GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

Check for updates

Dyslipidemia facilitates the progression of kidney function impairment in frequent administration of artemether-lumefantrine: An *in vivo* study

Idongesit Patrick Ita [1,*], Abasiama Ita Ukoh [2] and Herbert Mbagwu [3]

[1] *Department of Biochemistry, Faculty of Science, University of Uyo, Uyo, Nigeria.*
[2] *Department of Epidemiology, Monitoring and Evaluation, Achieving Health Nigeria Initiative (AHNi), Nigeria.*
[3] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Uyo, Nigeria.*

GSC Biological and Pharmaceutical Sciences, 2024, 28(02), 138–145

Publication history: Received on 29 June 2024; revised on 10 August 2024; accepted on 13 August 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.28.2.0298

Abstract

The study investigated the effect of frequent administration of artemether-lumefantrine on biochemical parameters of kidney functions and the role of dyslipidemia in the progression of kidney disease. Male *Wistar* rats, weighing between 230 and 330 grams, were divided into five subgroups (n=7) of Group (I), control and received no medication, (2) 8 mg/kg bodyweight (bw) of artemether-lumefantrine for three days, (3) 12 mg/kg bw for three days, (4) 8 mg/kg bw three days a week for three weeks with a two-week recovery interval, (5)12 mg/kg bw three days a week for three weeks with a two-week recovery interval. Biochemical parameters investigated include serum lipid profile and kidney function biomarkers. A significant ($p<0.05$) decrease in high density lipoprotein cholesterol concentration across treatment groups compared to the control was observed. Triglyceride levels significantly ($p<0.05$) increased in Group 5, while total cholesterol levels significantly ($p<0.05$) decreased in Group V. No significant ($p>0.05$) changes were observed in low density lipoprotein-cholesterol and VLDL-cholesterol levels. Kidney function tests revealed a significant ($p<0.05$) increase in urea and creatinine concentrations in the treatment groups compared to the control. Serum electrolytes showed increases and decreases that were not significant. These findings highlight the nephrotoxic effect of repeated exposure to artemether-lumefantrine, suggesting caution in its indiscriminate use.

Keywords: Artemether-lumefantrine; Kidney Functions; Lipid Profile; Malaria

1. Introduction

In many regions of the world, particularly in sub-Saharan Africa, malaria is still a major public health burden amidst public health initiatives to reduce its impacts. [1] The World Health Organization (WHO) advised artemether-lumefantrine for the treatment of uncomplicated malaria caused by the *Plasmodium* parasite due to the parasite's resistance to the numerous antimalarial and insecticides. [2] With a well-established efficacy, tolerance profile, and rapid parasite clearance in the blood, artemether-lumefantrine is considered amongst the best and safe antimalarial available today but they can become toxic under certain conditions. [3] In sub-Saharan Africa, artemether-lumefantrine is extensively administered regularly without parasitological confirmation as advised by the World Health Organization. [4] According to research, several people self-diagnose and purchase artemether-lumefantrine over-the-counter, which raises the possibility of abuse and overdose. [5-8] This widespread practice of self-medication gives rise to major concerns over the drug's long-term effects on health, particularly regarding vital cellular functions necessitating the need for close monitoring of its use.

Chronic kidney disease (CKD) is fast becoming a major public health concern due to its rising incidence and prevalence across the globe. [9,10] Global Burden of Disease (GBD), Injuries, and Risk Factors study reveals a significant financial burden associated with the rising rates of CKD-related morbidity and death observed globally. [10] According to Collins

* Corresponding author: Idongesit Patrick Ita

et al. [11], the cost of treating and caring for individuals with CKD is now higher than that of other common diseases. Although, the etiopathogenesis of nephropathy remains unclear, a number of risk factors have been identified. A report by Su *et al*., [12] cites that nephrotoxicity and kidney disease may result from a disturbance in the lipid balance. Numerous compounds that are present in lipids support signal transduction and membrane structure, thereby regulating an array of biological processes to maintain physiological homeostasis. [13] Research have demonstrated that dyslipidemia is prevalent in every stage of chronic kidney disease and that lipid disorders may accelerate the illness's progression by impairing the glomerular filtration barrier, which causes waste products to accumulate in the blood. [14]

While antimalarial drugs, such as artemether-lumefantrine, are essential for treating malaria, it has been demonstrated that these drugs can significantly alter vital biochemical parameters. [15-17] Therefore, frequent administration of artemether-lumefantrine may further complicate this scenario by posing a potential risk to kidney health. Hence, understanding the effect frequent administration of artemether-lumefantrine has on kidney health is crucial, especially in contexts where its misuse is widespread. This study was designed to investigate the significance of abnormalities in serum lipid profile in the development and exacerbation of renal function impairments in males.

2. Materials and Methods

2.1. Drugs, Chemicals and Instruments

Artemether-lumefantrine (brand name: Lokmal®) 80/480 mg per tablet from Emzor Pharmaceutical Industries Limited, Nigeria. The serum biochemical parameters were assayed using commercially available kits from Agappe diagnostic India adhering strictly to the manufacturers manual. All chemicals and reagents used were of analytical grade. Well-ventilated animal cages, Wood fillings, Feeders and drinkers, Needles and syringes, Microplate Reader [MayaMed BY010], Disposable micropipette tips, clean glass tubes and test tube racks, Micropipettes, Beakers (10 – 1000ml), Oral cannula, Rubber gloves, Weighing scale, Serum bottles, Centrifuge and Pasteur pipette.

2.2. Experimental animals

Thirty-Five (35) adult male Wistar rats used for this study was obtained from the animal house of the Department of Pharmacology and Toxicology, University of Uyo, Uyo, Akwa Ibom State, Nigeria. The animals were acclimatized for three weeks in a well ventilated rat cages prior to the commencement of drugs administration at a standard temperature of (25 ± 2) °C and humidity (70 ± 5) %, and a 12 h light and dark cycle. They were fed standard rat pellets and water ad libitum throughout the experimental period. All animals were treated humanely in accordance with the principles outlined in the declaration of Helsinki in research involving animal subject and handling. Ethical approval for the study was obtained from the Research Ethical Committee of the Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria.

2.3. Experimental Design

The Animals were randomly divided into five groups of seven (n = 7) each and administered graded doses of artemether-lumefantrine through oral gavage. The dose of artemether-lumefantrine (Lokmal®) used for this study was calculated from the manufacturer's recommended dose for a man weighing at least 70kg and calculated in mg/kg body weights of the experimental animals. The experimental design is as follow:

- Group 1: Control
- Group 2: Therapeutic dose of 8 mg/kg bodyweight of artemether-lumefantrine (AL) for 3 days divided into equal parts twice daily. This is to mimic the normal therapeutic dose of AL and duration of the drug in human.
- Group 3: Overdose of 12 mg/kg bodyweight of AL for 3 days divided into equal parts twice daily.
- Group 4: Therapeutic dose of 8 mg/kg bodyweight of AL for 3 weeks divided into equal parts and administered twice daily for 3days each week with a 2 weeks' interval in-between dosage.
- Group 5: Overdose of 12 mg/kg bodyweight of AL for 3 weeks divided into equal parts and administered twice daily for 3 days each week with a 2 weeks' interval in-between dosage.

2.4. Drug Preparation and Administration

The artemether-lumefantrine was ground to a powdered form, mixed with distilled water and administered as an aqueous suspension. The drug suspension was continuously agitated during the administration in order to deliver the

drug homogenously to the animals. The treatment was administered to all the rats twice daily using a 1.0 mL syringe by oral gavage

2.5. Collection and preparation of samples for analysis

At the end of the treatment, all rats were anaesthetized by chloroform inhalation in a closed chamber and thereafter, sacrificed. Blood was collected by cardiac puncture into a plain serum bottle and later centrifuged at 3500 rev/min at room temperature for 15 min to obtain serum by aspiration. The serum was kept frozen until it was used for biochemical analysis. The kidney was carefully harvested and immediately cleared of adhering tissues and weighed.

2.6. Serum Biochemical Assay

Serum lipid profile were assayed using Agappe diagnostic kits and their respective principles. High density lipoprotein cholesterol (HDL-c) was estimated using the method described by Rifai and Warnick (1994) [18]. Low-density lipoprotein cholesterol (LDL-c) was assayed based on the principles of Crouse *et al*. [19] Very low-density lipoprotein cholesterol (VLDL-c) was estimated from the relationships established by Friedewald *et al*. [20] using triglyceride concentration. Total cholesterol (TC) was assayed based on the principle laid down by Allain *et al*. [21] Triglycerides was determined based on Bucoloy and David, (1973) [22] principle. Electrolyte levels (Sodium, Potassium and Chloride) were estimated based on the principles of Tietz, (1995) [23]. Blood Urea level was determined based on the Urease-Berthelot method using the Weatherburn, (1967) [24] principle. Serum creatinine was estimated based on the method described by Haeckel, (1981). [24]

2.7. Statistical Analysis

Data obtained from the study were expressed as mean ± standard error of mean (SEM.) Statistical analysis was done using version 17 of SPSS with the aid of one-way analysis of variance (ANOVA) and Tukey post-hoc test. Differences between experimental groups are considered statistically significant at $p < 0.05$

3. Result and Discussion

The kidneys, being the primary organs responsible for eliminating waste products and foreign materials from the urine, also control blood's ionic composition, pH, osmolarity, blood volume, blood pressure, and blood sugar levels. They also support the regulation of processes like the synthesis of red blood cells (RBCs), the secretion of calcitriol, the active form of vitamin D, and erythropoietin (EPO), which stimulates the production of RBCs. [26-27] When kidney function declines, these processes become impaired.

3.1. Effect of frequent artemether-lumefantrine administration on serum lipids

The serum lipid profile of male Wistar rats administered artemether-lumefantrine at therapeutic and overdose levels for three days and three weeks, respectively, is displayed in Table 1. Analysis of the data revealed a significant ($p<0.05$) decrease in high density lipoprotein cholesterol in treatment groups compared to the control. This is consistent with the study of Nkereuwem *et al*. [28], which found that administering artemether significantly reduced HDL-c levels. Studies have shown a strong correlation between reduced HDL-c levels and the progression of chronic kidney disease (CKD). [29–31] Moreover, lowered HDL-c levels have been linked to increased oxidative stress and inflammation, two factors that may hasten the development of chronic renal disease. [30, 31] The significant reduction in HDL-c in this study raises the possibility of renal impairment since it may weaken the glomerular filtration barrier and cause renal function loss. Disruptions in lipoprotein metabolism are linked to renal dysfunction leading to dyslipidemia and buildup of atherogenic particles. [32] A study by Agrawal *et al*., [33] demonstrated how lipid metabolism is linked to the pathophysiology of kidney disease, highlighting dyslipidemia—a condition marked by abnormalities in the serum lipid profile—as a key factor affecting the onset and progression of kidney disease.

Triglycerides, total cholesterol, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol recorded some increase and decrease which were not significant ($p>0.05$) when compared to the control except for the significant increase in triglycerides in group V and a significant decrease in total cholesterol of group V rats. The significant rise in triglycerides suggests the possibility of hypertriglyceridemia, a known risk factor for the development of CKD. Increased triglyceride levels are associated with glomerular hypertrophy and glomerulosclerosis-related renal impairment. [34, 35] Triglyceride buildup in the kidney tissues can also result in lipotoxicity, which exacerbates nephropathy and may further damage renal cells. [35, 36] When paired with decreased HDL-c, the observed decrease in total cholesterol in Group V may indicate a lipid metabolic imbalance that could be harmful to kidney function. Although reducing total cholesterol could seem beneficial, lowering HDL-c—a protective lipid—at the same time might

be harmful. Changes in LDL-c and VLDL-c were not significant, but trends toward increased levels could still be clinically relevant. Increased levels of LDL and VLDL can lead to lipid accumulation in the kidneys, triggering inflammation and fibrosis, which can impair renal function. [37] Elevated levels of VLDL-c and LDL-c are well-known risk factors for cardiovascular disease and atherosclerosis, which are intimately related to chronic kidney disease. [37]

Table 1 Effect of frequent artemether-lumefantrine administration on serum lipids

Grouping/Dosage	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
Group I (Normal Control)	138.0 ± 3.31	40.01 ± 2.22	30.67 ± 1.75	96.84 ± 2.974	8.001 ± 0.844
Group II (8mg/kg/bw AL)	138.7 ± 3.90	40.39 ± 1.97	28.02 ± 2.48*	98.69 ± 5.243	8.078 ± 0.795
Group III (12mg/kg/bw AL for 3 days)	136.8 ± 4.67	41.73 ± 1.80	26.21 ± 4.05*a	98.72 ± 1.348	8.346 ± 0.423
Group IV (8mg/kg/bw AL every 3 days for 3 weeks	136.9 ± 2.20	41.97 ± 1.95	28.18 ± 3.16*a	98.45 ± 2.097	8.395 ± 0.011
Group V (12mg/kg/bw AL every 3 days for 3 weeks)	125. 6 ± 2.23*a	42.42 ± 1.81*a	24.97 ± 1.521*a	99.28 ± 4.041	8.485 ± 0.362

Values are expressed as Mean ± Standard Error of Mean (SEM); n= 7. TC= Total cholesterol; TG= Triglyceride; HDL-c= High density lipoprotein cholesterol; LDL-c= Low density lipoprotein cholesterol; VLDL-c= Very low-density lipoprotein cholesterol. * = $p<0.05$ relative to control Group 1, a = $p<0.05$ relative to Group II ($p < 0.05$).

3.2. Effect of frequent artemether-lumefantrine administration on blood urea and serum creatinine levels

Serum creatinine and blood urea levels show a substantial ($p<0.05$) rise in the treatment groups relative to the control group (Table 2). Additionally, the observed significant ($p<0.05$) increase in blood urea and serum creatinine levels is dose-dependent when compared to the control group. An impairment of the renal filtration capacity is suggested by the higher blood urea and creatinine levels in the treatment groups. This aligns with other research that reports that antimalarial drugs, including those containing artemisinin derivatives, may cause nephrotoxic consequences. [12–14].

Table 2 Effect of frequent artemether-lumefantrine administration on blood urea and serum creatinine levels

Grouping/Dosage	Urea (mg/dL)	Creatinine (mg/dL)
Group I (Normal Control)	3.240±0.227	0.30 ± 0.04
Group II (8mg/kg/bw AL)	2.740±0.119	0.55 ± 0.06
Group III (12mg/kg/bw AL for 3 days)	11.38±3.537*a	0.64 ± 0.027ab
Group IV (8mg/kg/bw AL every 3 days for 3 weeks	15.63±0.924*ab	0.57 ± 0.03ab
Group V (12mg/kg/bw AL every 3 days for 3 weeks)	16.25±0.188*ab	0.75 ± 0.04abc

Values are expressed as Mean ± Standard Error of Mean (SEM); n= 7; *= $p<0.05$ relative to the control; a= $p<0.05$ relative to the group 2; b= $p<0.05$ relative to the group 3. AL = Artemether- Lumefantrine

When glomerular filtration rate (GFR) is lowered, renal blood flow is decreased, or renal disease or obstruction of the urinary tract occurs, blood urea nitrogen levels are raised. [27] The breakdown of amino acids produces urea, which is typically eliminated in the urine. Varying amounts of urea are either released or reabsorbed in the collecting ducts and tubules following its filtration in the glomerulus. When there is a large drop in the glomerular filtration rate, as occurs in cases of renal disease, the urine is unable to properly remove urea, which instead builds up in the blood. [26–27]

The most reliable indicator of kidney function is considered to be the estimates of GFR (eGFR) [38,39] Prediction equations are used to estimate the GFR, and they consider several factors such as age, gender, race, and body size in addition to the serum creatinine concentration. [38,39] An assessment of the kidneys' ability to eliminate waste products such as creatinine from the blood is called creatinine clearance; a low creatinine clearance suggests compromised kidney function. [39] A lipid imbalance can affect the glomerular filtration barrier, which causes waste

products like urea and creatinine to remain in the bloodstream. The concentration of these waste products in plasma is mostly dependent on glomerular function.

3.3. Effect of frequent artemether-lumefantrine administration on electrolyte levels

Electrolyte levels presented in Table 3 showed no significant ($p>0.05$) difference in treatment groups when compared to the control except for the significant ($p<0.05$) decrease in chloride in Group 1V and Group V rats treated for 3 weeks which were not statistically significant when compared to the control group. Although the electrolyte disturbances observed in this study did not reach statistical significance, they suggest a potential trend that merits further investigation. Research reports have reported significant electrolyte imbalances due to antimalarial drug use [12-14], providing context for the minor disturbances observed here. Electrolyte imbalances, particularly involving sodium and potassium, can have serious consequences for renal function and overall homeostasis. [12-14]

Table 3 Serum Electrolytes of Male Wistar rats on repeated administration of AL

Grouping/Dosage	Na^+ (mmol/L)	K^+ (mmol/L)	CL^- (mEq/L)
Group I (Normal control)	129.3 ± 0.803	1.442 ± 0.036	170.6±5.940
Group II (8 mg/kg/bw AL)	129.1 ± 3.920	1.434 ± 0.111	166.9±3.195
Group III (12mg/kg/bw AL for 3 days)	129.5 ± 3.070	1.448 ± 0.081	171.2±6.545
Group IV (8 mg/kg/bw AL every 3 days for 3weeks)	129.5 ± 2.464	1.436 ± 0.058	151.6±1.235*
Group V (12 mg/kg/bw AL every 3 days for 3weeks)	129.9 ± 2.670	1.414 ± 0.029	149.6±4.035*

Values are expressed as Mean ± Standard Error of Mean (SEM); n= 7; *= $p<0.05$ relative to the control; a= $p<0.05$ relative to the group 2; b= $P<0.05$ relative to the group 3. AL = Artemether- Lumefantrine; Na = Sodium; K = Potassium; Cl = Chloride

The findings of this study suggests an interplay between lipoproteins alterations and acute kidney injury. Acute kidney injury (AKI), an abrupt clinical episode of reduction in kidney function leading to the accumulation of nitrogenous waste in the blood, elevated serum creatinine levels, electrolyte imbalances and volume overload [40] can cause loss of kidney function which may be reversible, requiring temporary dialysis, or may progress to end-stage renal disease (ESRD), necessitating permanent renal replacement therapy. [41] It is therefore crucial that clinicians monitor renal function and serum lipid profiles in patients receiving frequent artemether-lumefantrine therapy as early detection could facilitate timely interventions to mitigate the risk of chronic kidney disease and its associated cardiovascular complications. Although there are strong correlations between imbalance in serum lipid profile and the progression of chronic kidney disease, the underlying biochemical pathway and molecular mechanisms involved has not been confirmed by this study. Further research is encouraged to establish the mechanisms involved in artemether-lumefantrine-induced renal functions impairments and to identify potential protective strategies in new antimalarial.

4. Conclusion

The findings of this study suggests that repeated exposure to artemether-lumefantrine may result in deranged biochemical parameters of kidney function and serum lipid profile highlighting the potential nephrotoxic effects of frequent artemether-lumefantrine administration emphasizing the need for comprehensive monitoring, timely interventions and a cautious approach in the long-term use of artemether-lumefantrine.

Compliance with ethical standards

Acknowledgments

The technical contributions by Mr. Nsikan Malachy of the Department of Pharmacology and Toxicology, University of Uyo, Uyo and the Endocrine Research Unit, University of Calabar, Calabar, Nigeria are acknowledged. All authors reviewed and approved the manuscript

Disclosure of conflict of interest

There is no conflict of interest among the authors.

Statement of ethical approval

The experimental design was approved by the Ethical committee of the Faculty of Basic Medical Science, University of Uyo, in accordance with the principles outlined in the declaration of Helsinki in research involving animal subject and handling.

References

[1] World Health Organization, World Malaria Report 2021. Available from https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

[2] World Health Organization. Guidelines for the treatment of malaria: Roll Back Malaria,3rd Edition, 2015. Available from https://www.afro.who.int/publications/guidelines-treatment-malaria-third-edition

[3] Nosten F, White NJ. Artemisinin-based combination treatment of falciparum malaria. Am J Trop Med Hyg. 2007;77(6 Suppl):181-92. PMID: 18165491.

[4] Nwokolo E, Ujuju C, Anyanti J, Isiguzo C, Udoye I, BongosIkwue E, et al. Misuse of Artemisinin Combination Therapies by Clients of Medicine Retailers Suspected to Have Malaria Without Prior Parasitological Confirmation in Nigeria. Int J Health Policy Manag. 2018;7(6):542-548. doi: 10.15171/ijhpm.2017.122.

[5] Akanbi OM, Odaibo AB, Afolabi KA, Ademowo OG. Effect of self-medication with antimalarial drugs on malaria infection in pregnant women in South-Western Nigeria. Med Princ Pract. 2005;14(1):6-9. doi: 10.1159/000081915.

[6] Ebohon O, Irabor F, Ebohon LO, Omoregie ES. Therapeutic failure after regimen with artemether-lumefantrine combination therapy: a report of three cases in Benin City, Nigeria. Rev Soc Bras Med Trop. 2019;52: e20190163. doi: 10.1590/0037-8682-0163-2019.

[7] Okeke TA, Uzochukwu BS. Improving childhood malaria treatment and referral practices by training patent medicine vendors in rural south-east Nigeria. Malar J. 2009; 8:260. doi: 10.1186/1475-2875-8-260.

[8] Oladosu OO, Oyibo WA. Overdiagnosis and Overtreatment of Malaria in Children That Presented with Fever in Lagos, Nigeria. ISRN Infect Dis. 2013; 2013: 1–6. DOI:10.5402/2013/914675

[9] Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. doi: 10.1016/j.kisu.2021.11.003.

[10] GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020 ;395(10225):709-733. doi: 10.1016/S0140-6736(20)30045-3.

[11] Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease and end-stage renal disease in the United States. Am J Kidney Dis. 2012;59(1 Suppl 1): A7, e1-420. doi: 10.1053/j.ajkd.2011.11.015.

[12] Su H, Wan C, Lei CT, Zhang CY, Ye C, Tang H, et al. Lipid Deposition in Kidney Diseases: Interplay Among Redox, Lipid Mediators, and Renal Impairment. Antioxid Redox Signal. 2018; 28(10):1027-1043. doi: 10.1089/ars.2017.7066.

[13] Sunshine H, Iruela-Arispe ML. Membrane lipids and cell signaling. Curr Opin Lipidol. 2017; 28(5):408-413. doi: 10.1097/MOL.0000000000000443.

[14] Pei K, Gui T, Li C, Zhang Q, Feng H, Li Y, et al. Recent Progress on Lipid Intake and Chronic Kidney Disease. Biomed Res Int. 2020; 2020:3680397. doi: 10.1155/2020/3680397.

[15] Abolaji AO, Eteng MU, Omonua O, Adenrele Y. Influence of coadministration of artemether and lumefantrine on selected plasma biochemical and erythrocyte oxidative stress indices in female Wistar rats. Hum Exp Tox. 2013; 32(2):206-215. doi:10.1177/0960327112464666

[16] Etim O, Idongesit N, Ewere E, Bassey U. Toxicological evaluation of five brands of Artemether-Lumefantrine drugs in male albino Wistar rats. IBSPR. 2018; 6:1-7. doi.org/10.15739/ibspr.18.001

[17] Edagha IA, Ekpo AJ, Edagha EI, Bassey JV, Nyong TP, Akpan AS, et al. Investigating the Comparative Effects of Six Artemisinin-based Combination Therapies on Plasmodium-induced Hepatorenal Toxicity. Niger Med J. 2019; 60(4):211-218. doi: 10.4103/nmj.NMJ_152_18.

[18] Rifai N., Warnick, G. R. (1994). Laboratory measurement of lipids, lipoproteins, and apolipoproteins/edited by Nader Rifai, G. Russell Warnick. AACC Press. ISBN 0915274744, 9780915274741, 357 pages

[19] Crouse JR, Parks JS, Schey HM, Kahl FR. Studies of low density lipoprotein molecular weight in human beings with coronary artery disease. J Lipid Res. 1985 May;26(5):566-74. PMID: 4020295.

[20] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.

[21] Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974 Apr;20(4):470-5. PMID: 4818200.

[22] Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem. 1973 May;19(5):476-82. PMID: 4703655.

[23] Tietz NW. Clinical Guide to Laboratory Tests (ELISA). 3rd Edition, W.B. Saunders, Co., Philadelphia: 1995.

[24] Weatherburn MW. Phenol-hypochlorite reaction for determination of ammonia. Anal Chem, 1967; 39 (8): 971-974.

[25] R Haeckel, Assay of creatinine in serum, with use of fuller's earth to remove interferents., Clinical Chemistry, Volume 27, Issue 1, 1 January 1981, Pages 179–183, https://doi.org/10.1093/clinchem/27.1.179

[26] Tortora GJ, Derrickson B. The urinary system. In: Principles of Anatomy and Physiology. 11th ed. Hoboken, NJ: John Wiley & Sons Inc; 2006:992-1035.

[27] Smith, J. Learning Guide: Kidney Structure and Physiology. Health Education Press, 2023. https://www.healtheducationpress.org/kidney-guide

[28] Nkereuwen E, Paul OO, Elias A. Effect of Artemether treatment on plasma lipid profile in malaria. Pharmacology and Pharmacy. 2014; 5: 646 – 656. DOI:10.4236/PP.2014.57074

[29] Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol. 2006;290(2): F262-72. doi: 10.1152/ajprenal.00099.2005.

[30] Nam KH, Chang TI, Joo YS, Kim J, Lee S, Lee C, et al. Association between serum high-density lipoprotein cholesterol levels and progression of chronic kidney disease: results from the KNOW-CKD. J Am Heart Assoc 2019; 8: e011162. Doi: 10.1161/JAHA.118.011162

[31] Saini M, Vamne A, Kumar V, Chandel MS. The Study of Pattern of Lipid Profile in Chronic Kidney Disease Patients on Conservative Management and Hemodialysis: A Comparative Study. Cureus. 2022;14(1): e21506. doi: 10.7759/cureus.21506.

[32] Vaziri ND: Role of dyslipidemia in impairment of energy metabolism, oxidative stress, inflammation and cardiovascular disease in chronic kidney disease. Clin Exp Nephrol 2014; 18: 265–268.

[33] Agrawal S, Zaritsky JJ, Fornoni A, Smoyer WE: Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. Nat Rev Nephrol 2018; 14: 57–70. doi: 10.1038/nrneph.2017.155.

[34] Choi WJ, Hong YA, Min JW, Koh ES, Kim HD, Ban TH, et al. Hypertriglyceridemia Is Associated with More Severe Histological Glomerulosclerosis in IgA Nephropathy. J Clin Med. 2021;10(18):4236. doi: 10.3390/jcm10184236.

[35] Suh SH, Oh TR, Choi HS, Kim CS, Bae EH, Oh KH, et al. Serum triglycerides level is independently associated with renal outcomes in patients with non-dialysis chronic kidney disease: results from KNOW-CKD study. Front Nutr. 2022; 9:1037618.

[36] Bobulescu IA. Renal lipid metabolism and lipotoxicity. Curr Opin Nephrol Hypertens. 2010;19(4):393-402. doi: 10.1097/MNH.0b013e32833aa4ac.

[37] Lee C, Park JT, Chang TI, Kang EW, Nam KH, Joo YS, et al. Low-density lipoprotein cholesterol levels and adverse clinical outcomes in chronic kidney disease: results from the KNOWCKD. Nutr Metab Cardiovasc Dis 2022; 32:410-9.

[38] National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(Suppl 1): S1-327.

[39] National Institute of Diabetes and Digestive and Kidney Diseases. Kidney failure glossary. U.S. Department of Health and Human Services. 2003; NIH Publication No. 03–4894:1-14.

[40] Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85-98.

[41] Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4): R204-R212.