



ASSESSMENT OF SERUM PARAOXONASE LEVELS IN DYSLIPIDEMIC PATIENTS BEFORE AND AFTER THERAPY WITH LIPID LOWERING AGENTS IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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ABSTRACT

This Hospital based observational longitudinal study on Dyslipidemic patients naïve on lipid lowering agents and the level of serum paraoxonase evaluated at 0 month, 3 month and 6 month interval of starting Statin therapy in whom dyslipidemia were diagnosed by measuring mainly fasting HDL and LDL and subsequent effect of the statin was seen. CKD Patients, Thyroid disease patients, Pregnant women and children was excluded from study. Data analysed by Greenhouse-Geisser correction was applied showed significant correlation between serum paraoxonase and HDL level.

In conclusion, lipid lowering agents increased proportionately the percentage of serum HDL in dyslipidemic subjects, decreased significantly the LDL level, increased significantly the Serum Paraoxonase level.

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INTRODUCTION

Paraoxonases are a family of mammalian enzymes with arylalkylphosphatase activity. There are three paraoxonase isozymes PON1, PON2, PON3.¹ The association of PON1 with HDL suggests that impaired serum concentrations of the lipoprotein could have consequences for the susceptibility to oxidative stress.² Additional research on the inhibition and selective inhibition, specifically of PON1, has been done to shed some light on the connections between decreases in enzymatic activity of individuals with cardiovascular diseases.^{3,4} Evidence also suggests that this family of enzymes has some role in our innate immune system.⁷ Paraoxonase 1 that is synthesized in the liver is then transported into the blood stream where it will associate with high-density lipoprotein (HDL).^{5,6} Paraoxonase 1 also plays an important role as an antioxidant in preventing the oxidation of low-density lipoproteins (LDL), a process that is directly involved in the development of atherosclerosis. Its serum concentration is influenced by inflammatory changes and the levels of serum oxidised-LDL.^{7,8} Both paraoxonase 1 and 3 are bound to HDL and because of their similar properties as antioxidants, it is possible PON3 also plays a role in the prevention of LDL and HDL oxidation.^{9,10,11,12}

In our study we aimed to find out the relation of serum paraoxonase level with HDL and LDL level in dyslipidemic patients who were initially not on statin therapy. We also carried out a review of the available literature data on the above mentioned and compared it with our findings.

Aims & Objectives

Know association with high-density lipoprotein (HDL) and their effect on oxidized-LDL, PON1 and PON3 are implicated in lowering the risk of developing coronary artery disease and atherosclerosis. Clinical outcome in the form of death, myocardial infarction, heart failure NYHA class III or IV. Role of Anti-Dyslipidemic agents in modifying or preventing coronary atherosclerosis.

MATERIALS AND METHODS

This observational and cross sectional study was conducted in the Department of Cardiology, R.G.Kar Medical College, Kolkata, a tertiary care centre of Cardiology from March 2018 to February 2019. The study population comprised of 100 dyslipidemic patients of both adult gender irrespective of age who did not receive lipid lowering therapy before. CKD Patients, Thyroid disease patients, Pregnant women and children was excluded from study. Normal range of serum paraoxonase taken was 45-265U/ml, for LDL 58-135mg/dl and for HDL 35-61mg/dl.

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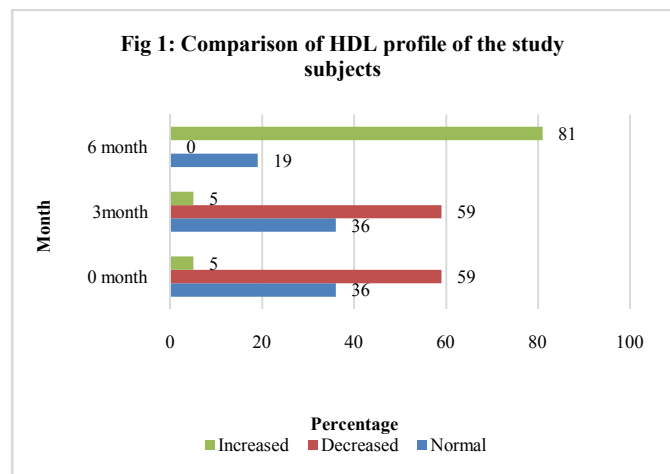
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In our study 19%,34%,47% of the patients belong to age group of 40-50 years,51-60 years and 61-70 years respectively with a mean age of mean age 58.4±7.4years defining again the importance of increased age with the incidence of dyslipidemia and coronary artery disease.

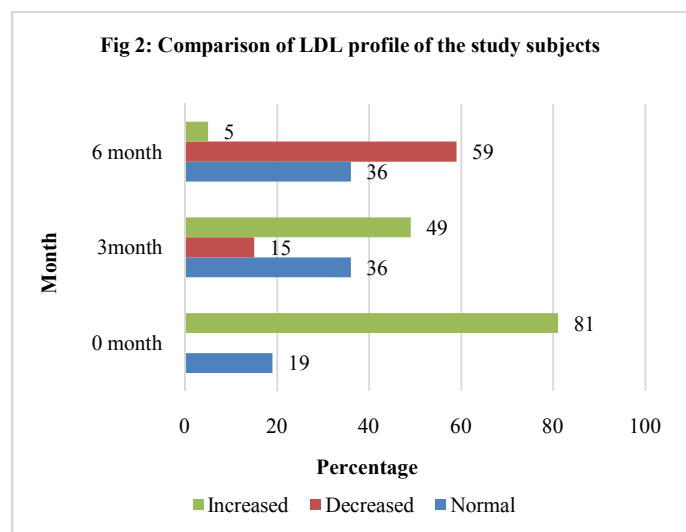
In our study 36% female patients and 64% male patients were included and the incidence of dyslipidemia were predominantly found more in male patients in the age group of 40-50 years after that both gender have almost equal prevalence of dyslipidemiaand hence more prone to develop atherosclerotic vascular disease.

Outcome profile of the study subjects revealed Acute myocardial infarction 11%, Heart Failure 8.0% during the entire study period. No death were found during the study.

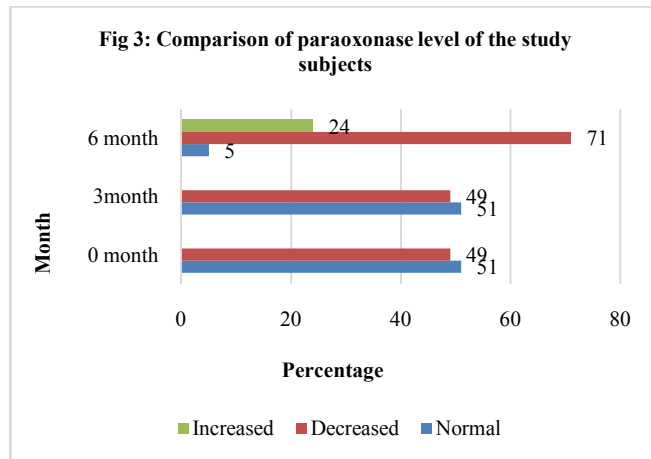
On comparison of HDL profile of the study subjects at 0, 3 and 6 month it was found that 36.0%,59.0%,5.0% having normal, decreased and increased level at 0 month which increased to 81% after 6 month of statin therapy respectively but was statistically insignificant(p=.703)



Comparison of LDL profile of the study subjects at 0, 3 and 6 month revealed marked reduction of serum LDL level from 81% to 59% of subjects and was statistically significant (p=.000)



Comparison of paraoxonase level of the study subjects at 0, 3 and 6 month although not proportionately increased from baseline 51% decreased to a level of 24% but was statistically significant(p=.033) i.e less than (p=.05)



DISCUSSION

In our study conducted in RG Kar medical college and hospital to evaluate the effect of statin on dyslipidemic patients naïve on statin and the effect of the same on the level of serum paraoxonase level.

So from our study it has been evaluated that the statins^{13,14} have reached the endpoint of decreasing the burden of dyslipidemia in the form of increased serum HDL level and decreased serum LDL level which was significant in case of serum LDL and also significant in case of Serum Paraoxonase^{15,16,17} level over a course of 6 months of statin therapy.

The incidence of Acute myocardial infarction and Heart failure were only 11% and 8% respectively in our study which is atleast in part the pleiotropic effect of statin and correcting the dyslipidemia^{18,19}, although other risk factors must be involved in the form of smoking, sedentary life style, hypertension^{20,21}, diabetes mellitus.^{22,23}

The limitations of our study was

1. Gene polymorphism of paraoxonase²⁴ molecule could not be tested because of financial constraints which is a major drawback.
2. Different HDL and LDL molecule subtractions²⁵ could not be done due to lack of proper setup.
3. The effect of statin on different subsets of PON i.e PON 1,PON 2,PON 3²⁶ could not be tested due to lack of financial support.

CONCLUSION

Our study is a small scale study in the eastern region of India, where there is lack of constructive data regarding the routine use of serum Paraoxonase and its advantage over Fasting lipid profile in aggressively preventing the LDL-oxidation and atherosclerotic vascular disease. We have concluded that after 6 months of statin therapy

- Statins increased proportionately the percentage of serum HDL in dyslipidemic subjects
- Statins decreased significantly the LDL level
- Statins increased significantly the Serum Paraoxonase level
- Only 11 patients and 8 patients had episode of Acute myocardial infarction and Heart failure respectively with no deaths reported.

So our view is adding serum paraoxonase level as an adjunct to fasting lipid profile measurement will be more helpful in detecting the effects of statin therapy or in addition to that any other anti-dyslipidemic drugs.

References

1. Bergmeier C, Siekmeier R, Gross W (December 2004). "Distribution spectrum of paraoxonase activity in HDL fractions". *Clin. Chem.* 50 (12): 2309–15. doi:10.1373/clinchem.2004.034439. PMID 15459089.
2. Litvinov, Dmitry, Halleh Mahini, and Mahdi Garelnabi. "Antioxidant and Anti-Inflammatory Role of Paraoxonase 1: Implication in Arteriosclerosis Diseases." *North American Journal of Medical Sciences* 4.11 (2012): 523–532. PMC. Web. 1 Mar. 2016.
3. Costa, Lucio G., and Clement E. Furlong. *Paraoxonase (PON1) in Health and Disease: Basic and Clinical Aspects*. Boston: Kluwer Academic, 2002. Print.
4. S.D. Nguyen, D.E. Sok. "Oxidative inactivation of Paraoxonase 1 an antioxidant protein and its effect on antioxidant action." *Free Radic Res*, 37 (2003), pp. 77–83
5. Egon A. Ozer, Alejandro Pezzulo, Diana M. Shih, Carlene Chun, Clement Furlong, Aldons J. Lusic, Everett P. Greenberg, Joseph Zabner. Human and murine paraoxonase 1 are host modulators of *Pseudomonas aeruginosa* quorum-sensing FEMS Microbiology Letters Dec 2005, 253 (1) 29-32; DOI: 10.1016/j.femsle.2005.09.023
6. Li HL, Liu DP, Liang CC (2003). "Paraoxonase gene polymorphisms, oxidative stress, and diseases". *Journal of Molecular Medicine*. 81 (12): 766–779. doi:10.1007/s00109-003-0481-4. PMID 14551701.
7. Mackness, B., Beltran-Debon, R., Aragones, G., Joven, J., Camps, J. and Mackness, M. (2010), Human tissue distribution of paraoxonases 1 and 2 mRNA. *IUBMB Life*, 62: 480–482. doi: 10.1002/iub.347
8. Ng CJ, Wadleigh DJ, Gangopadhyay A, *et al.* (November 2001). "Paraoxonase-2 is a ubiquitously expressed protein with antioxidant properties and is capable of preventing cell-mediated oxidative modification of low density lipoprotein". *J. Biol. Chem.* 276 (48): 44444–9. doi:10.1074/jbc.M105660200. PMID 11579088.
9. Reddy ST, Wadleigh DJ, Grijalva V, Ng C, Hama S, Gangopadhyay A, Shih DM, Lusic AJ, Navab M, Fogelman AM (April 2001). "Human paraoxonase-3 is an HDL-associated enzyme with biological activity similar to paraoxonase-1 protein but is not regulated by oxidized lipids". *Arterioscler. Thromb. Vasc. Biol.* 21 (4): 542–7. doi:10.1161/01.ATV.21.4.542. PMID 11304470.
10. Draganov DI, Teiber JF, Speelman A, *et al.* Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities. *J Lipid Res* 2005;46:1239-42
11. Reddy ST, Wadleigh DJ, Grijalva V, Ng C, Hama S, Gangopadhyay A, Shih DM, Lusic AJ, Navab M, Fogelman AM (April 2001). "Human paraoxonase-3 is an HDL-associated enzyme with biological activity similar to paraoxonase-1 protein but is not regulated by oxidized lipids". *Arterioscler. Thromb. Vasc. Biol.* 21 (4): 542–7. doi:10.1161/01.ATV.21.4.542. PMID 11304470.
12. Draganov DI, Teiber JF, Speelman A, *et al.* Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities. *J Lipid Res* 2005;46:1239-42
13. Kural, Birgül Vanizora; Örem, Cihanb; Uydu, Hüseyin A.c; Alver, Ahmeta; Örem, Asma Coronary Artery Disease: August 2004 - Volume 15 - Issue 5 - p 277-283 doi: 10.1097/01.mca.0000135221.32523.a1 Therapy and Prevention
14. Moushira Erfan Zaki, Hala El-Bassyouni, Sanaa Kamal, Mona El-Gammal, Eman Youness: Year: 2014 ;Volume: 18 Issue : 3;Page : 340-344
15. Laura Calabresi, Barbara Villa, Monica Canavesi, Cesare R Sirtori, Richard W James, Franco Bernini, Guido Franceschini: February 2004 Volume 53, Issue 2, Pages 153–158 DOI: <https://doi.org/10.1016/j.metabol.2003.09.007>
16. Tolga H Efe, Ahmet G Ertem, Alpaslan Altunoglu, Cemal Koseoglu, Ali Erayman, Murat Bilgin, Özge Kurmuş, Turgay Aslan, and Mehmet Bilge: *Acta Cardiol Sin.* 2016 Jan; 32(1): 75–80. doi: 10.6515/ACS20150429A
17. Ertem AG1, Erayman A, Efe TH, Duran Karaduman B, Aydın HI, Bilge M. *Anadolu Kardiyol Derg.* 2014 Mar; 14(2):115-20. doi: 10.5152/akd.2014.4742. Epub 2014 Jan 14. DOI: 10.5152/akd.2014.4742
18. Mehrdad Solati and Hamid-Reza Mahboobi: *J Nephropathol.* 2012 Oct; 1(3): 123–125. doi: 10.5812/nephropathol.8106
19. Prathibha K, Aliya Nusrath, Rajeshwari A: *Int J Res Med Sci.* 2016; 4(9): 4001-4004 doi: 10.18203/2320-6012.ijrms20162923:
20. Eroglu E, Kocyigit I, Unal A, Korkar H, Karakukcu C, Orselik O, Sipahioglu MH, Tokgoz B, Oymak O. *Int Urol Nephrol.* 2015 Aug;47(8):1409-14. doi: 10.1007/s11255-015-1051-8. Epub 2015 Jul 17.
21. Braunwald's Heart Disease A Textbook Of Cardiovascular Medicine 18th Edition.
22. 2018 ACC/AHA Cholesterol Guidelines.
23. P. N. Durrington, B. Mackness, and M. I. Mackness Originally published 1 Apr 2001 <https://doi.org/10.1161/01.ATV.21.4.473> Arteriosclerosis, Thrombosis, and Vascular Biology. 2001; 21:473–480
24. Dmitry Litvinov, Halleh Mahini, and Mahdi Garelnabi: *N Am J Med Sci.* 2012 Nov; 4(11): 523–532. doi: 10.4103/1947-2714.103310
25. Polat Dursun, Ezgi Demirtaş, Ahmet Bayrak, Hakan Yarali: *Human Reproduction*, Volume 21, Issue 1, January 2006, Pages 104–108, <https://doi.org/10.1093/humrep/dei284>
26. C Zhang, W Peng, M Wang, J Zhu, Y Zang, W Shi, J Zhang and J Qin: *Gene Therapy* (2010) 17, 626–633; doi:10.1038/gt.2010.11; published online 25 February 2010
