How to Cite:
Raju , D., & Kedari, G. S. R. (2022). Assessment of dyslipidemia and atherogenic index of plasma in stage 3 to Stage 5 chronic kidney disease. *International Journal of Health Sciences*, *6*(S1), 2232–2240. https://doi.org/10.53730/ijhs.v6nS1.5158

Assessment of Dyslipidemia and Atherogenic Index of Plasma in Stage 3 to Stage 5 Chronic Kidney Disease

Raju DSSK
Research Scholar of Biochemistry, Saveetha Medical College, Thandalam, Chennai, Tamil Nadu, India

Kedari G S R
Professor of Biochemistry, Saveetha Medical College, Thandalam, Chennai, Tamil Nadu, India

***Abstract*---**In Chronic Kidney Disease leading factor for morbidity and mortality is Cardiovascular disease. In CKD there is a risk of cardiovascular complications more than 50%. Dyslipidemia is one of leading risk cause for cardiovascular complication in normal healthy individual and also in chronic kidney disease. The Study contains 180 in which 45 as control group and 135 will be CKD individuals with stage 3 to stage 5 each stage consist of 45 each. In all the subjects Serum sample was estimated for blood urea, creatinine, triglycerides, cholesterol, and HDL-C by using fully automatic chemistry analyzer. VLDL, LDL and AIP was calculated. GFR was estimated by MDRD formula. Data was expressed by Mean ±SD. The mean value of triglycerides and VLDL in serum are raised in CKD stages 3 to stage 5 compared with control and it is shown statistically significant ($p<0.001$). The HDL-C mean value is decreased in CKD stages 3 to stage 5 when compared with control and it is shown statistically significant ($p<0.0001$). The mean value of serum total cholesterol and LDL-C is not significantly significant in CKD stages 3 to stage 5 compared with control. The mean serum Atherogenic Index of Plasma was significant raised in CKD stages 3 to stage 5 compared with Control and it is shown statistically significant ($p<0.0001$). The Assessment of dyslipidemia and atherogenic index will helpful as early alarming to prevent the cardiovascular complication.

***Keywords*---**atherogenic index, chronic Kidney disease, dyslipidemia and MDRD.

***Corresponding author**: Kedari, G. S.R.; Email: kedari.gsr@gmail.com*
Manuscript submitted: 18 Nov 2021, Manuscript revised: 09 Feb 2022, Accepted for publication: 27 March 2022

Introduction

The characteristic nature of Chronic Kidney Disease (CKD) is decline of functional nephrons due to irreversible sclerosis. The mass of the renal tissue gradually declined over a time, based on the cause of the disease[1]. Based on Glomerular Filtration Rate (GFR) estimation chronic kidney disease are classified five stages. In initial stages of chronic kidney disease the symptoms are remain silent and finally lead to End Stage Kidney Disease.

In Chronic Kidney Disease leading factor for morbidity and mortality is cardiovascular disease. The risk of cardiovascular complications is increases as CKD progresses[2]. Dyslipidemia is a one of the leading risk cause for cardiovascular complication in normal healthy individual as well as in chronic kidney disease. The dyslipidemia study is important for delay or prevention of cardiovascular complications[3]. In chronic kidney disease study of lipid abnormalities is not only detect the cardiovascular risk it also helpful in treat the dyslipidemia before they develop End Stage Kidney Disease.

In Chronic Kidney disease there will be decreased HDL, normal or slightly increased LDL and elevated triglycerdies[4]. Reduced HDL causes declined reversed cholesterol transport system. Most of the studies are done to find a best indicator for atherogenic factor in blood which can calculate the cardiovascular risk and also helpful for monitoring the treatment response. It revealed that Atherogenic index of plasma (AIP) will be good predictor for assessing the peril factor of cardiovascular disease[5]. Atherogenic index of plasma revels the association between atherogenic and protective lipoprotein it is also related to dimension of pre atherogenic and anti atherogenic lipoprotein level. Based on the AIP value cardiovascular risk will be assessed AIP lower than 0.11 consider low risk, If AIP among 0.11 to 0.21 consider as intermediate risk and AIP greater than 0.21as consider high risk[6].

Renal dysfunction is associated with disturbance of metabolism in lipoprotein and it leads to dyslipidemia and atherogenic lipoprotein accumulation. The dyslipidemia spectrum in Chronic kidney disease will differs from normal population[7]. The lipoproteins alteration is also depends upon on CKD stage. In present study lipid profile parameters and AIP measured in CKD stages 3 to stage 5 and compared with control.

Material and Methods

The current study was Case-Control study. The study was done in Biochemistry department with the association of Nephrology Department, Saveetha Medical College & Hospital. The present Study contains 180 in which 45 will be normal healthy individuals as control and CKD patients are 135 which includes stage 3 to stage 5 each stage consist of 45 each.

The patients Included are diagnosed with chronic kidney disease individuals who are attending the Nephrology Department, Saveetha Medical College. CKD cases are taken, those who have reduced GFR less than 60 mL/min/1.73m$^{2.}$ with an increased serum creatinine and blood urea level. Controls: Age and sex matched

healthy individuals. Age group of 30-70 years for both cases and controls. Patients are excluded if Patients with Viral hepatitis and HIV positive, A patient with history of malignancy or suffering with other life threatening illness, Cerebrovascular disease such as stroke or transient ischemic episodes. Patient history of liver diseases, Patients with age less than 30 and greater than 70 are excluded. Ethical committee approval was obtained by Institutional Ethical committee from the patients and controls groups Informed consent was obtained. Demographic data was collected

From the control and patient Serum sample blood urea, creatinine, triglycerides, total cholesterol, and serum HDL-Cholesterol was estimated by fully automatic chemistry analyzer. VLDL, LDL was calculated. Atherogenic index of plasma calculation done by using log (Triglycerides/HDL-C) formula[8]. Based on serum creatinine using MDRD formula estimated GFR was measured[9]. Data was expressed by Mean ± SD. Comparison of means across the groups was done by ANOVA and the correlation done by Pearson correlation. Significance was defined by p value less than 0.05.

Results and Discussion

The present study consists of 180 subjects in which 45 are controls and 135 are chronic kidney disease patients. In all the individual blood urea, serum creatinine was estimated. Based on serum creatinine using MDRD formula GFR was estimated. Based estimated GFR chronic kidney disease individuals are further classified in to stage 3 of CKD, stage 4 of CKD and stage 5 of CKD, each stage consist of 45 patients each. The blood urea and serum creatinine are increasing gradually from stage 3 of CKD to stage 5 of CKD due to decreased GFR. In present study estimated GFR by MDRD shown decline in CKD stages then compared with control this decrease is statistically significant (Table-1; $p<0.0001$). In this study we estimated lipid profile and atherogenic index in control and chronic kidney disease from stage 3 to stage 5.

Table 1
Blood urea, Creatinine and eGFR between Control and different stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	ANOVA
Blood Urea (mg/dL) Mean ± SD	27.31±6.44	45.57±11.31	65.0±11.94	81.20±14.35	F=332.38 p<0.0001
Creatinine (mg/dL) Mean ± SD	0.83±0.07	1.83±0.25	3.01±0.44	5.38±0.66	F=991.96 p<0.0001
eGFR (mL/min) Mean ± SD	95.58±10.80	38.06±7.40	21.62±4.25	10.74±2.36	F=1316.29 p<0.0001

In this present study revealed that serum triglycerides was increased significantly in CKD all stages compared with control (Table-2; $p<0.0001$). Rappaport et al.,[10] and Bagdade etal.,[11] studies also shown similar finding. In Chronic kidney disease due to low catabolism and high production of triglycerides leads hypertriglyceridemia.[12,13] Most common mechanism is declined catabolism of

triglycerides due to decreased lipoprotein lipase activity[14]. 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.[15] Chronic kidney disease generally linked with secondary hyperparathyroidism which can leads decreased LPL activity and then declined triglyceride rich lipoprotein catabolism.[16, 17] In addition impaired tolerance of carbohydrate metabolism and increased hepatic VLDL synthesis leads to hypertriglyceridemia.[18]

Table 2
Lipid profile parameters in control and different stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	ANOVA
Serum Triglycerides (mg/dl)	119.57±15.18	144.48±20.46	173.97±39.45	179.17±34.98	F=40.38 p<0.0001
Serum Total cholesterol (mg/dl)	175.48±14.92	181.75±19.86	183.46±22.68	185.48±28.70	F=1.718 p<0.165
Serum HDL-Cholesterol (mg/dl)	43.77±4.11	41.28±3.55	39.57±4.70	35.62±7.38	F=19.91 P < 0.0001
Serum LDL-Cholesterol (mg/dl)	107.79±14.62	111.56±19.90	109.09±23.57	114.03±28.98	F=0.684 p<0.563
Serum VLDL (mg/dl)	23.91±3.03	28.89±4.09	34.79±7.89	35.83±6.99	F=40.43 p<0.0001

In the present study shown that slight raise of serum cholesterol in CKD stages 3 to stage 5 compared with control but it is not statistically significant (Table-2; p<0.0001). Vasilis et al., [19] and Kaysen et al.,[20] studies revealed no significant increase of cholesterol in CKD. Whereas Tsumura eta al., [21] and Attman et al., [22] shown significant rise of cholesterol and mentioned raise of serum cholesterol is due to changed gene expression of HMG-COA reductase.[23] The serum LDL also not shown significant changes in CKD stage 3 to stage 5 compared with control. Elevated LDL is not common for chronic kidney disease it is a typical feature of nephritic syndrome. In chronic kidney disease LDL residence time in plasma will increases due to decreased catabolism of LDL. The uremic toxins in chronic kidney disease causes alteration of apoB in LDL. [24] It will causes failure of recognition of LDL by LDL receptor and LDL receptor related protein which results increased LDL. The increased LDL is counter balanced by decreased LDL production and results normal levels LDL. [25]

In present study shown HDL-Cholesterol was decreased significantly in all stages of CKD compared with control (Table-2; p<0.0001). Mordasini et al., [26] and Bagdade et al., [11] also shown similar findings. A declined level of HDL in all stages of Chronic Kidney Disease is because of declined activity of cholesteryl ester transfer protein higher activity and Lecithin Cholesterol Acyl Transferase. [27, 28] There is also decrease of HDL apoproteins like apo AI and AII all the above factors contribute for declined HDL-C.[29]

In present study shown that serum VLDL was increased significantly in CKD all stages compared with control (Table-2; p<0.0001). Bagdade etal., [11] study also shown similar finding the increased of VLDL is due to raised activity of cholesteryl

ester transfer protein it will leads more formation of VLDL. [30] In CKD increased apo c-III also contribute increased VLDL by decreasing LPL activity.

In present study revelaed that atherogenic index plasma was raised significantly in CKD all stages compared with control. In control the mean value of atherogenic index was 0.07±0.040, and in stage 3 of CKD, stage 4 of CKD and stage 5 of CKD are 0.17±0.075, 0.27±0.133 and 0.33±0.160 respectively (one way ANOVA F value= 46.56; p<0.0001; Figure-1). Atherogenic index of plasma was significantly increased as kidney disease progresses and it is noted that stage 5 of CKD shown high atherogenic index.

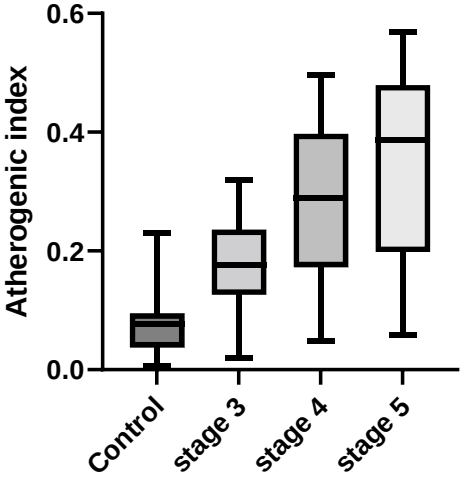

Figure 1. Atherogenic index in control and different stages of CKD

When atherogenic index of plasma correlated with GFR it shown negative correlation and it is shown statistically significant (r= -0.6680; 95%CI -0.7418 to -0.5783; p<0.0001; Figure-2).

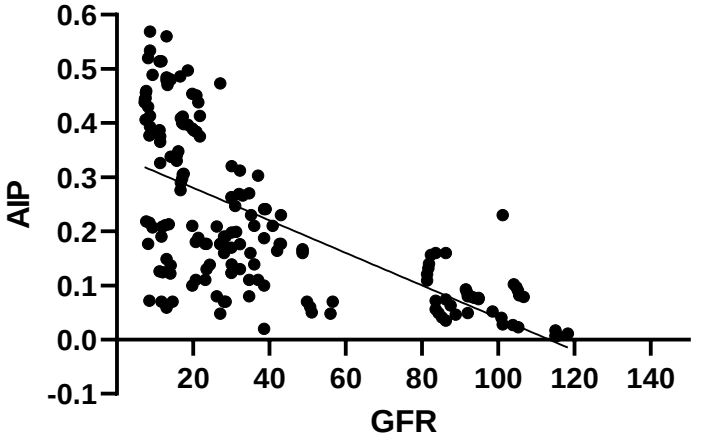

Figure 2. Correlation of Atherogenic index with GFR

Atherogenic index of Plasma (AIP) measures the balance between triglycerides concentration and HDL-C it indirectly measures the small dense LDL.[30] AIP was shown negative correlation with HDL and positive correlation with Triglycerides in Correlation of Multiple linear regression (Figure-3).

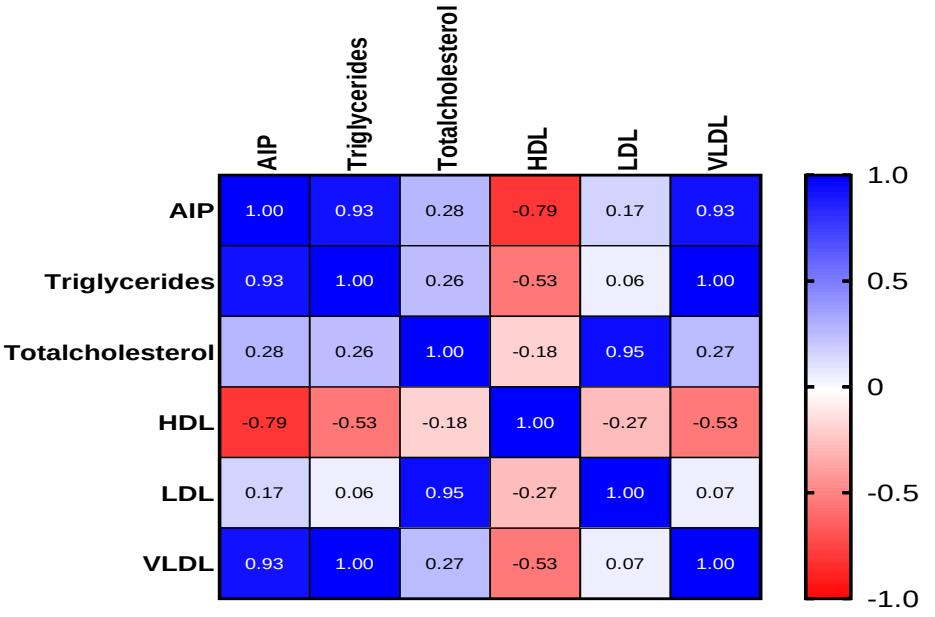

Figure 3. Showing multiple linear regression of various lipid parameters

AIP will determine intravascular cholesterol transport. Previous clinical studies revealed Atherogenic index of plasma assess the cardiovascular risk and it can be assessed easily and helpful in know the treatment response.[31] Low HDL-C, raised value of serum triglycerides and small dense LDL-C is consider as atherogenic lipoprotein. Instead of doing routine lipid profile measuring of AIP will be helpful more in management of atherogenic risk.

Conclusion

The study revealed that there is a dyslipidemia in Chronic kidney disease stage 3 to stage 5 it may leads increased atherogenic index. Atherogenic index of plasma was increased along with decreased GFR and it is evident that stage 5 of CKD is more risk for atherogenic index. The stage wise atherogenic index will gives a new insight of early diagnosis and prognosis of atherogenic risk.

Acknowledgements
We are acknowledge the Nephrology Department Saveetha medical college for support and help. We would also like to thank Saveetha University for providing the necessary facilities to complete this work.

References

1. Gooneratne IK, Ranaweera AK, Liyanarachchi NP, Gunawardane N, Lanerolle RD. Epidemiology of chronic kidney disease in a Sri Lankan population. International journal of diabetes in developing countries. 2008 Apr;28(2):60. https://doi.org/10.4103/0973-3930.43101
2. King W MA, Edward L Greene, Leopold Raij. Cardiovascular risk factors in chronic renal failure and hemodialysis populations. Am J kidney Dis.1992; 6:505-513. https://doi.org/10.1016/s0272-6386(12)80827-4
3. Lidner A, Charra B, Sherrard D. Accelerated atherosclerosis in prolonged maintainance hemodialysis. N Engl J Med.1974; 290:697-701. https://doi.org/10.1056/nejm197403282901301
4. Tetsuo Shoji, Eiji Ishimura, Masaaki Inaba, Tsutomu Tabata, Yoshiki Nishizawa. Atherogenic Lipoproteins in End stage renal disease. Am J kidney dis.2001; 38:S30-33. https://doi.org/10.1053/ajkd.2001.27393
5. Purohit P, Sharma P. Atherogenic index: A potential cardiovascular risk marker in coexisting hypothyroidism and diabetes mellitus at diagnosis. Journal of Obesity and Metabolic Research 2016 ; 3 (1): 46. http://dx.doi.org/10.4103/2347-9906.184174
6. Dobiasova M, Frohlich J, Sedova M, Cheung MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. *J Lipid Res.* 2011;52(3):566–571. https://doi.org/10.1194/jlr.p011668.
7. Deighan CJ, Caslake MJ, McConnell M, Boulton Jones JM, Packard CJ (2000) Related atherogenic lipoprotein phenotype in end-stage renal failure: origin and extent of small dense low-density lipoprotein formation. Am J Kidney Dis. 35: 852–862. https://doi.org/10.1016/s0272-6386(00)70255-1
8. Dobiasova M, Frohlich J. Th-P15:53 Atherogenic index of plasma (AIP) is an effective predictor of cardiovascular risk. Atherosclerosis Supplements. Elsevier BV; 2006 Jan;7(3):504. http://dx.doi.org/10.1016/s1567-5688(06)82013-1
9. Levey AS. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Annals of Internal Medicine. American College of Physicians; 1999 Mar 16;130(6):461. http://dx.doi.org/10.7326/0003-4819-130-6-199903160-00002
10. Rapoport J, Aviram M, Chaimovitz C, Brook JG. Defective High-Density Lipoprotein Composition in Patients on Chronic Hemodialysis. New England Journal of Medicine. Massachusetts Medical Society; 1978 Dec 14;299(24):1326–9. http://dx.doi.org/10.1056/nejm197812142992402
11. Bagdade JD, Albers JJ. Plasma High-Density Lipoprotein Concentrations in Chronic-Hemodialysis and Renal-Transplant Patients. New England Journal of Medicine. Massachusetts Medical Society; 1977 Jun 23; 296 (25): 1436 – 9. http://dx.doi.org/10.1056/nejm197706232962504.
12. Vaziri ND, Liang K. Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. Kidney International. Elsevier BV; 1996 Dec;50(6):1928–35. http://dx.doi.org/10.1038/ki.1996.515
13. Moberly J, Attman P-O, Samuelsson O, Johansson A-C, Knight-Gibson C, Alaupovic P. Apolipoprotein C-III, Hypertriglyceridemia and Triglyceride-Rich Lipoproteins in Uremia. Mineral and Electrolyte Metabolism. S. Karger AG; 1999;25(4-6):258–62. Available from: http://dx.doi.org/10.1159/000057457

14. Huttunen JK, Pasternack A, Vänttinen T, Ehnholm C, Nikkilä EA. Lipoprotein Metabolism in Patients with Chronic Uremia. Acta Medica Scandinavica. Wiley; 2009 Apr 24; 204 (1-6):211–8. http://dx.doi.org/10.1111/j.0954-6820.1978.tb08426.x.
15. Cheung AK, Parker CJ, Ren K, Iverius P-H. Increased lipase inhibition in uremia: Identification of pre-β-HDL as a major inhibitor in normal and uremic plasma. Kidney International. Elsevier BV; 1996 May;49(5):1360–71. http://dx.doi.org/10.1038/ki.1996.192
16. Akmal M, Kasim SE, Soliman AR, Massry SG. Excess parathyroid hormone adversely affects lipid metabolism in chronic renal failure. Kidney International. Elsevier BV; 1990 Mar;37(3):854–8. http://dx.doi.org/10.1038/ki.1990.58
17. Vaziri ND, Wang XQ, Liang K. Secondary hyperparathyroidism downregulates lipoprotein lipase expression in chronic renal failure. American Journal of Physiology-Renal Physiology. American Physiological Society; 1997 Dec 1;273(6):F925–F930. http://dx.doi.org/10.1152/ajprenal.1997.273.6.f925
18. Appel G. Lipid abnormalities in renal disease. Kidney International. Elsevier BV; 1991 Jan;39(1):169–83. http://dx.doi.org/10.1038/ki.1991.22
19. Tsimihodimos V. Dyslipidemia Associated with Chronic Kidney Disease. The Open Cardiovascular Medicine Journal. Bentham Science Publishers Ltd.; 2011 Feb 24;5(1):41–8. http://dx.doi.org/10.2174/1874192401105010041
20. Kaysen GA. Dyslipidemia in chronic kidney disease: Causes and consequences. Kidney International. Elsevier BV; 2006 Dec;70:S55–S58. http://dx.doi.org/10.1038/sj.ki.5001979
21. Tsumura M, Kinouchi T, Ono S, Nakajima T, Komoda T. Serum lipid metabolism abnormalities and change in lipoprotein contents in patients with advanced-stage renal disease. Clinica Chimica Acta. Elsevier BV; 2001 Dec;314(1-2):27–37. http://dx.doi.org/10.1016/s0009-8981(01)00681-7
22. Attman P O, Alaupovic P. Lipid and Apolipoprotein Profiles of Uremic Dyslipoproteinemia -Relation to Renal Function and Dialysis. Nephron. S. Karger AG; 1991;57(4):401–10. http://dx.doi.org/10.1159/000186303
23. Liang K, Vaziri ND. Gene expression of LDL receptor, HMG-CoA reductase, and cholesterol-7 alpha-hydroxylase in chronic renal failure. Nephrology Dialysis Transplantation. Oxford University Press (OUP); 1997 Jul 1;12(7):1381–6. http://dx.doi.org/10.1093/ndt/12.7.1381
24. Ikewaki K, Schaefer JR, Frischmann ME, Okubo K, Hosoya T, Mochizuki S, et al. Delayed In Vivo Catabolism of Intermediate-Density Lipoprotein and Low-Density Lipoprotein in Hemodialysis Patients as Potential Cause of Premature Atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. Ovid Technologies (Wolters Kluwer Health); 2005 Dec;25(12):2615–22. http://dx.doi.org/10.1161/01.atv.0000188555.60475.c2
25. Okeleke VO. A Comparative Study of Lipid Profile in Chronic Renal Failure Patients on Dialysis. Academia Journal of Medicine. College of Medicine and Health Science, DireDawa University; 2018 Jun 27;1(1). http://dx.doi.org/10.21276/ajm.2018.1.1.3
26. Mordasini R, Frey F, Flury W, Klose G, Greten H. Selective Deficiency of Hepatic Triglyceride Lipase in Uremic Patients. New England Journal of Medicine. 1977 Dec 22; 297(25):1362–6. http://dx.doi.org/10.1056/nejm197712222972502

27. Vaziri N. Hepatic HDL receptor, SR-B1 and Apo A-I expression renal failure. Nephrology Dialysis Transplantation. Oxford University Press (OUP); 1999 Jun 1;14(6):1462–6. http://dx.doi.org/10.1093/ndt/14.6.1462
28. Guarnieri GF, Moracchiello M, Campanacci L, Ursini F, Ferri L, Valente M, et al. Lecithin-Cholesterol Acyltransferase (LCAT) Activity in Chronic Uremic Patients. Enzymes in Health and Disease. S. Karger AG; 179–85. http://dx.doi.org/10.1159/000401738
29. Kimura H, Miyazaki R, Imura T, Masunaga S, Suzuki S, Gejyo F, et al. Hepatic lipase mutation may reduce vascular disease prevalence in hemodialysis patients with high CETP levels. Kidney International. Elsevier BV; 2003 Nov;64(5):1829–37. http://dx.doi.org/10.1046/j.1523-1755.2003.00285.x
30. Dobiášová M, Frohlich JJ. Advances in understanding of the role of lecithin cholesterol acyltransferase (LCAT) in cholesterol transport. Clinica Chimica Acta. Elsevier BV; 1999 Aug;286(1-2):257–71. http://dx.doi.org/10.1016/s0009-8981(99)00106-0
31. Frohlich J, Dobiášová M. Fractional Esterification Rate of Cholesterol and Ratio of Triglycerides to HDL-Cholesterol Are Powerful Predictors of Positive Findings on Coronary Angiography. Clinical Chemistry. Oxford University Press (OUP); 2003 Nov 1;49(11):1873–80. http://dx.doi.org/10.1373/clinchem.2003.022558