who postulated that the changing climatic conditions and conversion of this area to a desert caused a migration of peoples that could have carried the gene to India, Eastern Saudi Arabia and to Africa. Lehmann and Hunstan (1974) supported this hypothesis by citing the distribution of certain agricultural practices and anthropological evidence as well as the geographical distribution of the gene within Africa which manifested a decline in gene frequency from East to West Africa together with higher levels on the north compared to the south bank of the Zambesi River. This is compatible with the fact that the river acted as a barrier to a southern migration (Serjeant, 1992). This theory was also supported by Gelpi (1973), who considered that the evidence from blood groups and other genetic markers was more compatible with an origin in Equatorial Africa and subsequent diffusion of the gene to India, Arabia and the Mediterranean by the East Africa slave trade (Kamel and Awany, 1965).

The multiple mutation theory recently received support from the studies of DNA polymorphism. The use of restriction endonucleases to recognize and cut DNA at specific sequence has identified variations in DNA structure (polymorphism) that are inherited and may be used as genetic markers (Serjeant, 1992). The first of such polymorphism to be reported was a variation in the recognition site of the restriction endonuclease HPa 1 to the 3' side of the β -globin gene (Kan and Dozy, 1978). In most normal human DNA digested with HPa 1, the β -globin gene occurred on a DNA fragment 7.6 kd long. Polymorphism at this site in West African population resulted in β -gene occurring on the fragments 7.0 and 13.0 kd long. Subsequently the 13.0kd fragment was found to be relatively tightly linked to the β -gene, the frequency of the 13.0 kd fragment in the AS genotype being 0.31 and in the SS genotype 0.87(Kan and Dozy,1978). The immediate application of this observation was in antenatal diagnosis (Kan and Dozy, 1978), but it was also of potential value as a genetic marker in anthropological studies. The 13.0 kb fragment was found to be linked to the β^c gene (Feldenzer *et al.*, 1979).

3. Study of the kidney

The study of nephrology as a major discipline in medicine dates back to about five decades ago. The discipline has its origin in the writing of pioneers who used their observational skills to establish its basic framework. From their observations and analyses came the realization of the vital role of the kidney in the maintenance of health, particularly in relation to homeostasis of body fluids and electrolytes (Travis *et al.*, 1984). These pioneers recorded the profound changes in health that occurred with any of a variety of kidney disorders. While imaginative postulates about the physiology of the kidney in health and disease were beginning to evolve, detailed construct of the precise mechanisms by which various renal events took place were not easily obtainable. Opportunities to explore in detail the postulates were limited primarily by the primitive technology which was available then. Only recently when technological advances were made and applied that the theoretical bases and principles of renal physiology and molecular biology established and an understanding reached of the alterations that occurred in the disease state (Travis *et al.*, 1984). With technological advancement, there has been a deeper insight into the pathophysiologic mechanisms that interact to create renal disease.

The kidneys are essential for life. Normally more water and ions are ingested than the body requires. This excess intake is excreted in urine. The kidneys therefore regulate both the volume and the composition of the body fluids. As well as the surplus water and electrolytes, the urine contains metabolic waste products, foreign substances and their metabolic derivatives (Bray *et al.*, 1999). The kidneys also produce a variety of humoral agents, including erythropoietin, active metabolites of vitamin D, renin and prostaglandins. Each human kidney has about one million functional units- the nephrons; arranged in parallel (Risdon, 1985). The renal regulation of the volume and composition of the body fluids involves each of these nephrons in three processes: filtration at the glomerulus, tubular reabsorption and tubular secretion.

4. Renal manifestations in sickle cell disease

The kidney in SCD is affected by both the haemodynamic changes of a chronic anaemia and by the consequences of vaso-occlusion which are especially marked within the renal medulla. As a result, there are many abnormalities in renal structure and function (sergeant, 1992). Renal size in SCD varies with age of the patients and the method of examination. Renal weight at autopsy was normal in young children (Alleyne *et al.*, 1975), increased in older children and young adults and decreased in patients over 40 years (Morgan *et al.*, 1987). In children, bilateral renal enlargement was common in intravenous urography (Minkin *et al.*, 1997; Odita *et al.*, 1983) and in adults; renal length exceeded 15cm in at least one kidney in about 10% Jamaicans (McCall *et al.*, 1987) and Nigerians (Odita *et al.*, 1983). In the Nigerian study, the mean kidney length in patients with SCD was significantly greater than in normal controls. Renal structure on imaging in SCD revealed that intravenous urography in 189 Jamaican adults showed mild cortical scarring, the frequency increasing from 8% in the 16-25 years old, to 45% in those over 35 years (McCall *et al.*, 1987). Calyceal abnormalities included calyceal cysts, blunting and clubbing, which also increased with age. Radiological evidence of renal papillary necrosis occurred in 44 (26%) of adults patients in the Jamaican study. This high prevalence was also noted in Nigerians (Odita *et al.*, 1983). Functional changes occur with increasing age in patients with SCD. In children and young adults there are increases in effective renal blood flow (ERBF), effective renal plasma flow (ERPF) and glomerular filtration rate (GFR), although the filtration fraction is decreased (Hatch *et al.*, 1970). With age, there is a progressive decline in ERBF, ERPF and GFR and in patients over the age 40 years; GFR and ERPF tend to decline (Morgan and sergeant, 1981). But normal or above normal values may persist in some patients (Alleyne *et al.*, 1975). Progressive renal failure at older ages is a major cause of illness and death (Morgan *et al.*, 1987). Glomerular disease is common (15 - 30 percent) in homozygotes for sickle cell disease. Glomerular hyperfiltration and hypertrophy occur within the first 5 years of life. Approximately 15 - 30 % of patients develop proteinuria in the first three decades, and 5% develop ESRD. The glomerular pathology is usually focal segmental glomerulosclerosis, probably due to sustained glomerular capillary hypertension or membrane proliferative glomerulonephritis (MPGN). Predictors of chronic renal failure are worsening anaemia, proteinuria, nephrotic syndrome and hypertension (Powars *et al.*, 2005).

5. Sickle cell disease and glomerulopathy.

Patients with sickle cell anaemia (SCA) may develop glomerulopathy with proteinuria and progressive renal insufficiency leading to End Stage Renal Disease (ESRD) (Gausch *et al.*,

2006). These authors observed that the patients with sickle cell haemoglobin (Hb SS) have a more severe disease than individuals with other sickling haemoglobinopathies using clinical, haematologic and biochemical parameters in a group of patients with sickle cell haemoglobinopathies. It was reported that increased albumin excretion rate (AER) occurs in 68% of the patients; macroalbuminuria was present in 26% and microalbuminuria in 42% while only 32% of adults with 'SS' disease had normoalbuminuria. There was no gender differences reported in the prevalence of albuminuria. In a study of proteinuria among SCA patients in Nigeria, male predominance of sickle cell nephropathy was reported (Abdu et al., 2011). The concentration of 24hours urine protein in the SCA male subjects with proteinuria was significantly higher (0.25g/day;p<0.001) compared with the SCA female patients with proteinuria (0.09g/day)(Emokpae et al.,2010a). The sex differences in the mechanisms underlying renal injury suggest that androgens may permit or accelerate renal damage while estrogen may provide renoprotection (Ji et al., 2005; Standberg, 2008). The female sex hormone (estradiol) is thought to have antioxidant properties. Estradiol is capable of increasing superoxide dismutase and glutathione peroxidase expression as well as decreases NADPH oxidase enzyme activity and superoxide production (Lopez-Ruiz et al., 2008). The graded albuminuria according to age hence duration of disease showed that, in 'SS' disease the prevalence of abnormal AER increased from 61% in patients aged 18 to 30 years to as high as 79% in patients older than 40 years. Albumin excretion rate was reported to have increased as creatinine clearance decreased, but there was a large variability and a significant number of patients had increased AER despite a preserved creatinine clearance. In a four decade observational study of 1056 patients with sickle cell disease, Powars *et al.*, (2005) reported that 73% of the patients had one or more clinically recognized forms of irreversible organ damage. By the fifth decade, nearly one-half of the surviving patients (48%) had documented irreversible organ damage. ESRD (glomerulosclerosis), chronic pulmonary disease with pulmonary hypertension, retinopathy and cerebral micro infarctions were manifestations of arterial and capillary microcirculation obstructive vasculopathy. In an earlier report on chronic renal failure in sickle cell disease : risk factors, clinical course and mortality indicated that histologic studies showed characteristic lesion of glomerular "drop out" and glomerulosclerosis, in thirty six patients with sickle cell disease who developed sickle cell renal failure (Powards *et al.*, 1991; Powards *et al.*, 2002). Table 1 shows changes in biochemical parameters in sickle cell disease patients with or without proteinuria in northern Nigeria.

Renal insufficiency in SCA was defined as a creatinine clearance <90ml/min using Crockcroft- Gault, (1976) equation. It was reported that 21% of patients with SCA had renal insufficiency while 27% of patients with other sickling disorders also had renal insufficiency but the percentage of patients with renal insufficiency and advanced kidney failure (chronic kidney disease stage 3 or higher) was higher in SS disease than other sickling disorders (Guasch *et al.*, 2006). Guasch *et al.*(1997) previously showed renal insufficiency in SCA results from a glomerulopathy, which can be detected by the presence of albumin and other large molecular weight proteins in urine. Recently it was observed that glomerular involvement is extremely common in Nigerian sickle cell haemoglobinopathies (Abdu et al.2011). Increased AER occurs in approximately 70% of adults with haemoglobin SS disease and about 40% in adults with other sickling disorders. There was an indication of sickle cell glomerulopathy in a majority of older adults with SS disease and its prevalence was much higher than previously reported on the basis of a positive urinary dipstick for protein (Falk *et al.*, 1992).

	Males with no proteinuria	Males with proteinuria	p-value	Females with no proteinuria	Females with proteinuria	p-value
No of subjects	68	32		76	24	
Age (Years)	22.2 ± 3.8	26.4 ± 7.3	$P < 0.005$	21 ± 3.0	20.4 ± 7.6	NS
Weight (Kg)	45 ± 12.3	50 ± 7.2	$P < 0.001$	42 ± 7.6	47.4 ± 5.3	$P < 0.001$
Na+ mmol/l	134.7 ± 3.4	140 ± 3.8	$P < 0.001$	136 ± 5.4	141 ± 5.3	$P < 0.001$
K + mmol/l	4.2 ± 0.5	3.9 ± 0.5	$P < 0.05$	4.05 ± 0.35	3.9 ± 0.13	NS
Cl- mmol/l	97.4 ± 2.3	103 ± 4.1	$P < 0.001$	98.2 ± 5.3	101 ± 3.9	NS
Hco3- mmol/l	97.4 ± 2.3	103 ± 4.1	NS	22.3 ± 1.55	20.2 ± 3.0	$p < 0.05$
Urea mmol/l	2.46 ± 0.88	8.07 ± 2.2	$P < 0.001$	2.79 ± 1.77	2.46 ± 1.22	NS
CR µmol/l	59.2 ± 10.2	280 ± 22.3	$P < 0.001$	61.2 ± 12.4	67 ± 23.7	NS
eGFR ml/min	104 ± 22.8	70 ± 6.9	$P < 0.001$	97 ± 3.5	101 ± 2.5	NS

CR = creatinine, eGFR = estimated glomerular filtration rate, NS = not significant, Adapted from Abdu et al., 2011.

Table 1. Urea, electrolytes, creatinine and estimated glomerular filtration rates in sickle cell anaemia patients with proteinuria and those with no proteinuria.

The pathogenesis of glomerular damage in SCA is not well understood. Children with sickle cell anaemia have renal haemodynamic alterations characterized by renal hyperperfusion and glomerular hyperfiltration. These probably resulted from renal vasodilation associated with chronic anaemia. In some patients, these changes are followed by the development of glomerular proteinuria and progressive renal disease. Histologically, patients with SCA may develop glomerular hypertrophy and focal segmented glomerulosclerosis, features that are suggestive of haemodynamically mediated injury (Falk *et al.*, 1992). The causes of the haemodynamic injury to the glomerulus in SCA are unclear, but anaemia could cause glomerular damage by increasing blood flow. Other factors that are related to the rheology or stickiness of sickle erythrocyte could cause glomerular damage independently or in conjunction with the haemodynamic changes that are associated with anaemia (Guasch *et al.*, 1999). In the analysis of significance of abnormal albuminuria in SCA, several authors demonstrated by physiologic and pathologic studies that macroalbuminuria is the clinical manifestation of an underlying glomerulopathy (Falk *et al.*, 1992; Guasch *et al.*, 1999; Emokpae et al., 2010a; Abdu et

al.,2011). Twenty eight percent of patients with SCD patients were observed to have significant proteinuria in Nigerian SCD patients (Abdu et al.,2011), confirming the fact that proteinuria is a more sensitive marker than elevated serum creatinine values in detecting glomerular injury and early manifestation of sickle cell nephropathy. From that study, 50% of SCA male patients with proteinuria had CKD. However, it was observed that the high prevalence of CKD reported may be due to the fact that the study was conducted in a tertiary health care referral centre where there is likelihood of having patients population with more severe disease (Abdu et al., 2011). Table 2 shows haematological changes in SCD patients with or without proteinuria and those with chronic kidney disease in northern Nigeria.

	Control HbSS	Macroalbu minuria HbSS	<i>P</i> -value	CKD	<i>P</i> -value
No. of subjects	144	40	-	16	-
Age (years)	21.6±3.2	20.8±4.2	-	32.6	<i>P</i> <0.001
Haematocrit (%)	20.1±5.9	19.1±3.9	NS	18.7±1.19	NS
Haemoglobin (g/dl)	7.0±2.1	6.25±0.9	<i>P</i> <0.001	6.1±0.2	<i>P</i> <0.001
Total leukocyte Count (×10 ⁹ /L)	11.7±4.05	11.8±3.2	NS	11.9±1.04	NS
Red blood cells Count (×10 ¹² /L)	2.43±0.6	2.19±1.0	NS	2.07±0.2	<i>P</i> <0.001
Platelet count (×10 ⁹ /L)	373±135	348±92	NS	428±221	<i>P</i> <0.001
Mean cell Hemoglobin (pg)	29.6±2.6	35.7±3.3	NS	36.6±1.5	NS
Mean cell volume(fl)	82.2±6.9	84.9±4.2	NS	87±0.9	<i>P</i> <0.001
Mean cell hemoglobin Conc. (g/dl)	36.4±2.1	35.7±3.3	NS	36.6±1.5	NS
Absolute lymphocyte Count (×10 ⁹ /L)	4.0±1.3	3.2±0.6	<i>P</i> <0.001	2.8±0.4	<i>P</i> <0.001
Absolute neutrophil Count (×10 ⁹ /L)	5.2±1.7	6.0±0.8	<i>P</i> <0.001	6.4±0.6	<i>P</i> <0.001
Absolute Monocyte Count (×10 ⁹ /L)	0.5±0.2	0.4±0.03	<i>P</i> <0.001	0.4±0.04	<i>P</i> <0.001
Absolute eosinophil Count (×10 ⁹ /L)	0.2±0.1	0.2±0.02	NS	0.2±0.1	NS

Adapted from Emokpae et al., 2010a

Table 2. Haematological indices in SCD patients with macroalbuminuria, CKD and controls

In patients with macroalbuminuria but preserved GFR, the glomerular ultrafiltration coefficient was reduced versus normalalbuminuric sickle cell control subjects; indicating that

macroalbuminuria irrespective of the level of GFR reflects an underlying glomerular pathology (Guasch *et al.*, 2006). It was reported that in children the development of microalbuminuria follows an age dependent manner. In a study by Dhranidharka *et al.*(1998) in a group of sicklers, It was observed that microalbuminuria was not present in children who were younger than 7years but reached 43 percent in the second decade of life. In another similar study, Wigfall *et al.*(2000) observed an age-dependent occurrence of dipstick proteinuria: proteinuria was not present in children who were less than 6years, but occurs in 7% of children aged 7-10years and 10% of children who were aged 13 to 17years. It was therefore speculated that sickle cell glomerulopathy could evolve in five clinical stages.

- A normoalbuminuric stage of variable duration followed by a stage of
- Microalbuminuria which could lead to
- Macroalbuminuria but with preserved GFR and to
- Macroalbuminuria and progressive renal insufficiency and
- ESRD.

However, evidence of progression from micro to macroalbuminuria is lacking and such classification may remain a hypothesis (Guasch *et al.*, 2006). It was concluded that the prevalence of glomerular damage in SCA is much higher than previously thought; a majority of patients with SS disease are at risk for the development of progressive renal insufficiency and late renal failure especially because the life expectancy in patients with SS disease has improved with better medical care. Secondly, in contrast to most glomerular disease, the glomerulopathy in SS disease is not accompanied by the development of significant systemic hypertension. Lastly, the haemodynamic changes that are associated with chronic anaemia per se are not solely responsible for the development of sickle cell glomerulopathy and indicate that other mechanisms are involved in the pathogenesis of the glomerular damage in this population.

There is a large variability in the severity of the clinical manifestation of sickle cell anaemia (SCA), including renal involvement. Some patients develop multiorgan failure while others have relatively few end-organ complications (Guasch *et al.*, 1999). Epigenetic and environmental factors have been implicated to explain these differences in clinical severity. In children, lower haemoglobin levels and a relatively high degree of haemolysis are associated with a poorer clinical outcome while the persistence of high levels of foetal haemoglobin (HbF) is associated with less aggressive clinical manifestation (Platt *et al.*, 1994). Epidemiologic studies in African and Asian countries have suggested that differences in the degree of clinical severity are related to the geographical origin of the sickle cell mutation (Adedeji, 1988). The β -globin gene cluster is located on chromosome 11 and consists of a long segment of DNA (approximately 60,000 bp) that contains the β -globin gene and other globin genes. Distinct polymorphism in this gene cluster can be identified by restriction endonucleases that cleave the DNA at specific sites. When the restriction sites patterns are arranged by alleles, they form a haplotype. In the African, specific haplotypes are associated with different groups from different geographic area and define an individual's origin from Benin, Central African Republic, Senegal, Saudi Arabia or Cameroun (Nagel *et al.*, 1985). Since substitution of valine for glutamic acid at position six arose on different haplotypes, it must have arisen in different ethnic groups (Guasch *et al.*, 1999). Some studies have suggested that the severity of SCA varied with haplotype, with the Central African Republic (CAR) haplotype associated with a higher incidence of stroke, leg ulcer, acute chest syndrome, bone infarcts and kidney failure compared with non-CAR haplotypes (Powars *et al.*, 1990; Powars *et al.*, 1991). Guasch *et al.*, (1996) have emphasized

the development of proteinuria and progressive renal insufficiency, leading to end-stage renal disease in a subset of SCA patients. It was observed that glomerulopathy is the cause of the progressive renal insufficiency and can be detected as increased excretion of albumin in the urine.

The prevalence of renal insufficiency in patients with SCA has been reported to be low (<5%), based on the serum creatinine (Powars *et al.*, 1991). However, Guasch *et al.* (1996) found that serum creatinine is a very insensitive marker of renal insufficiency in SCA, becoming abnormal only after GFR is reduced to <30 to 40 mL/min per 1.73 m².

6. Renal matrix alterations in glomerulosclerosis

Progressive renal disease of many etiologies is characterized by increased accumulation of acellular material within the glomerular mesangium. Initially, this process is characterized by focal areas of glomerular hyalinosis, acellular material that stains with eosin but not with periodic acid Schiff, together with capillary collapse and adhesions of the glomerular tuft to Bowman's capsule. With time, the mesangial compartment is occupied by material that stains positively with both periodic acid Schiff and silver. Ultimately, the capillary tuft is replaced by this sclerotic material and ceases filtration (Rennke and Klein, 1989). Other features of progressive glomerulosclerosis are more variable. The mesangial compartment is in some cases occupied by an increased number of cells both mesangial cells and resident macrophages. In the case of diabetic nephropathy, there is an associated thickening and wrinkling of the glomerular basement membrane which contributes to compromised capillary lumens. In addition to an expanded mesangial compartment, some patients with diabetic nephropathy also exhibit a characteristic nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) (Rennke and Klein, 1989).

The mesangial components that are expressed as a consequence of inflammation or the sclerotic process belong to two classes. First, normal mesangial matrix molecules accumulate in excess quantities. These include laminin, type IV collagen, heparin sulphate proteoglycan and fibronectin. Second, the sclerotic mesangium contains matrix molecules that are not usually present in this location. These include interstitial collagens, particularly type III collagen and the small proteoglycan decorin. These matrix constituents are typical products of fibroblasts and related cell types. In a sense, the reappearance of these interstitial matrix products represents a return to biosynthetic activity of the embryonic renal interstitial mesenchyme (Yoshioka *et al.*, 1989).

Studies of matrix protein distribution in various primary renal diseases suggest that the proteins expressed and the regional pattern of expression differ considerably between different renal diseases (Oomura *et al.*, 1989; Yoshioka *et al.*, 1989). In all, with progressive glomerulosclerosis particularly with a mesangial proliferative component, the mesangial contains increased amounts of fibronectin, laminin, heparin sulphate proteoglycan and type III and IV collagen. Despite the widespread use in experimental animals of the nephron ablation model of progressive glomerulosclerosis, relatively little is known about the nature of or the mechanisms responsible for the accumulated glomerular matrix components.

Alterations in the renal expression of chondroitin sulphate proteoglycans are another component of the sclerosing process. The normal glomerulus expresses the small proteoglycan biglycan. In experimental glomerulonephritis induced by antibodies to the Thy-1-antigen, there is increased synthesis of biglycan as well as of another related proteoglycan, decorin by isolated glomeruli (Okuda *et al.*, 1990). Activated mesangial cells are a possible source for these proteoglycans.

Diabetes mellitus in humans and experimental animals is associated with evidence of deregulation of renal extracellular matrix proteins expression. More is known about the matrix alterations in this disorder than other forms of glomerulosclerosis, perhaps in part due to the availability of animal models. Biochemical investigation has shown increased accumulation of basement membrane components in diabetes glomeruli from experimental animals. Thus glomeruli from streptozotocin-diabetic rats contain more type IV collagen compared with glomeruli from normal rats (Hasslacher *et al.*, 1986). On the other hand, the data for glomerular content of heparin sulphate proteoglycan are conflicting, with an increase reported in streptozocin-diabetic rats and a decrease reported in diabetic human patients (Klein *et al.*, 1986; Shimonura and Spiro, 1987). The discrepancy underscores the need for caution in extrapolating from studies of diabetic rodents to mechanisms of human disease.

Immunohistochemical investigation of the sclerotic regions of human diabetic glomeruli show evidence of an increase in laminin, fibronectin and types IV and V collagen (Karttunen *et al.*, 1986).

While our understanding of the protein constituents of the sclerotic process has improved, the molecular mechanisms responsible for their accumulation are just being understood. It is likely that many factors including capillary physical forces, dietary constituents, metabolic injury and the effects of local growth factors and products of inflammation converge on a common pathway that generates matrix components within the glomerulus and mesangium. The process whereby matrix accumulates in response to injury, likely parallel the process of scarring and wound healing critical for the survival of other tissue types. In the kidney, however the generation of matrix may sufficiently disrupt the normal nephron architecture to render it useless. It may be possible in the future to modify the normal healing process in the glomerulus so that a loss of functioning nephrons does not hold the remaining glomeruli at increased risk for sclerosis.

7. Mechanisms whereby proteinuria cause progressive renal disease

The possibility that proteinuria may accelerate kidney disease progression to end stage renal failure has received support from the results of increasing numbers of experimental and clinical studies (Abbate *et al.*, 2006). Researches in nephrology in recent times have yielded substantial information on the mechanisms by which persisting dysfunction of an individual component cell in the glomerulus is generated and signaled to other glomerular cells and to the tubule. Spreading of disease is central to processes by which nephropathies of different types progress to end stage renal disease (ESRD). Independent of the underlying causes, chronic proteinuric glomerulopathies have in common a sustained or permanent loss of selectivity of the glomerular barrier to protein filtration. Glomerular sclerosis is the progressive lesion beginning at the glomerular capillary wall, the site of abnormal filtration of plasma proteins. Injury is transmitted to the interstitium favouring the self destruction of nephrons and eventually of the kidney (Abbate *et al.*, 2006). Baseline proteinuria was an independent predictor of renal outcome in patients with diabetes, non-diabetes as well as sickle cell nephropathies (Peterson *et al.*, 1995; Breyer *et al.*, 1996; Abdu *et al.*, 2011). Clinical trials consistently showed renoprotective effects of proteinuric reduction and led to the recognition that, the antiproteinuric treatment is instrumental to maximize renoprotection (Peterson *et al.*, 1995; Wapstra *et al.*, 1996). Findings that the rate of GFR decline correlated negatively with proteinuria reduction and positively with residual proteinuria provided

further evidence for a pathogenic role of proteinuria (Ruggenti *et al.*, 2003). It was documented that whenever proteinuria is decreased by treatments, progression to ESRD is reduced (Brenner *et al.*, 2001).

7.1 Glomerular proteinuria as signal for interstitial inflammation

In vitro studies using proximal tubular cells as a model to assess effects of apical exposure to plasma proteins proved highly valuable to approaching direct casual relationships. In monolayers of proximal tubular cells, the load with plasma proteins (albumin, IgG and transferrin) induced the synthesis of the vasoconstrictor peptide endothelin-1 (ET-1), a mediator of progressive renal injury by virtue of ability to stimulate renal cell proliferation and extracellular matrix production and to attract monocytes (Zoja *et al.*, 1995). Other investigators confirmed and extended the stimulatory effects of a diversity of plasma proteins on the expression of proinflammatory and profibrotic mediators in renal tubular cells (Yard *et al.*, 2001; Tang *et al.*, 2003). Among molecules attracted are monocytes/macrophages and T-lymphocytes, monocyte chemoattractant protein-1 (MCP-1) and RANTES which were over-expressed in proximal tubular cells that were challenged with plasma proteins (Wang *et al.*, 1997; Zoja *et al.*, 1998). Albumin upregulated tubular gene expression and production of interleukin 8 (IL-8), a potent chemotactic agent for lymphocytes and neutrophils (Tang *et al.*, 1999). The releases of ET-1 and chemokines in response to proteins was polarized mainly toward the basolateral compartment of the cell as to mirror a directional secretion that favoured the interstitial inflammatory reaction that was observed in-vivo. Protein overloading of human proximal tubular cells induced the synthesis of fractalkine, which in its membrane-anchored form promotes mononuclear cell adhesion via CX3CR1 receptor (Danadelli *et al.*, 2003). Fractalkine mRNA was overexpressed in kidneys of mice with protein overload proteinuria, and the gene product was detected in tubular epithelial cells mainly in the basal region. Treatment of mice with an antibody against CX3CR1 limited the interstitial accumulation of monocytes /macrophages (Danadelli *et al.*, 2003).

Investigation of the molecular mechanisms underlying chemokine upregulation in proximal tubular cells or protein challenge had initial focus on the activation of transcriptional NF- β (Zoja *et al.*, 1998). Other studies confirmed the pathway and revealed reactive oxygen as a secondary messenger (Drumm *et al.*, 2003). Protein overload elicited rapid generation of hydrogen peroxide in human proximal tubular cells, an effect that together with NF- β activation was prevented by antioxidants (Morigi *et al.*, 2002). Specific inhibitors of protein kinase C (PKC) prevented hydrogen peroxide generation, NF- β activation and MCP-1 and IL-8 genes up regulation that was induced by protein overload (Tang *et al.*, 2003), suggesting a cascade of signals from PKC- dependent oxygen radical generation to nuclear translocation of NF- β and consequent gene up regulation. A link also has been made between induction of NF- β activity by protein and mitogen-activated protein kinases, including p38 and extracellular signal-regulated kinase 1 and 2 (ERK1/ERK2) that are involved in chemokine synthesis (Dixon *et al.*, 2000; Danadelli *et al.*, 2003). In support of the hypothesis of protein overload as a key activator of signaling in proximal tubule is the finding that albumin activated the signal transducer and activator of transcription (STAT) proteins in cultured proximal tubular cells. Because the STAT pathway is the principal mechanism that converts the signal from a wide array of cytokines and growth factors into gene expression programs that regulate cell proliferation, differentiation, survival and apoptosis, it was suggested that albumin may stimulate proximal tubular cells in the manner of a cytokine (Rawlings *et al.*, 2004; Brunskill *et al.*, 2004).

Despite evidence that albumin overload elicits several responses by tubular cells in-vitro, it has been argued that albumin per se may not be toxic to the proximal tubular epithelium. Compounds that are bound to albumin, such as free fatty acids (FFA), instead have been implicated to be causative in pro inflammatory activation or injury of cultured proximal tubular cells (Schreiner, 1995). It was also observed that among various fatty acids, oleic acid and linoleic acids exert the most toxic and profibrogenic effects in human proximal tubular cells in culture. These studies collectively indicate that the ability of albumin to act as a carrier enhances the pro inflammatory activation of proximal tubular cells. In addition, in-vivo gene expression profile analysis of proximal tubules from mice with protein overload proteinuria identified 2000 genes that were differentially regulated by excess proteins. More than half of them were upregulated (Nakajima *et al.*, 2002). They included thymic shared antigen -1, the fibroblast-associated gene GS188 and glia maturation factor-B, a protein that originally was purified as a neurotrophic factor (Kaimori *et al.*, 2003). The expression of glia maturation factor- β was induced in renal proximal tubular cells of mice with protein overload proteinuria (Kaimori *et al.*, 2003). Proximal tubular cells that over expressed glia maturation factor- β acquired more susceptibility to death by sustained oxidative stress through p38 pathway activation.

There was a controversial issue relating to the concentration of albumin that was used in various in-vitro studies. Burton *et al.* (1999) discovered that the apical exposure of human proximal tubular cells to 1mg/ml albumin or transferrin did not increase MCP-1 or PDGF-AB release, an effect that was observed after exposure to a human serum fraction (40 to 100 KD) in the molecular weight range similar to albumin and transferrin. Studies that reported the effects of protein overload on NF- β activation showed responses from 0.5mg/mL in some experiments and usually >2.5 - >5mg/mL (Zoja *et al.*, 1995; Wang *et al.*, 1997). The latter concentration seems too far exceed the concentration reached in the proteinuric ultrafiltrate in-vivo (Gekle, 2005).

The proximal tubule bears other receptors for ultrafiltered proteins such as immunoglobulins and complement molecules (Braun *et al.*, 2004). The functional role of such receptors has not been established. It is likely that filtered proteins other than or in addition to albumin induces tubular dysfunction and injury in conditions of non selective proteinuria, in which large molecular weight proteins are a significant component. In contrast, relatively selective albuminuria induces delayed mononuclear cells infiltration and usually is associated with or mild chronic tubulo-interstitial injury. In this respect, the case of minimal-change disease has been considered sometimes an exception to the rule that interstitial infiltrates develop with time in proteinuric glomerulopathies. In addition, in minimal-change disease, a substantial percentage of patients respond to steroid and the regression of proteinuria prevents inflammation and renal function deterioration (Remuzzi and Giachelli, 1995).

7.2 Key role for the intra-renal activation of complement

Complement activation is a powerful mechanism underlying tubular and interstitial injury via cytotoxic, proinflammatory and fibrogenic effects. Abnormal complement, C₃ and C₅b-9 staining in proximal tubular cells and along the brush border is a long known feature both in human chronic proteinuric diseases and experimental models. Glomerular permeability dysfunction of proteinuric nephropathies allows complement factors to be ultrafiltered abnormally across the altered glomerular barrier into the Bowman's space and tubular

lumen. Plasma-derived C_3 (molecular weight 180kd) is likely to reflect more loss of glomerular permselectivity and to enhance cell dysfunction in the presence of abnormally filtered plasma proteins. Renal tubular cells also synthesize C_3 and other complement factors in ways that may have critical importance in disease, as found in experimental renal transplant rejection and post ischemic acute renal failure (Pratt *et al.*, 2002; Farrar *et al.*, 2006). Therefore both excess ultrafiltration and proximal tubular cell synthesis of complement could underlie complement-mediated injury in chronic proteinuric renal disease. Recent findings of C_3 mRNA upregulation and C_3 accumulation in proximal tubular cells in kidneys of mice with protein overload proteinuria are in support of a role for the local synthesis of complement (Abbate *et al.*, 2004). Complement is an important effector of interstitial mononuclear cell infiltration and fibrogenesis in this model as shown by significant attenuation of injury in C_3 deficient mice (Abbate *et al.*, 2004). A direct role for protein overload as a stimulus was indicated by findings that the exposure of cultured proximal tubular cells to total serum proteins at the apical surface upregulated C_3 mRNA expression and protein biosynthesis (Tang *et al.*, 1999).

7.3 Profibrogenic signal from proximal tubular cells in response to protein overload

Local recruitment of macrophages by tubular cells that are loaded with ultrafiltered plasma proteins may contribute to interstitial fibrosis by engaging matrix producing interstitial myofibroblasts. Macrophages also regulate matrix accumulation via release of growth factors such as TGF- β and PDGF, ET-1 and PAI-1, TGF- β stimulates the transformation of interstitial cells into myofibroblasts. In addition, proximal tubular epithelial cells communicate with interstitial fibroblasts to promote fibrogenesis via paracrine release of TGF- β . (Abbate *et al.*, 2006).

8. Pathogenesis of lipoprotein abnormalities in chronic kidney disease

Regardless of the aetiology of renal disease, patients with CKD develop complex qualitative and quantitative abnormalities in lipid and lipoprotein metabolism. These damages and the underlying molecular mechanism has been the subject of some reviews (Vaziri, 2006; Chan *et al.*, 2006). Classical uraemic dyslipidaemia is characterized by raised triglyceride, low high density lipoprotein (HDL) and normal total cholesterol. These qualitative defects become more pronounced with advancing renal failure and modified by renal replacement therapy, renal transplantation, co-morbid conditions such as diabetes mellitus and concurrent medication (for example steroids, cyclosporine) (Vaziri, 2000) Lipoprotein metabolism is a dynamic system that can be disturbed owing to alterations in apolipoprotein receptors. When GFR falls below 60ml/min, there is a fall in the ratio of apolipoprotein AI (apo A) to apolipoprotein C - III (apo C - III) in spite of normal cholesterol and triglyceride concentrations (Batsta *et al.*, 2004). As renal function deteriorates in non-nephrotic patients with CKD, triglyceride concentrations increase while HDL concentrations decline (Farbekhsh and Kasiske, 2005) and there is accumulation of the more atherogenic small dense low-density lipoprotein (LDL) particles.

In advanced CKD, there is decreased concentration of apoA-containing lipoproteins, increased concentrations of triglyceride-rich apo B containing lipoproteins and serum lipoprotein(a). Reduced catabolism and clearance of triglyceride-rich apo B containing lipoproteins is a consequence of : (a) decreased activity of lipolytic enzymes, such as

lipoprotein lipase (LPL) and hepatic lipase (HL), (b) reduced receptor-mediated uptake via hepatic LDL-receptor related protein (LRP) and VLDL receptors (c) accumulation of certain inhibitors of LPL such as pre- β HDL (Chan *et al.*, 2006). Impaired clearance of triglyceride-rich lipoproteins is further compounded by reductions in apolipoprotein C-III (apo C-III) and apolipoprotein E (apo E). Impaired divalent ion metabolism arising from parathyroid gland hyperplasia in CKD (stage 3–4) may also adversely affect lipoprotein metabolism by suppressing LPL and hepatic lipase activities (Nishizawa *et al.*, 1997). Post prandial lipoprotein metabolism is also impaired in CKD, resulting in accumulation of chylomicron particles and their remnants. Reduction in the expression of HL and down regulation of LRP in uremia may also account for the accumulation of remnant lipoprotein (Kim and Vaziri, 2005). Maturation of HDL is impaired due to decreased plasma lecithin: cholesterol acyltransferase (LCAT) activity and gene expression. Plasma HDL concentration also falls in uremia due to decreased expression of both apo AI and AII. (Vaziri *et al.*, 2001). These abnormalities can lead to impaired HDL mediated cholesterol uptake from the vascular tissue and contribute to the cardiovascular disease. In addition, LCAT deficiency can in part, account for elevated serum free cholesterol, reduced HDL/total cholesterol and elevated pre- β HDL in CRF. The latter can in turn depress lipolytic activity and hinder triglyceride-rich lipoprotein clearance in CRF (Vaziri *et al.*, 2001; Emokpae *et al.*, 2010a). Statistically significant decrease in LCAT and lipoprotein lipase (LPL) activities were observed in SCA subjects in steady state compared with HbAS and HbAA controls in both males and females. The activities of LCAT and LPL were lower in subjects with SCA than sickle cell trait and normal haemoglobin. It was concluded that this may contribute to the changes observed in lipid metabolism in SCA (Emokpae *et al.*, 2010b). Although Dyslipidaemia is present in patients with SCD and patients with renal insufficiency irrespective of the haemoglobin genotype, it was reported that the lipoprotein levels observed in Nigerian adults with SCA patients were more lower compared with the lipid levels observed in both African Americans and Saudi Arabian patients with SCD. The potential effects of lipids on cardiovascular disease risk as measured by three predictor ratios were higher in SCA compared to HbAS and HbAA patients with kidney disease (Emokpae *et al.*, 2010c). Plasma total cholesterol is frequently low to normal and only occasionally elevated in CRF patients. In addition 3-hydroxy-3-methyl-glutaryl-coA (HMG COA) reductase, the rate-limiting step in cholesterol biosynthesis and cholesterol 7 α -hydroxylase, the rate limiting step in cholesterol catabolism, are unaffected by CRF (Liang and Vaziri, 1997). Moreover, LDL receptor and scavenger receptor B1, the primary pathways of hepatic cholesterol uptake are normal in CRF (Vaziri *et al.*, 1999).

The dyslipidaemia of CKD has similar feature to the metabolic syndrome. The metabolic syndrome, including type 2 diabetes, is known to predispose to CKD (Kurella *et al.*, 2005), which in turn aggravates insulin resistance and promotes dyslipidaemia. Insulin resistance increases free fatty acid (FFA) supply from adipocytes to increase hepatic lipogenesis and this stimulates hepatic secretion of apo B-100 containing lipoprotein specifically large triglyceride rich VLDL particles (Prinsen *et al.*, 2004). Impaired insulin signaling in skeletal muscles and adipose tissue also slows the catabolism of all triglycerides-rich containing lipoproteins. Expansion in the VLDL particle pool size impacts on the remodeling of LDL and HDL in an atherogenic direction (Chang *et al.*, 2006). Table 3 indicates changes in lipoproteins, lecithin: cholesterol acyltransferase and lipoprotein lipase in subjects with sickle cell anaemia, sickle cell trait and normal haemoglobin in northern Nigeria.

	HbSS males	HbAS males	p-value	HbAA males	p-value
No of subjects	68	25	-	25	-
Age in years	22.2±3.8	28.7±7	-	28.8±7	-
Triglyceride (mmol/L)	1.10±0.4	1.19±0.18	NS	1.4±0.12	P<0.001
T. Cholesterol (mmol/L)	3.06±0.5	4.05±0.06	P<0.001	4.3±0.12	P<0.001
HDL Cholesterol (mmol/L)	0.72±0.17	1.18±0.03	P<0.001	1.2±0.06	P<0.001
LDL Cholesterol (mmol/L)	1.92±0.54	2.15±0.14	NS	2.52±0.16	P<0.001
VLDL Cholesterol (mmol/L)	0.48±0.06	0.42±0.07	NS	0.41±0.08	NS
LPL (umolglycerol liberated/hr/l Plasma)	4.12±1.2	5.12±0.4	P<0.001	5.56±0.23	P<0.001
LCAT (umolcholesterol liberated/hr/l Plasma)	66.8±2.8	69.2±3.0	P<0.001	70.2±2.96	P<0.001

Adapted from
Emokpae et al.,2010b

Table 3. Lipid, lipoproteins, LCAT and LPL in male sickle cell disease subjects compared with HbAS and HbAA controls.

9. Effect of oxidative stress

Reactive oxygen species or free radicals are highly reactive entity and very short-lived molecules which are constantly produced in a wide variety of normal physiological functions, they are however toxic when generated in excess (Parke and Sapota, 1996). The most important characteristic of toxic free radicals either in vivo or in vitro is peroxidation of lipid resulting in tissue damage and death of affected cells (Bandyopadhyay *et al.*, 1999). There are profound evidence implicating free radicals in induced lipid peroxidation in the pathogenesis of several pathological conditions including chronic inflammation (Vijayakumar *et al.*, 2006), renal disease (Dakshinamurthy *et al.*, 2006; Suryawanshi *et al.*, 2006), sickle cell renal disease (Emokpae et al.,2010d) and cardiovascular disease (Kaysen *et al.*, 2004). Table 4 indicates changes in oxidative stress and lipid peroxide parameters in control SCD, proteinuria and chronic kidney disease while table 5 shows inflammatory markers in subjects with SCD in northern Nigeria.

The harmful effect of reactive oxygen species is neutralized by a broad species of protective agents termed antioxidants which prevent oxidative damage by reacting with free radicals before any other molecules can become a target. The non enzymatic antioxidants are vitamins E, C and reduced glutathione while the antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX). They all play important roles in the protection of cells and tissues against free radical mediated tissue damage (Yu *et al.*, 1994; Airede and Ibrahim, 1999; Ray and Hussain, 2002). There was a significant reduction in the activity levels of antioxidant enzymes in the serum of SCD patients compared with control sickle cell trait and normal haemoglobin (Emokpae et al.,2010d). This is an indication that SCA patients produce greater quantities of reactive oxygen species than controls. In SCD, the production of reactive oxygen species can be grossly amplified in response to variety of pathophysiological conditions

such as inflammation immunologic disorders, hypoxia, metabolism of drugs or alcohol and deficiency in antioxidant enzymes. Sickle cell anaemia patients showed low activity levels of antioxidant enzymes which may be due to the consumption of these substances by pro-oxidants in SCA. This therefore place SCA patients at increased risk of oxidative stress and injury. The oxidative stress may contribute to sickling process with the formation of dense cells, the development of vaso-occlusive and shortened red blood cell survival. We also demonstrated increased serum levels of some acute phase proteins in SCA, which may be as a result of sub-clinical vaso-occlusion which in turn can lead to a hidden inflammatory response (Emokpae et al.,2010d). Based on the results of the study, increased level of malondialdehyde compared significantly with lower activities level of antioxidant enzymes and increased acute phase proteins. In SCD patients with CKD, it was observed that there were increases in stress and inflammatory markers. C-reactive protein and fibrinogen were increased in subjects with renal insufficiency and were associated with increased urea and creatinine levels. Proteinuria as observed in SCA patients with renal insufficiency may act in synergy with oxidative stress and inflammation to initiate and accelerate the progression of renal disease. Chronic exposure of renal tubular epithelium to high levels of filtered plasma proteins may cause tissue injury (Emokpae et al.,2010a).

In certain diseases such as renal disease and sickle cell disease, the toxic material produced by activated phagocytes during reaction can cause maximal damage to the membrane because they are active in the lipid phase. The damaging effects of elevated toxic radical are due to an increase in the formation of superoxide radicals within the cells which cause inactivation of superoxide dismutase enzyme (Suryawanshi *et al.*, 2006). Oxidative stress occurs when there is an imbalance between production and scavenging. Increase in lipid peroxidation in sickle renal disease is due to excess formation of free radicals. Glycosylated protein, auto-oxidation, reduced superoxide dismutase enzyme and ascorbic acid and lack of reduced glutathione are other causes for oxidative stress.

Oxidative stress Markers	Controls HbSS	Macroalbuminuria HbSS	P-value	CKD HbSS	P-value
No of subjects	144	40		16	
Age (years)	21.6±3.2	20.8±4.2	NS	32.6±3.0	P<0.001
Malondialdehyde (mmol/l)	2.5±0.4	3.82±1.0	P<0.01	5.8±0.4	P<0.001
Glutathione Peroxidase (mU/ml)	9.6±0.9	8.3±3.0	P<0.001	2.81±0.24	P<0.001
Superoxide Dismutase (ng/ml)	32.5±4.2	25.4±4.6	P<0.001	18.3±2.8	P<0.001
Catalase (µmol/min/ml)	156±5.9	152±1.9	P<0.001	148±1.06	P<0.001

Adapted from Emokpae et al., 2010a

Table 4. Oxidative stress markers in serum of SCD patients with macroalbuminuria, CKD and controls (mean ± SD)

Inflammatory Markers	Controls HbSS	Macroalbuminuria HbSS	P-value	CKD HbSS	P-value
No of subjects	144	40		16	
C-reactive protein ($\mu\text{g/ml}$)	1.120 \pm 0.02	1.23 \pm 0.1	$P < 0.001$	1.81 \pm 0.05	$P < 0.001$
Fibrinogen (mg/dl)	299 \pm 9.1	307 \pm 6.0	$P < 0.001$	317 \pm 4.1	$P < 0.001$
Urea (mmol/l)	2.6 \pm 0.25	3.4 \pm 0.2	NS	14.0 \pm 2.8	$P < 0.001$
Creatinine ($\mu\text{mol/l}$)	59.2 \pm 10.2	63 \pm 27	NS	496 \pm 78	$P < 0.001$
eGFR (ml/min)	103 \pm 22	101 \pm 2.5	NS	14.5 \pm 2.0	$P < 0.001$

Adapted from Emokpae et al., 2010a

Table 5. Serum levels of inflammatory markers, urea, creatinine and eGFR in SCD patients with macroalbuminuria, CKD and controls (mean \pm SD)

Oxidative stress Markers	Controls HbSS	Control Hb AA	CKD HbSS	CKD HbAA
No. of subjects	144	20	16	20
Age (years)	21.6 \pm 3.2	22.0 \pm 2.6	32.6 \pm 3.0*	48.6 \pm 15.2*
Malondialdehyde (mmol/l)	2.5 \pm 0.4	2.4 \pm 0.2	5.8 \pm 0.4*	5.03 \pm 0.8*
Glutathione Peroxidase (mU/ml)	9.6 \pm 0.9	10.3 \pm 2.7	2.81 \pm 0.24*	4.35 \pm 1.8*
Superoxide Dismutase (ng/ml)	32.5 \pm 4.2	34.5 \pm 1.6**	18.3 \pm 2.8*	17.2 \pm 12.0*
Catalase ($\mu\text{mol/min/ml}$)	156 \pm 5.9	163 \pm 5.8*	148 \pm 1.06*	153 \pm 3.0*
* $P < 0.001$				

Adapted from Emokpae et al., 2010a

Table 6. Oxidative stress markers in controls HbSS, HbAA, CKD HbSS and CKD HbAA

Sickle cell anaemia patients in both steady state and renal impairments undergo constant inflammatory process which may in turn leads to inflammatory response (Bourantas et al.,1998; Emokpae et al., 2010d). Haemoglobin S containing red blood cells auto-oxidize faster thereby generating more superoxide, hydrogen peroxide, hydroxyl radicals and lipid peroxides than HbAA. Reactive oxygen species can cause damage to biological macromolecules and membrane lipids readily react and undergo peroxidation. Studies have shown that there were increases in stress and inflammatory markers in SCD patients with renal insufficiency.

The mechanisms by which inflammation may lead to decline in renal function is not clear but cytokine could act directly on the endothelium and mesangium of the glomerulus (Fried et al.,2004). Studies in animal model have shown that kidney in SCD is susceptible to hypoxia because of occlusion of blood flow in the vasa recta which may lead to medullary and papillary necrosis and fibrosis (Emokpae et al.,2010a). There are evidence to suggest that prolonged glomerular hyperfiltration due to any cause especially in SCD could lead to glomerular damage resulting to glomerular sclerosis, proteinuria and progressive renal disease. It was suggested that filtered plasma proteins taken up by tubular epithelium

stimulate inflammatory genes, release inflammatory and vaso-active substances into the renal interstitium that induce scarring and sclerosis (Remuzzi and Bertani,1998).We also showed a solid association of chronic inflammation with CKD in SCA and this observation supported the hypothesis that inflammatory and oxidative stress markers contribute to the pathophysiology of glomerulopathy in SCD. Other contributing factors to the pathophysiology of glomerulopathy in SCD are possible iatrogenic acceleration by analgesic medication. There are indication that morphine induces mesangial cell proliferation and glomerulopathy via kappa-opioid receptors as well as the effect of nonsteroidal anti-inflammatory drug-induced damage (Allon et al.,1998;Weber et al.,2005).

Lipid metabolism in SCA patients appears to be different from sickle cell trait and normal haemoglobin in both steady state and renal disease. Alterations in lipid metabolism are often observed in all three Hb genotypes with CKD but marked differences in pattern and severity of lipid disorder differ and thus appear to be more severe in SCD subjects with CKD. Since proteinuria is observed in the early stages of SCD nephropathy, it is the hallmark of future deterioration of renal failure. It is therefore important to detect this early so that intervention at this early stage may prevent or delay renal damage in SCD patients more so as this group of subjects do not do well with renal replacement therapies.

10. References

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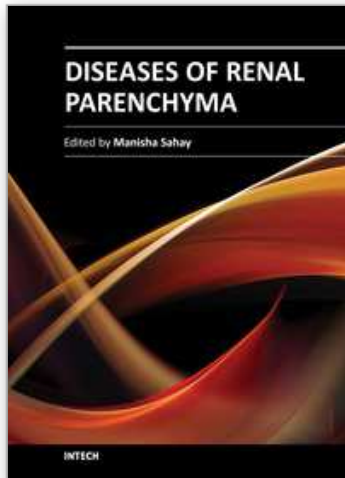
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Clinical nephrology is an evolving speciality in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

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