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RESEARCH ARTICLE

COMPARING CYSTATIN C AND KIM 1 TO CREATININE IN THE ASSESSMENT OF KIDNEY INJURY IN SICKLE CELL PATIENTS

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Abstract: Sickle cell disease (SCD) is a group of blood genetic disorders resulting in an abnormality in the oxygen-carrying protein hemoglobin found in red blood cells. This study was carried out to compare Cystatin C and KIM 1 to creatinine in the assessment of kidney injury in sickle cell patients attending the Sickle cell Department of Federal Teaching Hospital Ido-Ekiti, Ekiti State Nigeria. A total of one hundred and four (104) individuals were recruited for this study comprising of 83 (79.81%) individuals who had history of sickle cell (subjects) and 21 (20.19%) individuals without sickle cell disease (control). Blood samples were collected from each subject into plain bottle from which serum was separated and stored at -20^{0}C. Creatinine was determined spectrophotometrically using Jaffe's method, while KIM 1 and Cystatin C levels were determined using ELISA. Statistical analysis was done using SPSS and significant difference was pegged at $p<0.05$. From the results obtained, the mean ± SD of KMI 1 (pg/mL) in crisis subjects, steady subjects and control was 1.58±0.84, 1.44±0.97 and 0.67±0.42, BMI (kg/m^2) was 17.38±4.98, 21.42±2.20 and 22.21±1.77, Creatinine (mg/dl) was 2.45±1.80, 1.13±0.46 and 0.83±0.37, while Cystatin C (mmol/L) was 214.00±103.84, 194.12±132.96 and 55.89±17.21 respectively. Serum Cystatin C and KIM 1 levels were significantly higher ($p<0.05$) in both Steady and Crisis Subjects when compared with control. Serum creatinine levels was significantly higher ($p<0.05$) in crisis subjects compared with control. The research conclude that Kidney injury is a hallmark of Sickle cell Disease and that that Cystatin C and KIM 1 are better markers of Kidney Injury in Sickle Cell patients than creatinine.

KEYWORDS: Sickle Cell Disease, Renal Injury, Crisis, Steady State, KIM 1, Cystatin C

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INTRODUCTION:

Sickle cell disease (SCD) is a group of blood disorders typically inherited from a person's parents. It results in an abnormality in the oxygen-carrying protein hemoglobin found in red blood cells. This leads to a rigid, sickle-like shape under certain circumstances. The clinical manifestations of sickle cell disease start around 5 to 6 months of age [1]. Sickle cell disease (SCD), a genetically determined hematological disorder is common in Nigeria [2]. Sickle cell disease is an autosomal recessive inherited condition resulting from the presence of a mutated gene that codes for hemoglobin. It is the most common inherited blood disorder affecting 12,000–15,000 people with approximately 250,000 carriers of the sickle cell gene [1]. SCD is a most frequent inherited hematologic disease that results from homozygosity for the mutant form of the gene that encodes β-globin. Sickle cell anemia (SCA) is also the most severe form of SCD, and of no less importance is its renal manifestations [4]. These attendant renal complications are known to be less severe in the compound heterozygous forms of SCD i.e HbSC and HbSβ+-thalassemia. They are however, comparatively mild or nonexistent in individuals with the sickle cell trait [4].

Sickle cell disease is a genetic disorder of hemoglobin (Hb) which disproportionately affects persons of African and to a lesser extent, Hispanic descent. On the molecular level, it is characterized by the inheritance of a mutated Hb gene, Hb S along with or without any other abnormal Hb gene. The cause of sickle cell disease is a single nucleotide substitution on the beta globin gene on the short arm of chromosome 11. The resulting protein, hemoglobin S (HbS), polymerizes under low oxygen conditions, causing red blood cells to become rigid and sickle-shaped [5]. These sickled cells cause activation of other circulating cells, including neutrophils and blood vessel walls in processes similar to those observed in vasculopathies. Subsequently, the tissue loses its blood supply and the resultant ischemia causes tissue infarction [6]. SCD is characterized by red blood cell sickling, vaso-occlusion, hemolysis, acute anemia resulting in high morbidity and mortality and this is common in those with homozygous HbSS genotype [7]. Painful vaso-occlusive crisis (VOC) is the most frequent complication of sickle cell disease. The cause of VOC is believed to be ischemic tissue injury from the obstruction of blood flow by sickled erythrocytes. Sickling process leads to hypoxia and acidosis; a cycle that eventually leads to ischemic tissue injury [4].

The Kidneys are a paired organs system that is primarily charged with the responsibility of filtering waste products from the blood. Other functions involve homeostasis with respect to water, electrolyte and acid base balance [8]. The kidneys regulate blood pressure and red blood cell production in the body [8]. Kidney disease refers to conditions and problems with the kidneys and their function, Kidney problems can develop suddenly (acute) or over the long term (chronic). Diverse clinical conditions, diseases, and drugs can create situations that lead to acute and chronic kidney problems [9]. Kidney disease is seen in most adults with SCD and may affect glomerular and/or tubular function. Reports of renal Disease in SCD have focused primarily on patients with HbSS even as Therefore, a reduced glomerular filtration rate (GFR) or tubular function capability may serve as clinical signs of kidney damage in these individuals [10]. Renal dysfunction caused by vaso occlusive crisis or episodes is a common comorbidity in patients with sickle cell disease, especially in the adult group of patients [11].

Creatinine, the product of muscle creatine catabolism is also a non-protein nitrogenous waste product produced from the breakdown of creatine and its derivatives. The synthesis of creatine occurs in the liver, pancreas and kidneys and it involves the transamination of the amino acid's arginine, glycine and methionine [12]. Elevated Creatinine is not always representatives of a true reduction in GFR. A high reading may be due to increased production of creatinine not due to decreased kidney function, to

interfere with the assay, or to decreased tubular secretion of creatinine [13]. Cystatin C on the other hand is a non-glycosylated 13-kDa basic protein that acts as a cysteine proteinase inhibitor, and is produced at a relatively constant rate. This steady synthesis is apparently not influenced by the presence of inflammatory conditions, muscle mass, gender, body composition, or age [14]. A shortcoming of creatinine in the assessment of glomerular, hence renal function is that serum creatinine readings are not reliable indicators of early stage glomerulopathy in SCD because of the increased eGFR, lower muscle mass, and increased tubular secretion of creatinine in individuals with SCD [15].

In clinical practice, GFR is most frequently estimated using endogenous substances, of which serum creatinine remains the most common. Serum cystatin C and other markers such as kidney injury molecule 1 are relatively new endogenous markers that offers the advantages of constant production by all cells in the kidney [16]. The concentration of serum cystatin C and KIM 1 correlated better with directly measured values for GFR than did serum creatinine. Second, subtle decrements in GFR are less readily detected via creatinine concentration than by serum cystatin and perhaps KIM 1 [17]. High serum creatinine manifests late in patients with sickle cell disease (SCD) who develop severe renal dysfunction, because creatinine is secreted by the renal tubules. Serum cystatin C is a cysteine proteinase inhibitor which is produced by all nucleated cells in the body, does not undergo tubular secretion, and reflects glomerular filtration rate (GFR) accurately [18].

The rationale for combining serum creatinine and some novel marker of kidney injury originated from the finding that both markers show differing sources of error. Serum creatinine levels may be affected by muscle mass and no constant renal tubular handling, whereas serum cystatin C has a different volume of distribution and may vary with the volume status [19]. As creatinine is a poor indicator of mild kidney disease, this research was aimed at assessing and comparing creatinine with Kidney Injury Molecule 1 (KIM 1) and Cystatin C as markers of kidney injury in Steady and Crisis sickle cell patients.

MATERIALS AND METHODS:

Study Area.

The study was carried out in Federal Medical Centre, Ido-Ekiti, Ekiti State and its immediate environments. Ido-Ekiti is a town in the Ido-Osi Local Government Area of Ekiti State, Nigeria. It is situated in the northern part of the state where the routes from Oyo, Osun and Kwara states respectively converge. Ido-Ekiti is the headquarters of the Ido-Osi local council. It is bounded in the east by Ipere and Iludun, in the south by Igbole and Ifinsin and in the north and northwest by Usi Ekiti and Ilogbo Ekiti.

Study Design

A cross-sectional study using a stratified random sampling method was used. Stratification was by age and gender.

Sample Size.

The minimum sample size (N) was calculated by single proportion formula based on 2% estimated prevalence of sickle cell disease in Western part of Nigeria.

Allowance for error of 0.05 at 95% confidence interval (z) using the formular: $N = Z2\ p\ (1-p)/W^2$

Where: Z = confidence level at 95
N = Minimum sample size
W = allowance for error= 0.05
P = estimated prevalence of sickle cell patients in Western part of Nigeria at 2% = 0.02.
Q=1-P
N = 1.96 x 1.96 x 0.02 x 0.98 /0.0025 = 30.11

The total number of samples collected was 104. This was done so as to make up for possible dropouts and outliers. All values were subjected to outlier rules using the formula: mean ±2.8 S.D.

Inclusion Criteria.
Male and female sickle cell patients (steady and crisis) of different age groups who gave their consent were included in this study.

Exclusion Criteria.

Sickle cell patients with hypertension, diabetes mellitus, arthritis and other disease conditions and those who did not give their consent were excluded from this study.

Ethical Clearance.

Ethical approval was obtained from Ethics and Review Committee of Federal Medical Centre, Ido–Ekiti, Ekiti State. Informed consent was sought from each participant before sample collection.

Sample Collection.

Three milliliters (3ml) of venous blood were collected from the cubital fossa using a needle and syringe and dispensed into plain bottle. The blood was allowed to clot and centrifuged at 1200rpm for 5 minutes to separate serum from the red cells. The sample was stored at a temperature of -20 degree Celsius for up to 21days before been assayed.

Methods of determination of parameters

Body Mass Index (BMI).

The height and weight of each subject were measured using a stadiometer to which a weighing scale (ZT-120 health scale) was attached. Measurements were taken with patients standing erect, wearing light clothing and without putting on footwear. Height was measured to the nearest 0.01 metre (m) and weight to the nearest 0.5 kilogram (kg). The body mass index was calculated using this formula: BMI = Weight (kg) / Height (m^2)

Creatinine was determined spectrophotometrically using Jaffe's method**.** Creatinine in serum is determined by Jaffe's reaction where creatinine produces quantitatively an orange color with picric acid in alkaline medium. Without taking into consideration the acidic nature of standard, serum, 1% picric acid and 0.75N NaOH are used in this reaction for color development in standard and samples.

Cystatin C and KIM 1

Cystatin C and KIM 1 as markers of kidney injury were estimated using the ELISA based method. Anti-Cystatin C or KIM 1 polyclonal antibody was pre-coated onto 96-well plates. The biotin conjugated anti-Cystatin C polyclonal or KIM 1 antibody was used as detection antibodies. The standards, test samples and biotin conjugated detection antibody were added to the wells subsequently and wash buffer. TMB substrates were used to visualize HRP enzymatic reaction. TMB was catalyzed by HRP to produce a blue colour product that changed into yellow after adding acidic stop solution. The density of yellow is proportional to the Cystatin C or KIM 1 amount of sample captured in plate. The colour change was measured spectrophotometrically at a wavelength of 450nm. The concentration of Cystatin C or KIM 1 in the samples was determined by comparing the O.D. of the samples to the standard curve.

Statistical Analysis

The results obtained were presented as mean ± standard deviation. Statistical analysis was carried out using one way analysis of variance (ANOVA) and Student's t-test using Statistical Package for Social Sciences (SPSS) version 24.0. Significant difference was pegged at p-values <0.05.

RESULTS:

Table 1: Distribution of all subjects under examination

	Crisis (n = 39)	Steady (n = 44)	Control (n = 21)
Gender			
Male	19 (22.89%)	30 (36.14%)	8 (9.64%)
Female	20 (24.09)	14 (16.87)	13 (15.66%)
Age (years)	18.21±11.34	28.66±11.50	27.50±13.64

Table 1 showed the distribution of all subjects under examination. A total of one hundred and four (104) individuals were recruited for this study comprising of 83 (79.81%) individuals who had history of sickle cell (subjects) and 21 (20.19%) individuals without sickle cell disease (control). Among the eighty-three (83) sickle cell subjects, 39 (46.99%) of the subjects were in crisis, while 44 (53.01%) of the subjects were in steady state. Furthermore, among the eighty-three (83) sickle cell subjects, 49 (59.04%) were males, while 34 (40.96%) were females. The mean of subjects in crisis was 18.21±11.34, steady state was 28.66±11.50 and control group was 27.50±13.64 respectively.

Table 2: Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in steady subjects compared with control

GROUP (n)	STEADY (n=44)	CONTROL (n=21)	P-VALUE
KIM 1 (pg/mL)	1.44±0.97	0.67±0.42	0.028*
BMI (kg/m^2)	21.42± 2.20	22.21± 1.77	0.6206
Creatinine (mg/dl)	1.13±0.46	0.83±0.37	0.0987
Cystatin C mmol/L	194.12±132.96	55.89±17.21	0.000

*Values are significant at p<0.05

Keys: BMI – Body Mass Index, KIM 1 – Kidney Injury Molecule 1

Table 2 showed the Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in steady subjects compared with control. From the results obtained, the mean ± SD of KMI 1 (pg/mL) in steady subjects and control was 1.44±0.97 and 0.67±0.42, BMI (kg/m^2) was 21.42±2.20 and 22.21±1.77, Creatinine (mg/dl) was 1.13±0.46 and 0.83±0.37, while Cystatin C (mmol/L) was 194.12±132.96 and 55.89±17.21 respectively. Age, BMI and Creatinine were insignificantly higher (p>0.05) in steady subjects compared with control. On the other hand, Cystatin C and KIM 1 levels were significantly higher (p<0.05) in Steady state subjects compared with the control.

Table 3: Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in crisis subjects compared with control

Group (n)	Crisis (n=39)	Control (n=21)	p-value
KIM 1 (pg/mL)	1.58±0.84	0.67±0.42	0.001
BMI (g/m²)	17.38±4.98	22.20±1.77	0.000
Creatinine (mg/dl)	2.45±1.80	0.83±0.37	0.000
Cystatin C (mmol/l)	214.00±103.84	55.89±17.21	0.000

*Values are significant at p<0.05

Keys: BMI – Body Mass Index, KIM 1 – Kidney Injury Molecule 1

Table 3 showed the Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in crisis subjects compared with control. From the results obtained, the mean ± SD of KMI 1 (pg/mL) in crisis subjects and control was 1.58±0.84 and 0.67±0.42, BMI (kg/m^2) was 17.38±4.98 and 22.21±1.77, Creatinine (mg/dl) was 2.45±1.80 and 0.83±0.37, while Cystatin C (mmol/L) was 214.00±103.84 and 55.89±17.21 respectively. Age was insignificantly higher (p>0.05) in Crisis subjects compared with control. BMI, Creatinine, KIM 1 and Cystatin C levels were significantly higher (p<0.05) in subjects experiencing crisis compared with control.

Table 4: Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in steady state subjects compared with subjects in crisis

Group (n)	Steady (n=44)	Crisis (n=21)	p-value
KIM 1 (pg/mL)	1.44±0.97	1.58±0.84	0.061
Age (years)	28.07±11.56	18.00±11.54	0.000
BMI (kg/m²)	21.48±4.67	17.38±4.98	0.000
Creatinine (mg/dl)	1.13±0.46	2.45±1.80	0.6994
Cystatin C (mmol/l)	194.12±132.96	214.00±103.84	0.000

*Values are significant at p<0.05

Keys: BMI – Body Mass Index, KIM 1 – Kidney Injury Molecule 1

Table 4 showed the Mean ± SD of KIM 1, BMI, Creatinine and Cystatin C in crisis subjects compared with steady state subjects. From the results obtained, the mean ± SD of KMI 1 (pg/mL) in crisis subjects and steady subjects was 1.58±0.84 and 1.44±0.97, BMI (kg/m^2) was 17.38±4.98 and 21.42±2.20, Creatinine (mg/dl) was 2.45±1.80 and 1.13±0.46, while Cystatin C (mmol/L) was 214.00±103.84 and 194.12±132.96 respectively. Age, BMI, Cystatin C levels in Steady Subjects were significantly higher ($p<0.05$) compared with Subjects on Crisis, while Creatinine levels was insignificantly higher ($p>0.05$) in Steady Subjects compared with Subjects on Crisis.

DISCUSSION:

Sickle cell disease (SCD) is a group of inherited blood. It results in an abnormality in the oxygen-carrying protein hemoglobin found in red blood cells [1]. Sickle Cell Disease is associated with chronic end organ complications, which tend to be more prevalent with improved patient care and longer survival. As renal failure due to sickle nephropathy been documented to be a cause of increased morbidity and mortality, affecting 12-21% of adult sickle cell patients [7]. Kidney disease is seen in most adults with SCD and it affects glomerular and/or tubular function [20]. There are varied mechanism for renal changes seen in sickle cell diseases. The basic pathological process of the disease involves red cell sickling with subsequent ischemia of the end organs [21]. This research was designed to assess renal function comparing the serum levels of both the traditional Creatinine and the more recent Cystatin C and KIM 1 in steady and crisis sickle cell subjects.

Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters (kg/m^2). In this research, BMI was insignificantly higher ($p>0.05$) in steady sickle cell subjects but was significantly lower ($p<0.05$) in crisis sickle cell subjects compared with the control group. Furthermore, BMI in steady sickle cell subjects was significantly ($p<0.05$) higher compared to sickle cell subjects in crisis. This research agrees with Chawla *et al*. [22] who reported that BMI was lower in the Steady sickle cell subjects compared with apparently health control. It is however important to stress that the higher the BMI in SCD patients the healthier they appear and behave. Odetunde [23] had reported that BMI and other anthropometric variables among sickle cell anemia patients were low when compared with individuals with normal hemoglobin genotype with respect to age.

Creatinine is a breakdown product of creatinine phosphate in muscle and is usually produced at a fairly constant rate [24]. In this research, Serum Creatinine levels was insignificantly higher in steady subjects ($p=0.0987$), but was significantly higher in Crisis sickle cell subjects when both were compared with the control group ($p<0.05$). Also, an insignificantly higher mean serum creatinine level ($p=0.6994$) was observed in steady sickle cell subjects compared to crisis sickle cell subjects. This implies that serum creatinine may be an insensitive marker of renal function in SCD maybe due to its relatively high proximal tubular secretion. This Study agrees with the finding of Coresh *et al*. [17] where the utility of serum creatinine for measuring of renal injury was stated to be null in steady sickle cell patients compared with control. Al-Naama *et al*. [26] also reported the same. The findings of Silva-Junior *et al*.[27] and Pandey *et al*.[28] who found no significant difference in the level serum creatinine in sickle cell subjects compared with control also lends credence to the findings in this research. It is the thought of the investigators in this research that interpretation of serum creatinine must be personalized for sickle cell patients. Values tending towards the upper end of the reference interval should be classified as being clinically significant. On the other hand, as he amount of creatinine produced in the body each day is relatively constant, and relative to the muscle mass, coupled with the glomerular hyper filtration may be sole explanation for the the lower concentrations of creatinine in HbS smaller statured individuals characteristic of SCD patients compared to their HbA counterpart [29].

Cystatin C is a non-glycosylated 13-kDa basic protein that acts as a cysteine proteinase inhibitor, and is produced at a relatively constant rate. This constancy is apparently not influenced by the presence of inflammatory conditions, muscle mass, gender, body composition, or age (after 12 months) [14]. Serum Cystatin C levels was significantly higher ($p<0.05$) in both Steady and Crisis sickle cell subjects when both were compared with control. Also a significantly higher ($p<0.05$) serum Cystatin C levels was observed in steady sickle cell subjects relative to sickle cell subjects in crisis. This research agrees with Gregory [29]. The percentage (%) fold increase in Cystatin C in both Crisis and steady subjects relative to control was 247% and 282% respectively, while the Percentage (%) fold increase in crisis state relative to steady was 116%, meaning that Cystatin C is a more sensitive biomarker in the assessment of kidney injury compared to creatinine. It also implies that cystatin C will likely detect early renal injury as very little damage will add a glaring amount of cystatin C lot in blood. The utility of Cystatin C as a sensitive marker of impaired GFR had earlier been stressed in cross-sectional studies [30]. Additionally, cystatin C plays an important role in the development of CAD and has been thought to be a strong predictor of risk of cardiovascular events [31, 32]. In the light of the above findings and other works, cystatin C is more useful when trying to detect mild to moderate impairment of kidney function [33].

Kidney injury molecule 1 (KIM 1) is described as a type 1 membrane protein comprising an extracellular portion and a cytoplasmic portion and is expressed in the kidneys, liver and spleen and it is markedly increased in cases of acute kidney injury. In this research, it was found that there is an increased serum level of KIM1 in sickle cell disease patients in crisis state when compared to control subjects. Elevated values have been shown to acutely herald inflammation and chronic fibrosis. Moreover, its urinary excretion parallels tissue levels [34]. In one experimental study rats were exposed to nephrotoxic insults, and among other biomarkers, KIM-1 was subsequently quantified and its expression was found to correlate with histopathological, gold standard findings. This revealed the potential applications of KIM-1 as an early and sensitive noninvasive marker of renal injury [35, 36]. In the light of the findings in this research, KIM-1, used as a biomarker for predicting chemo-induced nephrotoxicity, can be adapted to assess early or mild kidney damage in SCD, to replace the insensitive creatinine. In summary the pattern of increase in KIM 1 levels over creatinine in steady and crisis state sickle cell disease is similar to that observed with cystatin C.

CONCLUSION:

From this research, it was deduced that Kidney Injury is a complication of Sickle Cell Disease. It was also observed that sickle cell patients are not only prone to kidney injury during crisis but also during the steady state. It further confirmed that both KIM 1 and Cystatin C are better than plasma creatinine estimation as markers for the assessment of kidney injury. Based on evidence from this study, KIM 1 and Cystatin C are recommended in the diagnosis of SCD related kidney injury as it will give a true prognosis and clinical outcome.

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