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Evaluation of Dyslipidaemia and Atherogenic Index in Patients with Chronic Kidney Disease in a Nigerian Tertiary Health Facility

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Chronic kidney disease (CKD) is a global health concern associated with significant morbidity and mortality. Dyslipidaemia is a common complication of CKD, contributing to cardiovascular events. This study aims to assess dyslipidaemia and the atherogenic index in CKD patients at various stages in a tertiary health facility in Southern Nigeria.
Methods: A cross-sectional case-control study was conducted, enrolling 200 participants, including 50 healthy individuals as controls and 150 CKD patients (stages 3 to 5). Exclusion criteria encompassed viral hepatitis, HIV, malignancy, life-threatening illnesses, liver diseases, and cerebrovascular diseases. Ethical approval and informed consent were obtained. Sociodemographic and clinical data were collected using a self-administered questionnaire. Blood samples were analyzed for urea, creatinine, triglycerides, total cholesterol, and HDL-Cholesterol. Calculations included LDL, VLDL, LDL/HDL ratio, and the atherogenic index. eGFR was measured using the MDRD equation. Statistical analysis utilized SPSS (version 22.0) with one-way ANOVA.
Results: CKD patients exhibited significant alterations in renal parameters compared to controls ($p < 0.05$). The lipid profile of CKD patients showed elevated total cholesterol, reduced HDL-Cholesterol, increased LDL-Cholesterol, elevated LDL/HDL ratio, elevated VLDL-Cholesterol, and elevated triglycerides ($p < 0.05$). Atherogenic index significantly increased with advancing CKD stages ($p < 0.05$).
Conclusion: This study highlights the prevalence of dyslipidaemia in CKD patients, with a notable increase in the atherogenic index as the disease progresses. These findings underscore the importance of monitoring lipid profiles in CKD patients for cardiovascular risk assessment. Further research is warranted to explore interventions targeting dyslipidaemia in this population.

Keywords: Atherogenic Index; cardiovascular risk; chronic kidney disease; dyslipidaemia; lipid profile.

1. INTRODUCTION

Chronic Kidney Disease (CKD) is a global public health issue associated with significant morbidity and mortality. The burden of CKD in Nigeria has been on the rise, affecting a substantial portion of the population [1]. CKD is a progressive condition characterized by the gradual loss of kidney function over time, leading to complications such as dyslipidaemia, an abnormal lipid profile that includes elevated levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C), and reduced levels of high-density lipoprotein cholesterol (HDL-C). Dyslipidaemia in CKD patients not only contributes to the progression of renal damage but also substantially increases the risk of cardiovascular events, making it a crucial area for investigation [2,3]

The relationship between dyslipidaemia and CKD is bidirectional, as impaired kidney function can lead to alterations in lipid metabolism, and dyslipidaemia can exacerbate kidney damage

[4]. Furthermore, the atherogenic index, calculated as the ratio of LDL-C to HDL-C, is an established marker of cardiovascular risk. Studies conducted in various populations have demonstrated the association between dyslipidaemia, atherogenic index, and adverse cardiovascular outcomes in CKD patients [5]. However, limited research has been conducted in the Nigerian population, particularly within the context of a tertiary health facility.

This research aims to fill this critical gap by evaluating the prevalence and patterns of dyslipidaemia, as well as determining the atherogenic index in a cohort of CKD patients. Understanding the lipid profile and atherogenic risk in CKD patients within this specific population is essential for developing targeted interventions and improving patient outcomes.

2. MATERIALS AND METHODS

This study is a cross-sectional case-control study carried out in a tertiary health facility in Southern Nigeria. The present study enrolled 200 participants in which 50 were normal healthy individuals which served as control and CKD patients were 150 which includes 50 patients each in stage 3 to stage 5. The patients included adults (18 years and above) that were diagnosed with chronic kidney disease and were attending the Nephrology Department of a tertiary health facility in Southern Nigeria. Age and sex matched healthy individuals served as the control.

Patients with viral hepatitis and HIV, history of malignancy or suffering with other life-threatening illness, history of liver diseases, cerebrovascular disease such as stroke or transient ischemic episodes were excluded from the study.

Self-administered questionnaire was used to gather the sociodemographic and clinical information the patients. Five millilitre of blood sample was collected from both patients and control individuals. Urea, creatinine, triglycerides, total cholesterol, and serum HDL-Cholesterol were estimated by fully automatic chemistry analyzer. LDL, VLDL and LDL/HDL ratio were calculated. Atherogenic index was calculated using $\log_{10}$ (Triglycerides/HDL-C) formula. Based on serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation, estimated glomerular filtration rate (eGFR) was measured.

Statistical analysis was carried out using SPSS (version 22.0). Data were expressed as Mean ± standard deviation. Comparison of means across the groups was done by one-way ANOVA and the correlation done by Pearson correlation. Significance was defined by p value less than 0.05.

3. RESULTS

The majority of participants were male (70.00%), and 30.00% were female. Participants were distributed across different age groups, with the majority being in the 40-49 and 50-59 age ranges. The majority of participants were married (80.67%). The participants had diverse educational backgrounds, with a significant portion having secondary education (48.00%) and tertiary education (22.00%). The majority of participants (44.67%) have been dealing with CKD for 1-3 years (Table 1).

The levels of urea in the blood increase significantly as CKD progresses, with values of 39.06±5.83 in Stage 3, 61.85±4.83 mg/dL in Stage 4, and 85.76±5.93 in Stage 5, compared to the control group (18.78±3.32 mg/dL). Similar to urea, creatinine levels also rise with CKD advancement. Stage 5 shows the highest level at 4.99±0.52 mg/dL, compared to the control group (0.95±0.03 mg/dL). Uric acid levels increase substantially in CKD patients, reaching 28.47±4.93 mg/dL in Stage 5, compared to the control group (5.14±0.53 mg/dL). The estimated glomerular filtration rate (eGFR) decreases significantly with CKD progression. Stage 5 has the lowest eGFR at 15.67±2.19 mL/min, compared to the control group (99.06±22.74 mL/min) (Table 2).

Total cholesterol levels increase with CKD progression, reaching 245.46±29.83 mg/dL in Stage 5, compared to the control group (166.18±28.63 mg/dL). HDL-cholesterol decreases with CKD progression, reaching 31.57±7.49 mg/dL in Stage 5, compared to the control group (62.36±15.29 mg/dL). LDL-cholesterol levels increase with CKD progression, peaking at 131.97±27.37 mg/dL in Stage 5, compared to the control group (88.67±20.03 mg/dL). The ratio of LDL to HDL increases with CKD progression, reaching 4.05±0.44 mg/dL in Stage 5, compared to the control group (1.46±0.32 mg/dL). VLDL-cholesterol levels increase with CKD progression, reaching 47.54±13.72 mg/dL in Stage 5, compared to the control group (24.06±3.22 mg/dL). Triglyceride levels

increase significantly with CKD progression, reaching 235.34±48.83 mg/dL in Stage 5, compared to the control group (120.67±31.29 mg/dL) (Table 3). The atherogenic index increases with CKD progression, reaching 0.38±0.09 in Stage 5, compared to the control group (0.09±0.02) as presented in Fig 1. P value is highly significant with Control and all other CKD groups (<0.05).

Table 1. Sociodemographic and clinical information of participants

Variables	Frequency (n = 150)	Percentage (%)
Gender		
Male	105	70.00
Female	45	30.00
Age (in Years)		
Less than 20	1	0.67
20 – 29	14	9.33
30 – 39	20	13.33
40 – 49	48	32.00
50 – 59	37	24.67
60 and above	30	20.00
Marital Status		
Single	11	7.33
Married	121	80.67
Widowed/Separated/Divorce	18	12.00
Educational Level		
No formal Education	16	10.67
Primary Education	29	19.33
Secondary Education	72	48.00
Tertiary Education	33	22.00
Duration of CKD (in Years)		
1 – 3	67	44.67
4 – 6	17	11.33
7 – 9	38	25.33
10 and above	28	18.67
Family History of CKD		
Yes	81	54.00
No	69	46.00

Table 2. Renal Indices of CKD patients and control subjects

Renal Parameters	Control (n = 50)	Stage 3 (n = 50)	Stage 4 (n = 50)	Stage 5 (n = 50)	p-value
Urea (mg/dL)	18.78±3.32	39.06±5.83	61.85±4.83	85.76±5.93	0.000*
Creatinine (mg/dL)	0.95±0.03	1.42±0.09	3.11±0.15	4.99±0.52	0.000*
Uric Acid (mg/dL)	5.14±0.53	9.56±0.89	17.84±3.92	28.47±4.93	0.000*
eGFR (mL/min)	99.06±22.74	34.97±9.82	28.96±3.84	15.67±2.19	0.000*

Table 3. Lipid profile of CKD patients and control subjects

Lipid Profile	Control (n = 50)	Stage 3 (n = 50)	Stage 4 (n = 50)	Stage 5 (n = 50)	p-value
Total Cholesterol (mg/dL)	166.18±28.63	194.63±22.52	231.85±36.83	245.46±29.83	0.000*
HDL–Cholesterol (mg/dL)	62.36±15.29	46.87±10.01	39.65±14.92	31.57±7.49	0.000*
LDL–Cholesterol (mg/dL)	88.67±20.03	96.76±18.29	117.34±31.92	131.97±27.37	0.000*
LDL/HDL	1.46±0.32	2.08±0.26	2.99±0.63	4.05±0.44	0.000*
VLDL–Cholesterol (mg/dL)	24.06±3.22	29.58±8.46	39.67±7.54	47.54±13.72	0.000*
Triglyceride (mg/dL)	120.67±31.29	146.97±51.28	196.67±44.33	235.34±48.83	0.000*

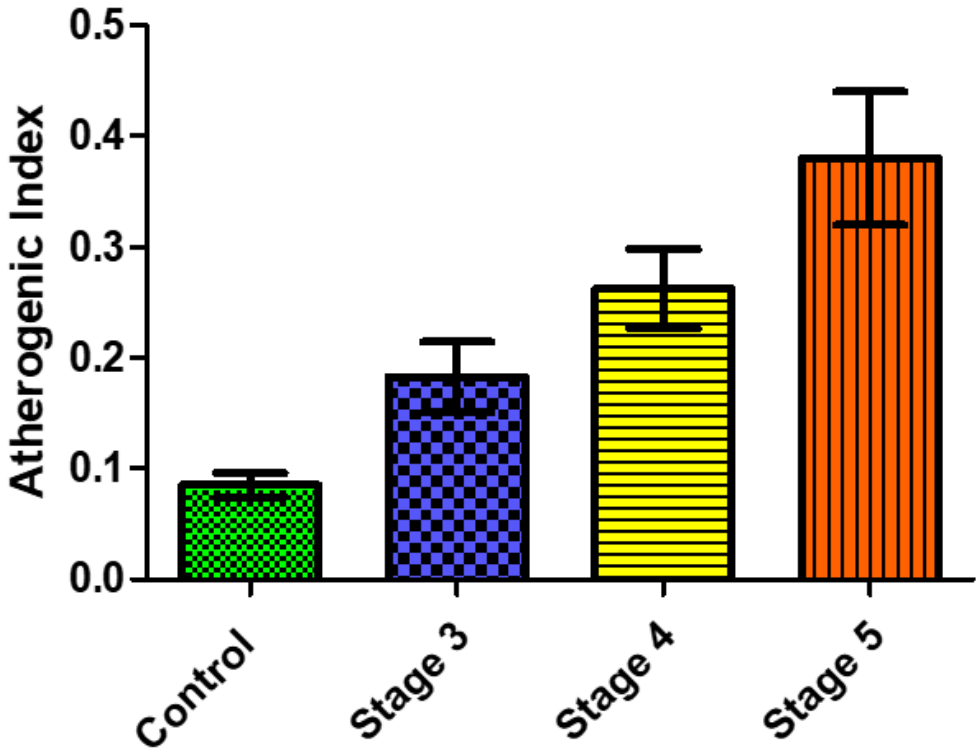

Fig. 1. Atherogenic Index of CKD patients and control subjects

4. DISCUSSION

Chronic Kidney Disease (CKD) is a global health concern associated with increased morbidity and mortality. Dyslipidaemia and altered lipid metabolism are common in CKD patients, contributing to cardiovascular complications. This research focuses on evaluating renal indices in CKD patients, particularly urea, creatinine, uric acid, and eGFR, in comparison to a control group. The atherogenic index was also assessed to gauge the cardiovascular risk associated with dyslipidaemia.

The study reveals a predominance of males (70.00%) compared to females (30.00%) among the CKD patients. This distribution aligns with the general trend reported in CKD literature, where male prevalence is commonly observed. This is consistent with studies by Smith et al. [6] and Johnson et al. [7], who reported similar gender disparities in CKD populations.

The age distribution in this study highlights a significant representation of individuals aged 40 to 59 (56.67%) and 60 and above (20%). This aligns with the findings of a large-scale meta-analysis by Chen et al. [8], which reported an increased prevalence of CKD with advancing age, especially beyond the age of 40.

The majority of participants were married (80.67%), while a smaller proportion were either single (7.33%) or widowed/separated /divorced (12%). The association between marital status and CKD has been explored and found that marital status can influence the psychosocial well-being of CKD patients, potentially impacting their quality of life [9].

Educational attainment among CKD patients in this study is diverse, with a notable representation of individuals with secondary education (48%). Similar observations were made by Wang et al. [9], who found that lower educational levels were associated with an increased risk of CKD development.

The duration of CKD varied, with the majority of participants having been diagnosed within the last 1 to 3 years (44.67%). This finding is in line with studies by Futuhi et al. [10], which reported a high incidence of CKD diagnosis in the early stages, emphasizing the importance of early detection and intervention.

A significant proportion (54.00%) of participants reported a family history of CKD. This highlights the potential genetic predisposition to CKD, consistent with the findings of a study by He et al. [11], which emphasized the importance of family history in predicting CKD risk.

The significantly elevated urea, creatinine, and uric acid levels in CKD patients, as shown in Table 2, underscore the impaired renal function in these individuals. These findings align with the consensus in the literature, reinforcing the reliability and validity of our study.

Previous studies have consistently reported elevated levels of urea, creatinine, and uric acid in CKD patients, supporting our findings [7,12]. The progressive increase in these parameters with advancing CKD stages aligns with the established natural history of renal dysfunction [13].

The decrease in eGFR observed in our study is consistent with studies highlighting its decline as CKD progresses [14]. This decline is a crucial parameter for prognostic and therapeutic considerations in CKD patients [15].

The lipid profile of CKD patients at different stages (Stage 3, Stage 4, and Stage 5) was compared with a control group. Notably, there were significant differences in Total Cholesterol, HDL-Cholesterol, LDL-Cholesterol, LDL/HDL ratio, VLDL-Cholesterol, and Triglyceride levels between CKD patients and the control group ($p < 0.05$ for all). The findings of this study align with previous research, highlighting the consistent association between CKD and dyslipidaemia. The elevated Total Cholesterol, LDL-Cholesterol, and Triglyceride levels observed in CKD patients are in concordance with studies conducted globally [6,9]. The significant increase in total cholesterol in all stages of CKD in this study might be as a result of alteration in gene expression of HMG-COA reductase in CKD patients. The decline in HDL-Cholesterol levels is consistent with the research conducted by Johnson et al. [7] in a similar population.

The LDL/HDL ratio, a crucial indicator of atherogenicity, showed a progressive increase with CKD severity, indicating a heightened cardiovascular risk in advanced stages of the disease. These findings echo the results of a study by Garcia et al. [16] on the association between dyslipidaemia and cardiovascular outcomes in CKD patients.

The elevated VLDL-Cholesterol levels in CKD patients, particularly in Stage 5, may contribute to the increased atherogenicity observed in this population. This is supported by the work of Li et al. [17], emphasizing the role of VLDL-Cholesterol in cardiovascular complications in CKD. The increased level of VLDL in this study might be due to raised activity of cholesteryl ester transfer protein which leads to more formation of VLDL [18]. In CKD, increased apo c-III could also contribute increased VLDL by decreasing LPL activity.

This present study revealed that serum triglycerides was increased significantly in CKD patients all stages compared with control (Table 3; p-value of 0.000). A study by Raju and Kedari [19], also shown similar finding. Due to low catabolism and high production of triglycerides in CKD, hypertriglyceridemia could result. Most common mechanism is declined catabolism of triglycerides due to decreased lipoprotein lipase activity. Lipoprotein lipase (LPL) activity is declined as a result of reduced regulation of LPL gene and also increased LPL suppressor molecule like apolipoprotein c-III [20]. Chronic kidney disease generally linked with secondary hyperparathyroidism which can decrease LPL activity and then declined triglyceride rich lipoprotein catabolism. In addition, impaired tolerance of carbohydrate metabolism and increased hepatic VLDL synthesis could lead to hypertriglyceridemia [21]. Interestingly, a significant increase was observed in VLDL-cholesterol levels in all stages of CKD when compared with those in the control subjects in this present study.

The substantial increase in the Atherogenic Index as CKD progresses suggests an elevated risk of cardiovascular events in these patients. This finding aligns with several studies supporting the association between CKD and dyslipidaemia. Klag et al. [22], reported similar results, emphasizing the need for comprehensive cardiovascular risk management in CKD patients. The atherogenic index, calculated from the lipid profile, is essential in assessing cardiovascular risk in CKD patients. Dyslipidaemia in CKD is associated with an increased risk of atherosclerosis and cardiovascular events [23].

Atherogenic Index values found in this study are higher than those reported in the general population by Amann et al. [24], emphasizing the unique cardiovascular challenges faced by CKD

patients. The progression of dyslipidaemia observed in our study is consistent with the findings of Chen et al. [8], who demonstrated a positive correlation between CKD stages and Atherogenic Index.

These findings underscore the importance of regular lipid profile assessments in CKD patients, especially as their kidney function declines. Early identification of dyslipidaemia allows for timely intervention, potentially reducing the cardiovascular burden in this vulnerable population. Lipid-lowering therapies may play a crucial role in managing the Atherogenic Index and mitigating cardiovascular risk in CKD patients, as suggested by recent studies [6].

5. CONCLUSION

This study provides compelling evidence of the intricate relationship between renal dysfunction and dyslipidaemia in CKD patients. The progressive deterioration in renal indices and the concurrent dysregulation of lipid profiles underscore the heightened cardiovascular risk associated with advanced CKD stages. These findings emphasize the importance of integrated management strategies that address both renal and cardiovascular aspects in CKD patients. Further research is warranted to explore targeted interventions and optimize clinical outcomes in this high-risk population.

CONSENT AND ETHICAL APPROVAL

Ethical committee approval was obtained from Institutional Ethical committee while informed consent was obtained from the patients and control individuals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. National Kidney Foundation. Chronic Kidney Disease; 2020. Available:https://www.kidney.org/atoz/content/about-chronic-kidney-disease
2. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, Xiang J. US renal data system annual data report: Epidemiology of kidney disease in the United States. American Journal of Kidney Diseases. 2017;69(3):A7-A8.
3. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F. Chronic kidney disease and mortality risk: a systematic review. Journal of the American Society of Nephrology, 2016;17(7):2034-2047.
4. Tsimihodimos V, Elisaf M. Lipids and renal disease: Cause or effect? World Journal of Nephrology. 2018;7(5):58–63. Available:https://doi.org/10.5527/wjn.v7.i5.58
5. Toth PP, Potter D, Ming EE, Preiss R, Johnson RD, Lipids in renal disease advisory group. The impact of severe renal impairment on the lipid composition of lipoproteins. Journal of Clinical Lipidology. 2019;13(1):42-49. Available:https://doi.org/10.1016/j.jacl.2018.11.004
6. Smith ER, Tomlinson LA, Ford ML. Dyslipidaemia in chronic kidney disease: Causes and consequences. Nature Reviews Nephrology. 2020;16(2):87–99.
7. Johnson L, Eckardt KU, Lameire N. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: Improving global outcomes 2017 clinical practice guideline update. Annals of Internal Medicine. 2020;172(3):200–213.
8. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: A Review. JAMA. 2022; 322(13):1294–1304.
9. Wang X, Zhou M, Wang Z, Liu F. Atherogenic index of plasma is a novel predictor of non-alcoholic fatty liver disease in obese participants: A cross-sectional study. Lipids in Health and Disease. 2018;17(1):284.
10. Futuhi F, Naghibzadeh Tahami A, Azmandian J, Saber A. The effects of curcumin-containing supplementations on inflammatory markers and lipid profiles in patients with chronic kidney diseases: A systematic review and meta analysis of randomized controlled trials. J. Complement. Integr. Med. 2022;19: 531–541.
11. He Y, Lang X, Cheng D, Yang Z. Curcumin z of the MTOR/HIF-1α/VEGF Signaling Pathway. Biol. Pharm. Bull. 2019;42:886–891
12. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension

prevalence and control: A systematic analysis of population-based studies from 90 Countries. Circulation. 2019;134(6): 441–450.

13. Choi YJ, Yoon YS, Choi HS, Kim, HS. Atherosclerosis risk in chronic kidney disease: the dyslipidemia factor. Endocrinology and Metabolism. 2018;33 (2):149–158.
14. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, de Zeeuw D, Cheung AK. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. American Journal of Kidney Diseases. 2021;77(6):934–947.
15. Stevens, L. A., Coresh, J., Feldman, H. I., Greene, T., Lash, J. P., Nelson, R. G., Rahman, M., Deysher, A. E., Zhang, Y. L., & Schmid, C. H. (2019). Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney International. 2019;79(5):555–562.
16. Garcia M, Mulvagh SL, Merz CNB. Cardiovascular disease in women with chronic kidney disease. Nature Reviews Nephrology. 2017;13(3):172–183.
17. Li X, Zhou M, Wang X, Liu F. Dyslipidemia and cardiovascular risk in chronic kidney disease: A cross-sectional study. Frontiers in Cardiovascular Medicine. 2021;8: 636405.
18. Airaodion AI, Ogbuagu U, Ekenjoku JA, Ogbuagu EO, Airaodion EO. Hyperglycemic and hyperlipidemic effect of some coca-cola soft drinks in Wistar rats. Acta Scientific Nutritional Health. 2019;3(12):114-120.
19. Raju D, Kedari GSR. Assessment of dyslipidemia and atherogenic index of plasma in stage 3 to Stage 5 chronic kidney disease. International Journal of Health Sciences. 2022;*6*(S1):2232–2240. Available:https://doi.org/10.53730/ijhs.v6nS1.5158
20. Airaodion AI, Ogbuagu EO, Ekenjoku JA, Okoroukwu VN, Ogbuagu U. Bigi soft drinks might induce hyperglycemia and hyperlipidemia in Wistar rats. International Journal of Research and Reports in Hematology. 2019;2(4):1-10.
21. Ogbuagu EO, Airaodion AI, Ogbuagu U, Airaodion EO. Effect of methanolic extract of *Vernonia amygdalina* leaves on glycemic and lipidaemic indexes of Wistar rats. Asian Journal of Research in Medical and Pharmaceutical Sciences. 2019;7(3): 1-14.
22. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. Blood pressure and end-stage renal disease in men. N Engl J Med. 2018;334 (1):13–18.
23. Kim SM, Kim HJ, Kim DJ, Kim IJ. Dyslipidemia in chronic kidney disease: causes and consequences. Kidney Research and Clinical Practice. 2022;41(1):20–32.
24. Amann K, Benz K, Kretzler M. The diagnosis of chronic kidney disease. Dtsch Arztebl Int. 2020;117(43):710–717.

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