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2 **ORIGINAL ARTICLE**

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4 **HYPERHOMOCYSTEINEMIA IN CHRONIC KIDNEY DISEASE PATIENTS IN A**
5 **TEACHING HOSPITAL IN NIGERIA**

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24 **LIST OF ABBREVIATIONS**

25 BMI – Body Mass Index

26 CHD – Coronary Heart Disease

27 CKD – Chronic Kidney Disease

28 CVD – Cardiovascular Disease

29 ESRD –End Stage Renal Disease

30 EIA – Enzyme Immuno Assay

31 FBS – Fasting Blood Sugar

32 GFR – Glomerular Filtration Rate

33 Hcy – Homocysteine

34 IQR – Inter Quartile Range

35 KDIGO – Kidney Disease Improving Global Outcomes

36 SD – Standard Deviation

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Original Research Article

HYPERHOMOCYSTEINEMIA IN CHRONIC KIDNEY DISEASE PATIENTS IN A TEACHING HOSPITAL IN NIGERIA

ABSTRACT

Aim: To determine the prevalence of hyperhomocysteinemia amongst chronic kidney disease (CKD) patients at a Teaching Hospital in Nigeria and to determine its relationship with the severity of kidney disease.

Study design: A comparative cross sectional study carried out in the department of Medicine in a Teaching Hospital in Nigeria between April 2012 and May 2013

Methodology: A comparative cross sectional study among 138 patients with CKD and 69 healthy consenting hospital staff individuals. Glomerular filtration rate was estimated for both patients and controls, using measured serum creatinine in the Cockcroft-Gault formula and the patients were grouped into the different stages of chronic kidney disease. All subjects had the homocysteine levels measurements using the enzyme-linked immunosorbent assay. Homocysteine levels were compared between healthy persons and CKD patients as well as within different stages of chronic kidney disease.

Results: Most of the CKD patients (47.8%) were stage 4, followed by (33.3%) stage 3 and stage 5 (14.5%). While stages 1 and 2 were the least (2.2% each). The mean age of the patients was 45.9 ± 16.5 years and 42.3 ± 14.7 years for control subjects. The prevalence of hyperhomocysteinemia was 57.9% amongst cases and 4.3% among control subjects with median homocysteine (Hcy) level being $19.1 \mu\text{mol/l}$ (IQR - 13.8) in cases and $8.3 \mu\text{mol/l}$ (IQR - 2.9) in controls, this was significant ($P < .001$) with the chronic kidney disease patients having higher median homocysteine levels as the degree of kidney disease worsened.

Conclusion: The prevalence of hyperhomocysteinemia is high in CKD patients compared to controls and it increases as CKD progresses.

78 Keywords: chronic kidney disease, homocysteine, hyperhomocysteinemia, cardiovascular
79 disease

80 **INTRODUCTION**

81 Chronic kidney disease (CKD) is a public health problem that is present worldwide
82 with an incidence that's on the rise, unfavourable outcomes and very high cost [1].

83 Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients
84 with CKD that is well documented [2]. Although patients with CKD are at risk of ultimately
85 developing end- stage renal disease (ESRD), about 50% of CKD patients die of CVD before
86 commencement of dialysis [3-6]. In patients requiring haemodialysis (usually stage 5 CKD
87 patients) the morbidity and mortality from CVD is extremely high [7]. Based on data from the
88 U.S. Renal Data System Coordinating Center Case-Mix Adequacy Study, clinical coronary heart
89 disease (CHD) is seen in 40% of haemodialysis patients and CVD in them is 10 to 30 times
90 higher than in the general population despite stratification by gender, age, race, and the presence
91 of diabetes [7].

92 CKD patients usually develop accelerated atherosclerosis and the risk of premature death
93 from CVD is higher. The predisposition of these patients to atherosclerosis is driven mainly by
94 inflammation, dyslipidemia and oxidative stress, and these are features associated usually with
95 CKD [2]. Chronic inflammation is prevalent in CKD patients and numerous studies have
96 demonstrated that chronic inflammation may be a contributor to the morbidity and demise
97 among end stage renal disease (ESRD) patients [8, 9]. The increased cardiovascular morbidity
98 and mortality among CKD patients may not be fully explained by conventional risk factors.

99 A number of abnormalities in the metabolism of protein and amino acid are seen in
100 patients with CKD especially ESRD, an increase in the plasma concentration of homocysteine, a
101 sulphur containing amino acid is one of such abnormalities that may be seen[10].

102 Homocysteine is associated with inflammation and is been considered as an
103 inflammatory marker [11,12]. It acts as an atherogenic and thrombophilic agent which
104 potentiates hypertension and smoking as well as other risk factors that predispose to peripheral
105 arterial disease [10]. All of which increase morbidity as well as mortality in CKD patients.
106 Hence homocysteine is attracting a lot of attention among renal patients.

107 Hyperhomocysteinemia in itself has also been shown to be an independent
108 cardiovascular risk factor in patients with chronic kidney disease [10, 13] however, the
109 mechanism is not clear. Elevated levels of homocysteine and cardiovascular disease are common
110 in patients with decreased renal function. An increase in Homocysteine represents a potent risk
111 factor for coronary, cerebrovascular and peripheral arterial disease as well as for deep vein
112 thrombosis [14]. Hyperhomocysteinemia is seen in the early stages of CKD at levels of
113 glomerular filtration rate (GFR) of about 60ml/min and its prevalence increases to about 85-
114 100% in ESRD[15]. In the general population moderate hyperhomocysteinemia is seen in
115 approximately 5 – 7 % [16].

116 The burden of CKD in terms of morbidity and mortality is huge, worse in developing
117 countries where access to, and affordability of care is not readily available. A major factor
118 contributing to this burden is CVD. To reduce this burden, cardiovascular risk factors in CKD
119 patients must be sought and addressed. The paucity of data on hyperhomocysteinemia in chronic
120 kidney disease in a developing country like Nigeria necessitated this study.

121 **MATERIALS AND METHODS**

122 This was a hospital-based comparative cross-sectional study carried out in the
123 Nephrology unit, in a tertiary hospital in Nigeria. Patients presenting at the Nephrology
124 clinic/Dialysis/Accident and Emergency units who met the inclusion criteria -adults above 18

125 years of age in CKD stages 1 – 5, on conservative or renal replacement therapy and who gave
126 their consent, were consecutively recruited. Exclusion criteria were patients below 18 years of
127 age, non-consenting patients, patients on methotrexate, phenytoin or theophylline therapy,
128 menstruating women, patients with acute kidney injury, hypothyroidism, acute lymphoblastic
129 leukemia and cancers of the breast, ovaries and pancreas. Controls were recruited from amongst
130 hospital staff (doctors and nurses) who were apparently healthy and not on medication for any
131 acute or chronic ailments who gave their consent. Approval for the study was obtained from the
132 Ethics and Research Committee of the hospital. All participants gave written informed consent.

133 **SAMPLE SIZE**

134 Studies on the prevalence of hyperhomocysteinemia revealed a range of 56% - 90% [7, 10, 16,
135 19, 20, 21]. The sample size was extrapolated from the formula for sample size determination in
136 an infinite population [22] using a prevalence of 90% and a degree of precision of 0.05. A
137 sample size of 138 was arrived at. A total of 138 chronic kidney disease patients and 69 controls
138 in a ratio 2:1 were recruited for this study.

139 Upon recruitment, a researcher administered questionnaire was completed. Data on
140 physical characteristics such as weight, height, hip and waist circumference and blood pressure
141 were recorded. Weight was measured in kilograms using hospital health scale ZT-120 with
142 patients putting on light clothing without foot wears. The height was measured in meters using
143 the same scale. The body mass index BMI defined as weight in kilogram divided by the square
144 of patient's height in meters was calculated. The waist circumference in centimetres was
145 measured in the horizontal plane at the level of the natural waist line taken to be at the umbilicus
146 using a non-stretchable tape. All patients and controls were instructed to be on overnight fast for
147 8-10 hours before blood sample collection on the next day. About 10ml of venous blood was
148 collected, 5ml into a lithium heparin sample bottle for serum creatinine estimation using the
149 Jaffe's reaction and 5ml into an EDTA bottle and centrifuged for 15 minutes within 30 minutes

150 of collection and plasma stored at < 20oC for homocysteine level assay using the Axis®
151 Homocysteine FHCY100 Enzyme Immunoassay (EIA) [17].

152 The results were categorized as follows: moderate hyperhomocysteinemia - 15-
153 30µmol/L, intermediate hyperhomocysteinemia - >30-100µmol/L, and severe
154 hyperhomocysteinemia - >100µmol/L [16].

155 Fasting blood sugar (FBS) was measured using an Accucheck glucometer and strips.

156 Glomerular filtration rate was calculated using the Cockcroft-Gault formula to estimate
157 creatinine clearance (CCr): $CCr = (140 - \text{age}) \times (\text{weight})/72 \times SCr \times (0.83 \text{ if female})$, where SCr
158 is in mg/ dL, weight in kg and age in years and results were stratified according to the KDIGO
159 guidelines [17] into CKD stages 1-5.

160 **DATA ANALYSIS**

161 Data entry, storage, and management were performed on the SPSS version 17.

162 Normally distributed continuous variables were presented as means and standard
163 deviation (SD) and skewed data as medians with inter-quartile ranges (IQR) or standard
164 deviation while discrete variables were presented as percentages. The student t-test was
165 employed for comparing the means of data with normal distribution while Wilcoxon Signed
166 Ranks was used for skewed data in cases versus controls. Chi-square was used in testing for
167 significant differences between proportions and frequencies of cases and controls that had
168 hyperhomocysteinemia.

169 The confidence interval was set at 95% limit, with a level of significance, $P < 0.05$.

170 **RESULTS**

171 The ages of patients ranged from 18 to 80 years with the mean age of the study
172 population being 45.9 years \pm 16.4 for cases and 42.2 years \pm 14.6 for control ($P = 0.119$). The

173 cases consisted of 89 males (64.5%) and 49 females (35.5%) while controls were made up of 42
 174 males (60.9%) and 27 females (39.1%), $P = 0.610$

175 There was no statistically significant difference between mean ages, sex and marital status of
 176 cases and controls as shown in table I.

177 **TABLE 1: SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION**

CHARACTERISTICS	CASES	CONTROLS	t	P -value
	n = 138 (Mean ± S.D)	n = 69 (Mean ± S.D)		
Age	45.9 ± 16.4	42.2 ± 14.6	1.570	0.119
	n = 138(%)	n = 69(%)	X ²	
Sex				
Male	89 (64.5%)	42 (60.9%)	0.260	0.610
Female	49 (35.5%)	27 (39.1%)		
Marital status				
Unmarried	34 (24.6%)	15 (21.7%)	0.214	0.644

Married

104 (75.4%)

54 (78.3%)

178

179 Table II shows the mean BMI, waist-hip ratio (WHR), FBS, estimated GFR and
180 homocysteine levels in cases and controls. The homocysteine and FBS levels were significantly
181 higher in the patients ($P = 0.0001$), while the estimated GFR was significantly lower in cases.

182 **TABLE 2:** CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF STUDY
183 POPULATION

VARIABLE	CASES (n=138)	CONTROLS (n=69)	t	P- value
BMI (kg/m ²)	23.71 ± 4.94	26.7 ± 3.6	0.303	0.762
Waist-Hip Ratio	0.92 ± 0.07	0.90 ± 0.45	0.562	0.575
Fasting Blood Sugar (mg/dl)	107.2 ± 34.0	92.6 ± 9.9	4.637	< 0.01

	Median (IQR)	Median (IQR)	Wilcoxon	P- value
Estimated GFR (mg/dl)	29.9(IQR-18.9)	96.7(IQR-16.7)	187.00‡	<0.01
Homocysteine level(μmol/L)	19.0(IQR- 13.8)	8.3(IQR - 2.9)	1820.00‡	<0.01

184 BMI – Body Mass Index, GFR – Glomerular filtration rate

185

186 Three (2.2 %) of the patients with CKD were in stage 1, another three (2.2%) were in
187 stage 2, 46 (33.3%) in stage 3, 66 (47.8%) in stage 4 and 20 (14.5%) in stage 5.

188 The frequency of hyperhomocysteinemia was 57.9% among CKD patients and 4.3%
189 among the controls $P < 0.01$, OR = 30.34 (95% CI = 9.09,- 101.29). Forty-two percent of the
190 CKD patients had normal levels of homocysteine, 30.4% moderate hyperhomocysteinemia and
191 27.5% intermediate hyperhomocysteinemia. None had severe hyperhomocysteinemia as depicted
192 in table 3.

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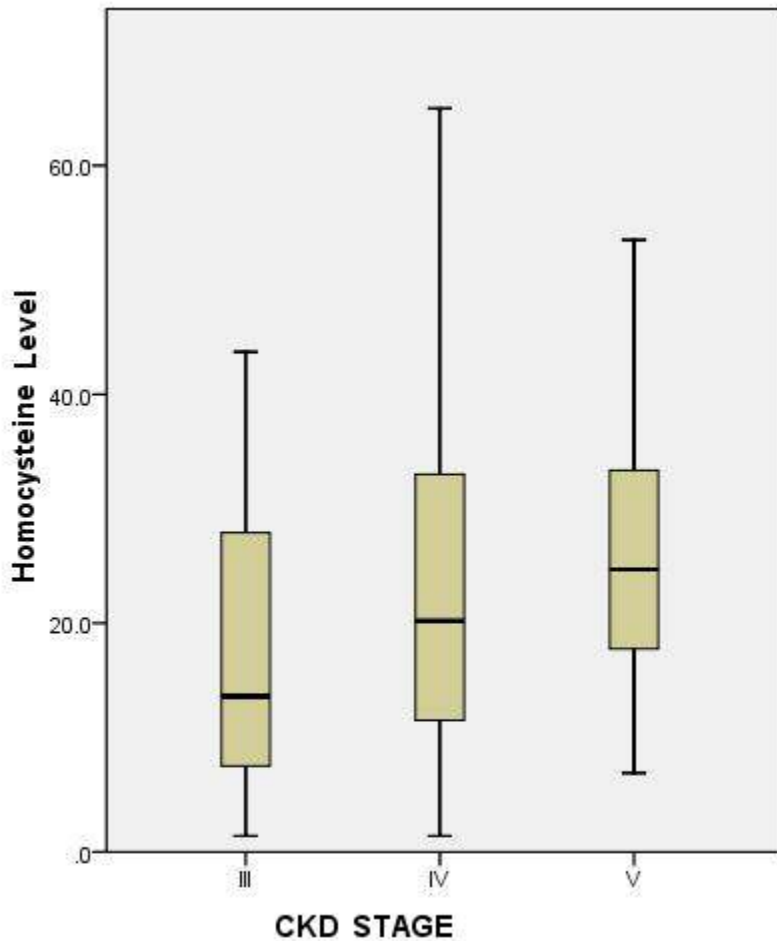
194 **TABLE 3: COMPARISM OF PREVALENCE OF HOMOCYSTEINEMIA (CASES**
195 **VERSUS CONTROLS)**

	CASES	CONTROL
Elevated	80(57.97%)	3(4.35%)
Normal	58(42.03%)	66(95.65%)
Total	138(100%)	69(100%)

196 **df = 2, P- value <0.01, OR = 30.34 (95% CI = 9.09,- 101.29)**

197 The median values of Hcy increased from stage 1 to 5. There was a significant correlation
198 between the stages of CKD and the degree of homocysteine levels (spearman's rho = 0.204, $P =$
199 0.016) as shown on figure 1.

200



201

202 Fig I: Boxplot showing correlation between CKD stage and median homocysteine levels

203 **DISCUSSION**

204 Increased cardiovascular morbidity and mortality in CKD patients has been associated
 205 with elevated homocysteine levels which is a common finding in them [10,11]. This study
 206 shows that hyperhomocysteinemia is significantly higher among CKD patients. Using the
 207 classification by Kang et al, 57.9% of the CKD patients had hyperhomocysteinemia. This is
 208 comparable with 56% reported by Menon *et al* in England in which baseline homocysteine was
 209 measured in 2 different populations; population A with estimated GFR 25 – 55 ml/min had a

210 prevalence of hyperhomocysteinemia of 56% [21]. It is, however, lower than that reported by
211 Ajith *et al* in New York [23], in which 147 patients; 85 males and 62 females aged 58 ± 15 years
212 requiring hemodialysis had a prevalence of 82%. The difference in prevalence rate may be due to
213 the fact that the index study assessed the prevalence in both dialyzing and non-dialyzing patients.

214 Cases with moderate and intermediate hyperhomocysteinemia were 30.4%, and 27.5%
215 respectively, none had severe hyperhomocysteinemia, which is not surprising as cases of severe
216 hyperhomocysteinemia usually due to homozygous defects in genes encoding for enzymes of
217 homocysteine metabolism leading to accumulation of Hcy in blood and urine, are extremely rare.
218 An example of this is a disorder caused by homozygosity for a defective gene which encodes
219 for cystathionine beta-synthase. In this condition Hcy can be as high as 400umol/L [24]. In the
220 index study, however, a majority of the patients with hyperhomocysteinemia had moderate
221 hyperhomocysteinemia which may be due to deficiencies in vitamins that play major roles in
222 Hcy metabolism, depending on the arm of the 2 metabolic pathways that is defective, that is
223 vitamin B12 and folate deficiency in the remethylation pathway. These vitamins may be lacking
224 in CKD patients as renal disease results in a catabolic state, a syndrome of malnutrition,
225 inflammation and atherosclerosis with reduced intake and minimal absorption usually prevalent
226 in patients especially those in end-stage [25].

227 The significant difference in homocysteine levels between cases and control in this study
228 is also in keeping with the findings by Muhammad *et al* in Pakistan [26]. The mean tHcy value of
229 the controls 8.3 ± 2.85 is also comparable to that reported by Okubadejo *et al* amongst their
230 control subjects – 10.1 ± 7.7 [27] and also with that reported by Osunkalu amongst otherwise
231 healthy subjects with a mean tHcy of 9.5 ± 2.4 [28]. This is expected as the kidneys help in
232 clearing homocysteine, and with kidney disease the renal clearance of homocysteine is impaired.

233 This study also revealed an association between the severity of kidney disease and the
234 level of hyperhomocysteinemia as it shows a steady rise in the prevalence rate of total
235 hyperhomocysteinemia from CKD stage 1 through to 5. This association was significant; and is
236 in concordance with findings from other studies [10, 29, 30, 31]. Shankar *et al* found that higher
237 plasma homocysteine levels were seen in patients with CKD, independent of BMI, smoking,
238 diabetes mellitus, hypertension, cholesterol levels, and other confounders. Pooled data from 41
239 trials and 27,000 patients show that homocysteine levels are significantly inversely correlated
240 with estimates of GFR [32], with higher levels of homocysteine seen in patients with reduced
241 GFR indicating higher homocysteine levels as CKD worsens. This inverse correlation is even
242 more robust when using clearance methods in measuring GFR [32].

243 There is good evidence that normal kidneys play a major role in amino acid and Hcy
244 clearance and metabolism however it may be difficult to identify the source of clearance defect
245 of Hcy owing to the lack of data on Hcy extraction and metabolism by diseased kidneys. The
246 existence of Hcy-metabolizing enzymes and uptake systems in renal tubular cells has been
247 confirmed, and Hcy extraction studies in animal kidneys documented significant Hcy uptake [33,
248 34]. Logically the loss of metabolically active kidney tissue normally involved in Hcy handling
249 should decrease Hcy clearance and increase plasma levels. The inverse relationship between Hcy
250 levels and GFR, which is consistent throughout the different stages of CKD, supports the fact
251 that it is reduced renal function, not the accumulation of uremic toxins that causes Hcy levels to
252 increase.

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254

255 **CONCLUSION**

256 This study has shown that hyperhomocystienemia is prevalent in CKD patients and worsens as
257 renal function declines.

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