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Glomerular Filtration Rate Decline and increased Serum Creatinine Concentration in Abia State University Teaching Hospital Aba

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Abstract:
Glomerular filtration Rate (GFR) is essentially the most reliable index of kidney function in health. A decrease in GFR is a pointer to decline in Kidney function and persistent or progressive GFR decline is a specific diagnostic criterion for chronic kidney disease (CKD). In defining CKD, we consider GFR of less than 60ml/min/1.73m² for three months or more. Markers of Kidney function test assess the normal function of kidneys. These markers may be biochemical or even radioactive. They assist in measuring GFR, as well as the concentrating and diluting property (tubular function) of kidneys. One of such biochemical markers is Serum Creatinine.
An increase or decrease in the serum level of these biomarkers can be of help in determining the efficiency of kidney function. Endogenously produced creatinine is an accepted biomarker of kidney function. It is produced from the metabolism of skeletal muscle creatine. It is released into the plasma in a stable rate in normal subjects, and freely filtered at the glomerulus. However, creatinine is secreted into the urine in the proximal tubule which can occasionally overestimate GFR by 10- 20 %.A number of GFR estimating equations have been developed to overcome some of the limitations of estimating GFR from serum creatinine. The CG equation (Cockcroft Gault) was developed in 1973 and is used widely. A new equation Modification of diet in renal disease (MDRD) study equation was developed in 1999 and has since been validated in a number of populations. The MDRD equation was used in estimating GFR in this study.

Keywords: *Glomerular filtration Rate (GFR), Serum Creatinine, Chronic Kidney disease (CKD), Cockcroft- Gault (CG) equation, Modification of Diet in Renal disease, (MDRD) equation*

1. Materials and Methods

This is a 5-year retrospective study carried out in Abia State University Teaching Hospital Aba, in South East Nigeria within 2015 and 2020.

A total of 199 patients were seen, comprising of 132 males and 67 females giving a male female ratio of 2:1. Blood chemistry test was carried out for creatinine, urea and electrolytes. The weight of each patient was measured by simple weighing scale. The GFR was determined using the MDRD formula with the available parameters of weight, sex, race and serum creatinine level.

The data was analyzed using SPSS package (SPSS, version 17).

2. Aims and Objectives

- To validate the association between Glomerular filtration Rate declineand increased serum creatinine concentration.
- To validate serum creatinine as a biomarker for determining GFR in patients with Kidney failure.

3. Results

This study was carried out in Abia State University Teaching Hospital Aba, South East Nigeria. The aim was to validate the correlation between Glomerular Filtration Rate (GFR) decline and increased serum creatinine between 2015

to 2020.Records were accessed for the period of this study from the hospital medical records department. Therewas a totalof 199patients selected, 132males and67females with a male to female ratio of 2:1. The serum creatinine values were weighed against the glomerular filtration rate of each patient with the Hemoglobin level of each patient also determined.These patients ranged from 18 to 93 years of age, with the mean age 52 years.The glomerular filtration rate was calculated using MDRD and staging of CKD was done from stage according to K/DOQI (2002) and modified by NICE 2008 (table 6).

The mean serum creatinine level for Stage 1 CKD was0.9mg/dl and GFR was 114.1 ml/min/1.73m^2.58 people had mean creatinine level of 0.9mg/dl. Pearsoncorrelation was used, and there was association between rise in serumcreatinine and GFR decline (2-tailed sig=.000).Thus, correlation wasstatistically significant at the 0.001 level (2-tailed).

The mean creatinine value for stage 2 CKD was1.2mg/dl and GFR was75ml/min/1.73m^2**.** 69 people had mean creatinine level of 1.2mg/dl. Pearson correlation was used, and there was association between rise in serumcreatinine and GFR decline (2-tailed sig=.000). Thus, correlation was statistically significant at the 0.01 level (2-tailed).

Stage 3 CKD had mean creatinine value at 1.8mg/dl and GFR 47.45 ml/min/1.73m^2.26 people had mean creatinine level of 1.2mg/dl.Pearsoncorrelation was used, and there was association between rise in serum creatinine and GFR decline (2-tailed sig=.000). Thus, correlation was statistically significant at the 0.01 level (2-tailed).

Stage 4 CKD had a mean creatinine value was 47.5 mg/dl and GFR at 23.2ml/min/1.73m^2.25 people had an average creatinine of 47.5mg/dl. Pearson Correlation was used and there was association between rise in serum creatinine and GFR decline (2-tailed sig=.000). Thus, correlation was statistically significant at the 0.01 level (2-tailed).

In Stage 5CKD, 27 had a mean GFR of 7.8 ml/min/1.73m^{2,} with 25 having amean creatinine level of 10mg/dl. PearsonCorrelation was used and there was association between rise in serum creatinine and GFR decline (2-tailed sig=.018). Thus, correlation was statistically significant at the 0.05 level (2-tailed).

4. Result of the Correlation Analysis

variables		**mean**	**Std Deviation**	**Frequency**
Stage1	Creatinine Mg/dl	0.85	0.122	58
	GFR in MDRD	114.08	20.611	58

Inferential statistics			
variables		Creatinine in mg/dl	GFR in MDRD
Creatinine in mg/dl	Pearson correlation	1	-.683
	Sig.(2-tailed)		.000
	Sum of squares and cross products	.847	-97.818
	Covariance	.015	-1.716
	Number(frequency)	58	58
GFR in MDRD	Pearson correlation	.683	1
	Sig.(2-tailed)	.000	
	Sum of squares and cross products	-97.818	242214.396
	Covariance	-1.716	424.814
	Number(frequency)	58	58
	Correlation is statistically significant at the 0.001 level (2-tailed)		

Table 1: Stage One CKD (Age, Sex, Serum Creatinine, Hb, GFR in View)
Stage 1: Descriptive Statistics

Variables		mean	Std Deviation	frequency
Stage 2	Creatinine in mg/dl	1.18	0.205	69
	GFR in MDRD	75.02	8.961	69
Inferential statistics				
variables		Creatinine in mg/dl		GFR in MDRD
Creatinine in mg/dl	Pearson correlation	1		-.732
	Sig.(2tailed)			.000
	Sum of squares and cross products	2.861		-91.532
	covariance	.042		-1.346
	Number(frequency)	69		69
GFR in MDRD	Pearson correlation	.732		1
	Sig.(2tailed)	.000		
	Sum of squares and cross products			5460.852
	covariance	-1.346		80.307
	Number(frequency	69		69

Table: 2: Descriptive Statistics

Correlation is Statistically Significant at the 0.01 level (2-tailed)

Variables		mean	Std Deviation	Frequency
Stage 3	Creatinine in mg/dl	1.75	0.385	26
	GFR in MDRD	47.47	8.275	26
Inferential statistics				
variables		Creatinine in mg/dl		GFR in MRD
Creatinine in mg/dl	Pearson correlation	1		-.676
	Sig.(2-tailed)			.000
	Sum of squares and cross	3.714		-53.869
	covariance	.149		-2.155
	Number(frequency)	26		26
GFR in MRD	Pearson correlation	.676		1
	Sig.(2-tailed)	.000		
	Sum of squares and cross	-53.869		1711.73
	covariance	-2.155		68.469
	Number(frequency	26		26

Table 3: Descriptive Statistics

Correlation Is Statistically Significant at the 0.01 Level (2-Tailed)

Variables		Mean	Std Deviation	Frequency
Stage 4	GFR in MDRD	23.29	4.420	25
	Creatinine in mg/dl	47.47	0.787	25
Inferential statistics				
variables		Creatinine in mg/dl		GFR in MDRD
Creatinine in mg/dl	Pearson correlation	1		
	Sig.(2-tailed)			.000
	Sum of squares and cross products	468.958		-67.236
	Covariance	19.540		
	Number(Frequency)	25		25
GFR in MDRD	Pearson correlation	.806		1
	Sig.(2-tailed)	.000		
	Sum of squares and cross products	-67.236		14.847
	Covariance	-2.808		0.619
	Number(Frequency)	25		25

Table 4: Descriptive Statistics

Correlation Is Statistically Significant at the 0.01 Level (2-Tailed)

Variables		Mean	Std Deviation	Frequency
Stage 5	GFR in MDRD	7.81	3.790	27
	Creatinine in mg/dl	9.98	6.147	25
Inferential statistics				
variables		GFR in MDRD		Creatinine in mg/dl
GFR in MDRD	Pearson correlation	1		-.469
	Sig .(2-tailed)			.018
	Sum of squares and cross products	373.559		-259.151
	covariance	14.368		-10.798
	Number (Frequency)	27		25
Creatinine in mg/dl	Pearson correlation	.468		1
	Sig .(2-tailed	.018		
	Sum of squares and cross products	-259.151		91.881
	covariance	-10.798		38.120
	Number (Frequency)	25		25

Table 5: Descriptive Statistics
Correlation Is Statistically Significant at the 0.05 Level (2-Tailed)

Variables		mean	Std Deviation	Frequency
Stage5D	Creatinine in mg/dl	9.98	6.174	25
	GFR in MDRD	7.77	3.607	25
Inferential statistics				
variables		Creatinine in mg/dl		GFR in MDRD
Creatinine in mg/dl	Pearson correlation	1		-.523
	Sig. (2-tailed)			.007
	Sum of squares and cross products	914.881		-279.606
	covariance	38.120		-11.650
	Number(frequency)	25		25
GFR in MDRD	Pearson correlation	.523		1
	Sig. (2-tailed)	.007		
	Sum of squares and cross products	-279.606		312.214
	covariance	-11.650		13.009
	Number(frequency)	25		25

Table 6: Descriptive Statistics
Correlation Is Statistically Significant at the 0.01 (2-Tailed)

		CREATININE		GFR	HB	
AGE	SEX	mg/dl		MDRD	g/dl	
67	M	0.6		128	11	
29	F	0.9		95	8.8	
29	F	0.9		95	8.8	
52	M	1.1		90	17.9	
70	M	0.9		107	7.2	
62	M	0.9		110	6	
65	M	0.8		125	13.4	
70	M	0.9		107	7.2	
62	M	0.9		110	6	
65	M	0.8		125	13.4	
85	M	0.91		102	14.5	
62	M	0.82		122	13.4	
47	M	0.9		116	16.4	
76	F	0.7		108	7.8	
45	M	0.72		152	13.4	
36	F	0.9		91	14.9	
74	M	0.7		142	10	
63	M	0.8		125	16.4	
57	M	0.9		112	15	
39	M	1		107	14.8	
46	M	0.9		117	11.6	
30	M	0.9		127	14	
36	F	0.9		91	14.9	
30	F	0.9		95	13.1	
29	F	0.9		95	7.5	
79	F	0.6		124	12.4	
40	F	0.8		102	11.2	
39	M	1		107	14.8	
42	F	0.7		118	8.9	
30	F	0.7		126	12.8	
33	M	1.2		90	14.9	
29	F	0.9		98	14.5	
66	M	0.9		109	13.7	
29	F	0.9		95	7.5	
61	M	1		98	14.5	
44	M	1		104	13.4	
42	M	0.9		119	0.9	
50	M	0.9		91	10	
69	M	0.9		91	10	
69	M	0.9		108	14.9	
60	M	0.9		111	13.4	
41	M	1		106	11.9	
50	M	0.8		132	11.9	
65	M	0.9		109	14.5	
65	M	0.8		125	11.6	
35	M	0.62		190	15.9	
50	F	0.8		98	11.3	
68	M	0.7		114	14.2	
60	M	0.9		111	13.4	
43	F	0.6		140	11.2	
12	M	0.8		137	10.9	
50	M	0.8		114.9	13.3	
72	M	0.9		107	13.4	
50	F	0.8		98	11.3	
40	M	0.9		120	14.2	
36	F	0.7		122	10.3	
38	M	0.6		194	15.7	

Table 7: Stage One

		CREATININE		**GFR**	**HB**	
AGE	SEX	mg/dl		MDRD	g/dl	
80	F	0.8		89	13	
80	F	0.8		89	13	
67	M	1.4		65	14.6	
52	M	1.3		75	11.9	
38	F	1.1		72	10.4	
82	M	1.1		82	14.6	
70	M	1.1		85.6	11.9	
60	M	1.1		88	11.9	
60	F	0.9		82	10.7	
67	M	1.4		65	14.6	
60	M	1.1		88	14.2	
60	F	0.9		82	10.7	
82	M	1.1		82	14.6	
52	M	1.3		75	11.9	
38	F	1.1		72	10.4	
70	M	1.1		85	11.9	
52	M	1.1		90	17.9	
34	M	1.6		64	13.4	
41	F	1.2		64	12.7	
70	M	1.1		85	13.4	
38	M	1.3		80	13.4	
76	F	0.83		86	8.5	
47	M	1.25		80	11.2	
60	M	1.5		61.4	15.7	
63	M	1.6		62	16.4	
63	F	1.1		65	15.5	
68	M	1.3		71	13.3	
49	F	1.1		67.9	14.6	
58	F	1		73	11.9	
50	F	1		75.5	12.8	
30	M	1.4		77	14.3	
70	F	1.1		63	13.7	
83	M	1.3		68	11.9	
48	M	1.3		76	12.8	
38	F	1		80	11.9	
54	M	1.1		90	15.2	
40	F	0.9		89	9.7	
75	M	1.3		69	14.5	
70	M	1.3		70	12.8	
37	F	1.1		71	12.7	
59	M	1.5		62	11.9	
59	M	1.4		67	17.3	
45	M	1.5		65	10.3	
40	F	1.1		71	11.3	
54	M	1.5		63	12.9	
61	M	1.5		61	15.7	

		CREATININE		GFR	HB	
55	M	1.4		68	16.4	
83	M	1.3		68	11.3	
38	F	1		80	11.9	
50	F	0.9		85	11.9	
27	M	0.9		85	15.7	
83	M	1.3		68	11.9	
63	M	1.5		61	13.9	
47	M	1.5		65	12.8	
55	M	1.4		68	14.8	
56	M	1.3		73	14.9	
68	M	1.2		77	14.6	
67	M	1.1		86	11.6	
43	M	1.2		85	10.7	
48	F	1.2		61.7	14.3	
74	F	0.9		79	13.9	
35	F	1.1		73	12.1	
56	M	1.2		81	14.9	
78	F	0.8		89	6.3	
80	M	1.2		75	12.8	
70	F	1		71	13.4	
60	M	1.2		79	14.9	
37	F	1		80	14.2	

Table 8: Stage 2

	SEX	creatinine	GFR	HB
AGE		mg/dl	MDRD	g/dl
47	M	1.7	56	9.2
29	M	3	30	10.3
46	F	1.9	37	7.5
56	M	1.7	56	9.2
65	F	1.5	45	7.5
65	F	1.5	45	7.5
63	M	2	44	6
29	M	1.87	55	18.6
65	M	1.7	37	11.5
34	M	1.7	59	16.4
70	M	1.9	45	8.9
38	M	1.8	55	14.2
38	F	1.3	59	13.4
35	M	2	49.1	7.8
29	F	1.6	49	12.7
63	M	2.4	35	11.9
68	M	2.2	39	8.5
65	F	1.2	58	13.3
63	F	1.4	49	12.2
63	F	1.4	49	12.2
45	F	1.3	57	10.1
35	F	1.9	38.7	10.9
73	F	1.7	38	10.4
58	M	1.8	50	11.9
70	F	1.3	52	10.4

Table 9: Stage 3

AGE	SEX	GFR MDRD		CREATININE mg/dl			Hb
48	F	29		2.3			6.7
68	M	23		3.4			7
48	F	25		2.6			7.5
75	M	17		4.3			10.6
52	M	17		4.6			10.8
42	M	19		4.4			8.9
75	F	22		2.7			10.8
37	M	23		3.8			7.5
56	M	29		2.9			9.5
29	M	30		3			10.3
75	M	17		4.3			10.6
52	M	17		4.6			10.8
42	M	19		4.4			8.9
75	F	22		2.7			10.8
29	M	30		3			10.3
56	M	29		2.9			9.5
65	M	22		3.62			8.2
75	M	29		2.8			12.7
65	M	22		3.65			8.5
34	M	27		1.6			13.4
58	M	21		3.8			16.12
85	F	23		3.8			11.9
67	M	27		3			11
55	M	20		4			9.7

Table 10: Stage 4

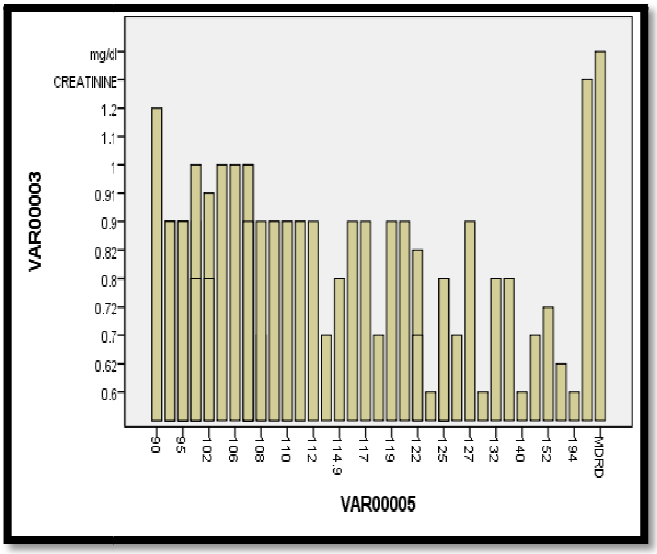
		CREATININE			GFR
AGE	SEX	MG/DL			MDRD
20	F	11			6
35	M	19.5			3.5
56	F	9.9			5
65	M	11.1			6
45	M	7.2			11
43	M	9.5			8
57	M	7.7			9
18	M	8.6			4.3
61	F	8.2			8.6
32	F	14.6			5
53	M	6.9			10.8
63	M	5.3			14
65	M	11.4			6
56	F	5.6			10
54	M	22.1			10
55	F	4.6			13
46	F	4.6			13
46	F	4.6			13
73	F	6.1			9

		CREATININE			GFR
35	M	22			3.1
30	F	0.59			2.1
88	F	15.4			3
75	M	23			3
65	F	5.7			9.6
46	F	4.4			8.2

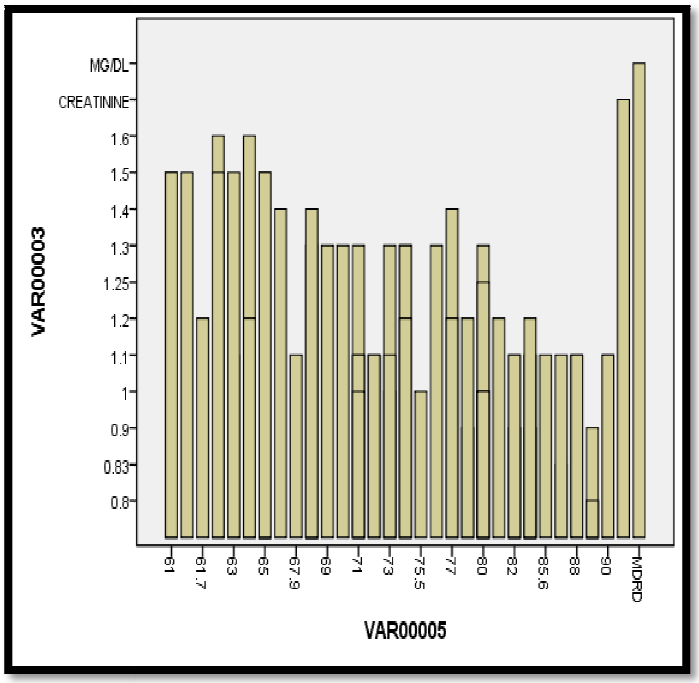
Table 11: Creatinine/ Gfr Ratio

		CREATININE			GFR
AGE	**SEX**	**mg/dl**			**MDRD**
20	F	11			6
35	M	19.5			3.5
56	F	9.9			5
65	M	11.1			6
45	M	7.2			11
43	M	9.5			8
57	M	7.7			9
18	M	8.6			4.3
61	F	8.2			8.6
32	F	14.6			5
53	M	6.9			10.8
63	M	5.3			14
65	M	11.4			6
56	F	5.6			10
54	M	22.1			10
55	F	4.6			13
46	F	4.6			13
46	F	4.6			13
73	F	6.1			9
35	M	22			3.1
30	F	0.59			2.1
88	F	15.4			3
75	M	23			3
65	F	5.7			9.6
46	F	4.4			8.2

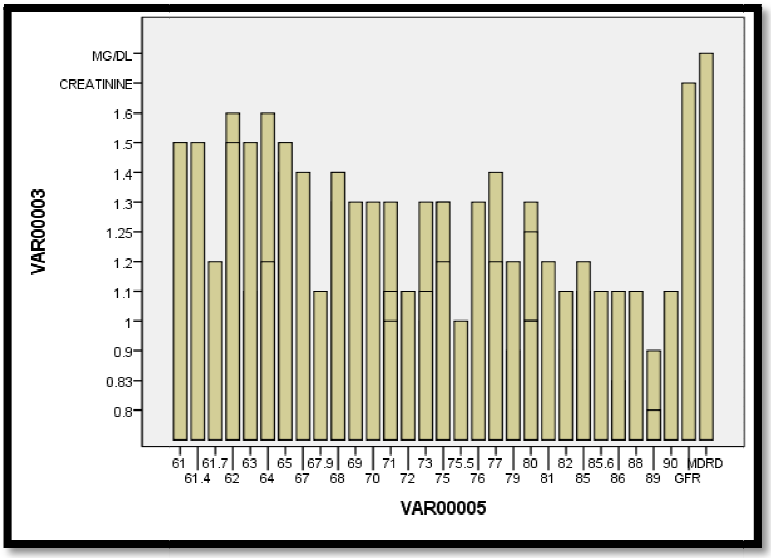
Table 12: End Stage Renal Disease



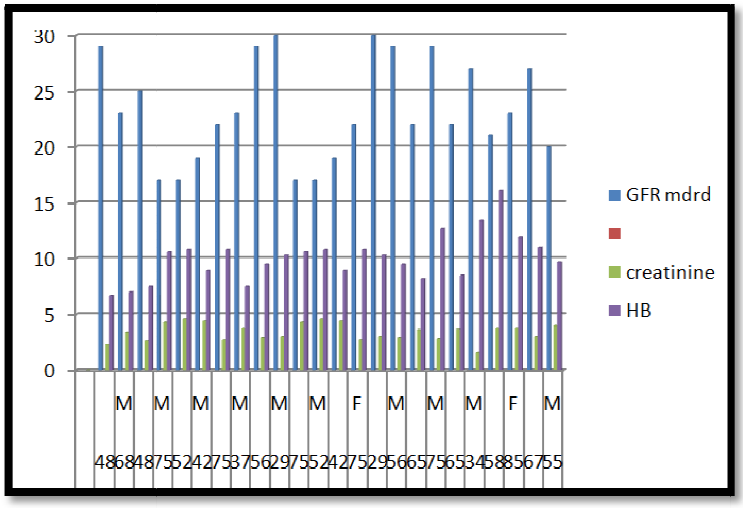
1 (Stage1 creatinine/GFR)



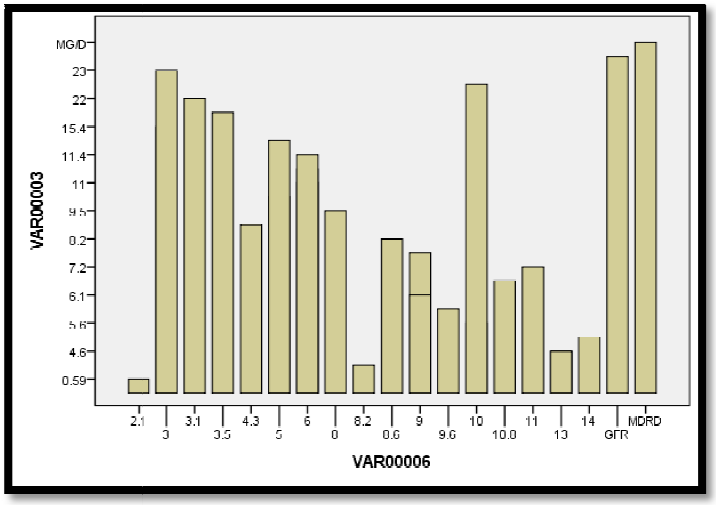
2: stage 2 (creatinine/GFR)



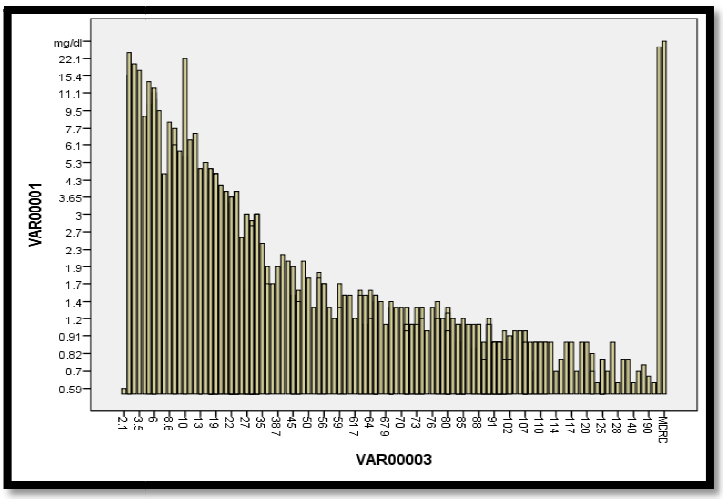
3(stage 3: creatinine/GFR)



4(stage 4 creatinine/GFR ratio)



5(STAGE 5 CREATININE/GFR RATIO)



5.1(Creatinine/ GFR ratio (stages 1-5)

CKD STAGES	definition
1	Normal or increased GFR, evidence of kidney damage reflected by microalbuminuria, hematuria, radiological changes.
2	Mild decrease in GFR (89-60ml/min/1.73m^2 With some evidence of kidney damage reflected by microalbuminuria, proteinuria, hematuria as well as radiologic changes
3	GFR 59-30 ml/min/1.73m^2
3a	GFR 59-45 ml/min/1.73m^2
3b	GFR 44-30ml/min/1.73m^2
4	GFR 29-15 ml/min/1.73m^2
5/ESRD	GFR < 15ml/min/1.73m^2

Table 13: Classification of Chronic Kidney Disease (Ckd) According to Kiddo 2002 and Modified by Nice 2008
Ckd =Chronic Kidney Diseases; K/Doqi= Kidney Disease Outcomes Quality Initiative; Nice= National Institute of Health and Clinical Excellence; Gfr= Glomerular Filtration Rate; Esrd= End Stage Renal Disease.

5. Discussion

The GFR is essentially considered the best overall index of kidney function in health [1]. Early detection of CKD requires identification of patients with a GFR level of < 60mls/min/1.73m^{2}for 3 months or more[2].

Estimation of GFR has been done traditionally by 24hr urine sample of creatinine excretion and measurement of Serum Creatinine, then computation of creatinine clearance (Ccr). Since collection of urine for determination of Ccr is difficult in practice, clinicians rely on Serum Creatinine alone as an index of GFR. A further study showed that urea is reabsorbed by the renal tubule. The arithmetic mean of renal urea and renal creatinine clearance are a good approximation of kidney function in advanced state of kidney disease[3].

Several formulas have been developed to estimate GFR from serum creatinine concentration, age, gender and body size[4, 5, 6]. There are limitations however from each formula. The Cockcroft-Gault formula was developed in 1973 using data from 249 men with creatinine clearance (Ccr) from approximately30-130 ml per minute. It is not adjusted for body surface area. The modification of diet for renal diseases (MDRD) study equation was developed in 1999 using data from 1628 patients with CKD and GFR from approximately 5-90 ml/min/1.73m^2. It estimates GFR adjusted for body surface area and is more accurate than measured creatinine clearance from 24hr urine collection or estimated by the Cockcroft- Gault formulae. The MDRD equation was used in our study.

Early detection of CKD and by implication GFR decline can prevent cardiovascular complications[7-10]. This is pertinent to developing countries where support for renal replacement therapy is lacking for most patients with advanced kidney failure[11].

Creatinine is produced none enzymatically, in skeletal muscles, hence the amount of creatinine production and 24 hr creatinine excretion are directly related to muscle mass[12].Also, dietary intake of meat has been shown to influence Serum Creatinine levels[13].Creatinine is an important indicator of kidney health because it is an easily measured byproduct of muscle metabolism and excreted unchanged by the kidneys. It is produced through the biological system involving creatine, phosphocreatine and adenosine triphosphate (ATP). It is synthesized primarily in the liver from the methylation of glycocyamine (guanido acetate, synthesized in the kidney from amino acids argenine and glycine), by S-Adenosyl methionine. It is then transported through blood to the other organs, muscle and brain, where through phosphorylation becomes the high energy compound phosphocreatine[14]. Creatine conversion to phosphocreatine is catalyzed by creatine Kinase; spontaneous formation of creatinine occurs during the reaction [15].

Men tend to have higher concentrations of creatinine than women since men have greater skeletal muscle mass[16]. Each day 1% to 2% of muscle creatine is converted to creatinine. The limitations posed by creatinine clearance as a measure of GFR is found in the overestimation of GFR by Crcl in severe Kidney dysfunction occurring because of hypersecretion of creatinine by the proximal tubules, leading to increase in total creatinine clearance[17]. Drugs like ketoacids, cimetidine and trimethroprim reduce creatinine tubular secretion, and therefore, increase the accuracy of the GFR estimate particularly in advanced kidney disease. Thus, a rise in blood creatinine concentration is a late marker, observed only with severe damage to functioning nephrons. It is therefore unsuitable for detecting early-stage kidney disease.

Elevated levels of serum creatinine mark the presence of reduction in GFR. Serum creatinine levels>1.2mg/dl in women and 1.6mg/dl in men have been found to be approximately 90% sensitive for detecting GFR of < 60ml/min/1.73m^2.[18]

Diagnosis of CKD requires persistent reduction in GFR for at least 3 months[19]. The estimate of reduced GFR in our study is based on a simple measurement of Ccr. However, simple measurements of serum Creatinine are considered appropriate for epidemiologic and screening purposes[20].

6. Conclusion

Glomerular filtration rate (GFR) is the most reliable determinant of kidney function, and a decline in GFR remains a pointer to declining kidney function. Amongst biochemical markers used in assessing the excretory ability of the kidneys, creatinine is readily available. However, factors such as age and muscle bulk could over value results in reference to serum creatinine levels. Elevated serum creatinine level signifies impaired kidney function or kidney disease. As kidneys become impaired, the creatinine level in the blood rises due to poor creatinine clearance by the kidneys. It is for

this reason that routine test for serum creatinine can serve as a screening test in kidney health. In the study GFR was determined by the MDRD formula. Increasing serum creatinine became evident with GFR decline especially GFR< 60 mls/min/1.73m^2, which pointed to chronic kidney disease. As much as the study revealed, there was evidence-based association between GFR decline and increased serum creatinine. It was more obvious from stage 3 to 5 CKD as shown in the tables.

7. What the Study Reveals

- The study showed evidence-based association between GFR decline and increased serum creatinine concentration especially from GFR < than 60mls /min/1.73m^2.
- GFR decline is a pointer to progressive decline in kidney function.

8. What The Study Adds

- Serum creatinine is a valuable biomarker for determining GFR despite some known limitations.

9. Competing Interest

The authors declare no competing interest.

10. Authors' Contribution

JA, MO and OC were involved in the initial conception of this manuscript and patient care. JA collected the data while OC analyzed the data. JA and OC were involved in writing of the manuscript. UE read and eventually approved the final draft before submission.

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