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Original Research Article

An Analytical Case Control Study Assessing Serum Lipoproteins and Their Role in Senile Dementia

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Abstract

Aim: The aim of the present study was to assess the levels of lipoproteins and their role in Alzheimer's dementia patients and compared with heathy control subject.

Methods: The present study was carried out in the department of Biochemistry at Netaji Subhas medical College and Hospital, Bihta, Patna, Bihar, India for one year. The blood samples was collected and analysed in clinical Biochemistry laboratory. The present study conducted on 70 healthy controls and 70 Alzheimer's dementia patients by using standard methods.

Results: There were no difference found in age, systolic, diastolic blood pressure, BMI between Alzheimer's dementia subject and control group. The subjects in Alzheimer's dementia groups had significantly lower MMSE score compare to control group. ($P < 0.0001$). Negative correlation was observed but not significant correlation between Total Cholesterol, HDL-C and MMSE in Alzheimer's dementia subjects. In the control group of subject there was lower correlation between Total Cholesterol, Triglyceride, HDL- C, LDL-C and VLDL-C but not statistically significant. The Alzheimer's dementia subjects had statistically significantly higher serum Total Cholesterol, Triglyceride, HDL-C, LDL- C and VLDL-C ($P < 0.001$) as compared to healthy controls.

Conclusion: The determination of serum lipoproteins is a routine, not required invasive procedure and cheap method, therefore we suggest that monitoring lipoproteins in older subjects with dementia may be the additional tool to understand basic mechanism of nerve degeneration, memory loss by evaluating lipoprotein levels and their association in Alzheimer's dementia.

Keywords: Lipoproteins, Alzheimer's Dementia, Neurofibrillary Tangles.

Introduction

Dementia is a common disease in older individuals living in western societies. In the past years, numerous studies have suggested the existence of a relationship between lipids metabolism and dementia. However, studies that explored the relationship between plasma lipids and dementia have reported conflicting findings. Some [1,2] but not all [3,4] epidemiological studies suggested that elevated total cholesterol (TC) levels in the middle age might be a risk factor for

dementia in late life. On the contrary, cross-sectional studies have consistently reported an association between low TC levels and the diagnosis of dementia in the elderly subjects. [5-7]

Only a few studies have evaluated the association between dementia and specific lipoprotein fractions, such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C. This is an important issue since apo B–containing lipoproteins (LDL-C or non-HDL-C) and apo A–containing lipoproteins (HDL-C) have "opposite" functions in human physiology and have been associated with a pro- and antiatherogenic profile, respectively. Increased levels of LDL-C have been associated with Alzheimer's disease (AD), [8,9] as well as dementia with stroke [10], but other studies failed to confirm these associations. [11]

The main culprit of Alzheimer's disease is Amyloid- b (Ab). The increased peripheral lipoproteins, membrane cleavage taking place by b-secreatase and y-secreatase results in amyloidogenic forms that aggregates as extracellular of plaques and Ab production in Alzheimer's dementia. The increased Cholesterol induces Ab deposition in the brain and promote production of neurofibrillary tangles (NFT). Ab induces tau phosphorylation and ROS formation in brain. The peptidyl radical damages mitochondrial DNA, RNA, lipids, protein leads to synapse damage and death of neuronal cell. This is taking place at memory centre and hippocampus of the brain. [12] Lipids and lipoproteins were increased in very few studies and associated with dementia at present. The previous studies found decreased levels of lipoproteins in dementia. [13] A recent study reported increased levels of lipid and lipoproteins and their association with dementia.

The aim of the present study was to assess the levels of lipoproteins and their role in Alzheimer's dementia patients and compared with heathy control subject.

Materials and Methods

The present study was carried out in the department of Biochemistry at Netaji Subhas medical College and Hospital, Bihta, Patna, Bihar, India for one year. The blood samples was collected and analysed in clinical Biochemistry laboratory.The patients selected for the present study were attending indoor/outdoor patient department from Netaji Subhas medical College and Hospital, Bihta, Patna, Bihar, India.

Inclusion criteria

1. Newly diagnosed cases, not on treatments
2. Male subjects, above 7 0 to 7 5 years.
3. MMSE Score of less than 12.

Exclusion criteria

1. Patients addicted to alcohol or drug abuse.
2. Patients suffering from major psychiatric disorder, chronic illness.
3. Any other concurrent drug intake

The healthy control subjects

70 healthy control subjects in the age group of 70 to 75 years were included in the study. Their physical examination included Systolic blood pressure, Diastolic blood pressure, body mass index, and Mini Mental State score examination was done at our hospital by General Medicine and Psychiatric department. The healthy control subjects shown all tests within normal limit, their MMSE Score was normal (26) and were completely free from psychiatric disorder, addicted to alcohol or intake of any other drug.

The dementia subjects

70 Alzheimer's type of dementia in the age group of 70 to 75 years was included in the study. Their physical examination included Systolic blood pressure, Diastolic blood pressure, body mass index, and Mini

Mental State score examination Score was done at our hospital by General Medicine and Psychiatric department. Physical examination included Systolic blood pressure, Diastolic blood pressure, body mass index were within normal limits except Mini Mental State score examination Score in Alzheimer's dementia subjects. The Alzheimer's dementia was diagnosed by DSM-IV criteria and Mini Mental State examination score. The Mini Mental State score examination less than 12 of patients were selected in our study. This Mini Mental State score examination test administered by senior resident of psychiatric department, which includes questionaries' related to place, time, attention and calculation, recall, language etc. A score of less than 23 points on the Mini Mental State score examination indicated cognitive impairment.[14] The informed written consent was taken from the subjects with the help of subjects family and study was approved by institute ethical committee. The fasting blood samples were collected from patients and healthy controls with all aseptic precautions in plain polythene tubes for the estimation of lipoproteins. Serum was separated by centrifuging the samples at 3000 rpm for 10 minutes and preserved in freezer till the laboratory estimation proceeds.

The Serum Total Cholesterol was estimated by method CHOD-PAP (with LCF) end point. The Serum Triglycerides was estimated by method GPO-Trinder end point. The serum HDL-C was estimated by direct method. LDL-C and VLDL was estimated by calculated using the empirical relation of Friedewald's (1972). The statistical analysis was carried by Microsoft office 2019 and SPSS software version. The Pearson correlations were used as measures of association for the variables. The probability values $P < 0.0001$ was considered as significant and also data were expressed in mean ±SD form.

Results

Table 1: Standard Characteristics of Alzheimer's Dementia (AD) patients and Control groups

Parameters	AD group MMSE	Control group MMSE	P value
Age (Year)	72.38 ± 3.16	73.07 ± 3.80	0.540
SBP (mm in H g)	131.39±2.40	127.33±1.20	0.220
DBP (mm in H g)	83.17±1.16	82.28±2.16	0.460.
BMI (Kg/m2)	25.65±1.10	26.14±0.36	0.710
MMSE Score	26.14±1.14	27.23±1.66	0.0001

There were no difference found in age, systolic, diastolic blood pressure, BMI between Alzheimer's dementia subject and control group. The subjects in Alzheimer's dementia groups had significantly lower MMSE score compare to control group. ($P < 0.0001$).

Table 2: Pearson correlation analysis between Lipoproteins and MMSE score in patients of Alzheimer's Dementia (AD) and Control group

Parameters	AD group MMSE	Control group MMSE
Total Cholesterol	r = -0.58	r = 0.26
Triglyceride	r = 0.12	r = 0.32
HDL-C	r = -0.0001	r = 0.60
LDL-C	r = 0.40	r = 0.38
VLDL-C	r = 0.22	r = 0.15

Negative correlation was observed but not significant correlation between Total Cholesterol, HDL-C and MMSE in Alzheimer's dementia subjects. In the control group of subject there

was lower correlation between Total Cholesterol, Triglyceride, HDL- C, LDL-C and VLDL-C but not statistically significant.

Table 3: The Serum Levels of Lipoproteins in Alzheimer's dementia (AD) and Control group

Parameter Groups	Healthy Control Mean Age (72.38 ± 3.16)	Alzheimer's Dementia Mean Age (73.07 ± 3.80)
Total Cholesterol mg/dl	174.42±16.48	272.38±12.60
Triglyceride mg/dl	92.38±30.70	200.10±18.20
HDL-C mg/dl	64.36±16.14	36.64±10.35
LDL-C mg/dl	97.23±25.55	170.40±20.35
VLDL-C mg/dl	17.43±06.08	28.62±04.18

The Alzheimer's dementia subjects had statistically significantly higher serum Total Cholesterol, Triglyceride, HDL-C, LDL- C and VLDL-C ($P < 0.001$) as compared to healthy controls.

Discussion

Serum lipoprotein levels, especially among people with cardiovascular disease, may be a common and potentially modifiable risk factor for cognitive disorders. The findings of studies that have investigated the relationship between serum lipoprotein levels and risk of cognitive impairment are conflicting. Some cross-sectional studies [15,16] suggest that high total cholesterol levels are associated with an increased risk of Alzheimer disease (AD), while others [17] report that low total cholesterol levels are associated with the risk of developing AD. Cross-sectional studies of this question can be misleading because dementia may cause changes in lipoprotein levels by altering diet or metabolism. Dementia is a syndrome, chronic or progressive in nature in which there is deterioration in cognitive function it affects memory, thinking, orientation, calculation, learning capacity, language and judgement". [18] The diagnosis of dementia clinically made by Diagnostic and statistical manual of mental disorders. [19] The most common type of dementia are Alzheimer's disease, Vascular dementia, Lewy body dementia, Frontotemporal dementia and HIV associated dementia. [20] When dealing with plasma lipids and dementia, it has to be kept in mind that cholesterol contained in the central nervous system (CNS) and plasma cholesterol form two independent pools, and modifications in plasma levels do not necessarily reflect modification in CNS pool. Of consequence, extreme caution is needed when considering the possible causative relationship between plasma lipids and dementia or vice versa. Several previous studies found increased midlife cholesterol was associated with Alzheimer's dementia. [21] In other studies also shown that Cholesterol in diet increases Aβ deposition in the brain, whereas reduces by cholesterol lowering drugs. [22,23] The several different studies shown that oxidized products of excess cholesterol i.e oxysterols (24-s-hydroxycholetsterol and 27-dehydro-cholesterol) are highly neurotoxic capable passing blood brain barrier leads to neuroinflammation, apoptosis and exocytosis and brain injury, effects on memory centre and progression of Alzheimer's dementia. [24,25] The underlying mechanism is due to increased peripheral Cholesterol, increases Aβ deposition in the brain and promote production of neurofibrillary tangles (NFT). NFT contains hyperphosphorylation tau and Aβ induces tau phosphorylation. [26]

There were no difference found in age, systolic, diastolic blood pressure, BMI between Alzheimer's dementia subject and control group. The subjects in Alzheimer's

dementia groups had significantly lower MMSE score compare to control group. Negative correlation was observed but not significant correlation between Total Cholesterol, HDL-C and MMSE in Alzheimer's dementia subjects. In the control group of subject there was lower correlation between Total Cholesterol, Triglyceride, HDL- C, LDL-C and VLDL-C but not statistically significant. The Alzheimer's dementia subjects had statistically significantly higher serum Total Cholesterol, Triglyceride, HDL-C, LDL- C and VLDL-C ($P < 0.001$) as compared to healthy controls. Several other large studies according to the recent longitudinal cohort study published in neurology, shown increased levels of midlife TG are predictive the presence of Aβ and tau in cognitively healthy individual after 20 years. In this study longitudinal study increased fasting TG levels was associated with increased risk of brain Aβ with tau 20 years later, the se findings were independents of sex, age, APO - E E4. [27]

The underlying mechanism was due to increased inflammatory activity and low-grade systemic inflammation decreases HDL-cholesterol concentration. The inflammatory response is important in neurodegeneration process, HDL-cholesterol diminish a local inflammatory reaction by acting on astrocytes. The inflammatory markers are found in and around in amyloid plaques. [28,29] The another reason was HDL-cholesterol having antioxidant activity, due to decreased levels of HDL- cholesterol and increased LDL-cholesterol results in to oxidized LDL-cholesterol, this oxidized LDL can bind with Aβ and increases Aβ deposition and neurotoxicity in the brain. Aβ aggregation amyloid genesis and deposition of Aβ leads to plaque formation. [30]

In a previous cross-sectional study we found that older subjects with vascular dementia, but not individuals with late-onset AD, were characterized by lower levels of HDL-C compared with controls. [31] By analyzing a sample of older individuals from the Paquid Study, Bonarek and colleagues found that elevated HDL-C levels were significantly associated with a decreased risk of dementia, after adjustment for apo E status and other potential confounders. [32]

Conclusion

The determination of serum lipoproteins is a routine, not required invasive procedure and cheap method, therefore we suggest that monitoring lipoproteins in older subjects with dementia may be the additional tool to understand basic mechanism of nerve degeneration, memory loss by evaluating lipoprotein levels and their association in Alzheimer's dementia. However further studies are required as serum lipoproteins might be serve potential biomarkers in Alzheimer's disease.

References

1. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population-based study. Bmj. 2001 Jun 16;322(7300):1447-51.
2. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Dietary intake of antioxidants and risk of Alzheimer disease. Jama. 2002 Jun 26;287(24):3223-9.
3. Kalmijn S, Foley D, White L, Burchfiel CM, Curb JD, Petrovitch H, Ross GW, Havlik RJ, Launer LJ. Metabolic cardiovascular syndrome and risk of dementia in Japanese American elderly men: the Honolulu-Asia Aging Study. Arteriosclerosis, thrombosis, and vascular biology. 2000 Oct;20(10):2255-60.
4. Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, D'Agostino

RB, Wolf PA. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Archives of Internal Medicine. 2003 May 12;163(9):1053-7.
5. Kuusisto J, Koivisto K, Mykkänen L, Helkala EL, Vanhanen M, Hänninen T, Kervinen K, Kesäniemi YA, Riekkinen PJ, Laakso M. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population-based study. Bmj. 1997 Oct 25; 315(7115):1045-9.
6. Siest G, Bertrand P, Qin B, Herbeth B, Serot JM, Masana L, Ribalta J, Passmore AP, Evans A, Ferrari M, Franceschi M. Apolipoprotein E polymorphism and serum concentration in Alzheimer's disease in nine European centres: the ApoEurope study.
7. Czyzewski K, Lalowski MM, Pfeffer A, Barcikowska M. Lipid metabolism parameters in patients with Alzheimer's disease and their first-degree relatives. Acta Neurobiologiae Experimentalis. 2001;61(1):21-6.
8. Lesser G, Kandiah K, Libow LS, Likourezos A, Breuer B, Marin D, Mohs R, Haroutunian V, Neufeld R. Elevated serum total and LDL cholesterol in very old patients with Alzheimer's disease. Dementia and geriatric cognitive disorders. 2001; 12(2):138-45.
9. Lehtonen A, Luutonen S. High-density lipoprotein cholesterol levels of very old people in the diagnosis of dementia. Age and ageing. 1986 Sep 1;15(5):267-70.
10. Moroney JT, Tang MX, Berglund L, Small S, Merchant C, Bell K, Stern Y, Mayeux R. Low-density lipoprotein cholesterol and the risk of dementia with stroke. Jama. 1999 Jul 21;282 (3):254-60.
11. Caramelli P, Nitrini R, Maranhao R, Lourenço AC, Damasceno MC, Vinagre C, Caramelli B. Increased apolipoprotein B serum concentration in Alzheimer's disease. Acta neurologica scandinavica. 1999 Jul; 100(1):61-3.
12. Lepara O, Valjevac A, Alajbegović A, Zaćiragić A, Nakaš-Ićindić E. Decreased serum lipids in patients with probable Alzheimer's disease. Bosnian Journal of Basic Medical Sciences. 2009 Aug;9(3):215.
13. Klein WL. Cholesterol Modulates - Secretase Cleavage of Amyloid Precursor Protein. J Biol Chem. 1996 ;271(8):4436–4440.
14. Folstein MF, Folstein SE. Mini mental state A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3) :189–198.
15. Evans RM, Emsley CL, Gao S, Sahota A, Hall KS, Farlow MR, Hendrie H. Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. Neurology. 2000 Jan 11;54 (1):240-.
16. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J, Nissinen A. Serum total cholesterol, apolipoprotein E {FC12} e4 allele, and Alzheimer's disease. Neuroepidemiology. 1998;17(1):14-20.
17. Romas SN, Tang MX, Berglund L, Mayeux R. APOE genotype, plasma lipids, lipoproteins, and AD in community elderly. Neurology. 1999 Aug 1;53(3):517-.
18. World Health Organisation (WHO). Dementia; 2019.
19. Text Revision. In: and others, editor. Washington: American Diagnostic and Statistical Manual of Mental Disorders American Psychiatric Association; 2000.
20. Huang J. MSD Manual Professional version. Dementia, last full review/revision March; 2018.
21. Singh-Manoux. Low HDL Cholesterol Is a Risk Factor for Deficit and Decline

in Memory in Midlife. Arterioscler, Thromb Vasc Biol. 2008;28(8):1556–1562.
22. Altman R, Rutledge JC. The vascular contribution to Alzheimer's disease. Clin Sci. 2010;119(10):407–421. S
23. Refolo LM. A Cholesterol lowering drug reduces beta amyloid pathology in a transgenic mouse model of Alzheimer's disease. Neurobiol Dis. 2001; 8:890–899.
24. Refolo LM, Pappolla MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Tint GS, Sambamurti K, Duff K. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiology of disease. 2000 Aug 1;7(4):321-31.
25. Ma MT, Zhang J, Farooqui AA, Chen P, Ong WY. Effects of cholesterol oxidation products on exocytosis. Neurosci Letters. 2010;476(1):36–41.
26. Reitz C. Dyslipidemia and the risk of Alzheimer's disease. Curr Atherosclerosis Res. 2013;15(3).
27. Papassotiropoulos A, Lütjohann D, Bagli M, Locatelli S, Jessen F, Rao ML, Maier W, Björkhem I, von Bergmann K, Heun R. Plasma 24S-hydroxycholesterol: a peripheral indicator of neuronal degeneration and potential state marker for Alzheimer's disease. Neuroreport. 2000 Jun 26;11 (9):1959-62.
28. McGeer EG, McGeer PL. The importance of inflammatory mechanisms in alzheimer disease. Exp Gerontol. 1998;33(5):371–378. d
29. Eikelenboom P, Veerhuis R. The role of complement and activated microglia in the pathogenesis of Alzheimer's disease. Neurobiology of Aging. 1996; 17(5):673–680.
30. Keller JN, Hanni KB. Oxidized low-density lipoprotein induces neuronal death implications for calcium, reactive oxygen species, and Caspases. J Neurochem. 1999; 72:2601–2609.
31. Papassotiropoulos A, Lütjohann D, Bagli M, Locatelli S, Jessen F, Rao ML, Maier W, Björkhem I, von Bergmann K, Heun R. Plasma 24S-hydroxycholesterol: a peripheral indicator of neuronal degeneration and potential state marker for Alzheimer's disease. Neuroreport. 2000 Jun 26;11 (9):1959-62.
32. Bonarek M, Barberger-Gateau P, Letenneur L, Deschamps V, Iron A, Dubroca B, Dartigues JF. Relationships between cholesterol, apolipoprotein E polymorphism and dementia: a cross-sectional analysis from the PAQUID study. Neuroepid emiology. 2000;19(3):141-8.