Hyperlipidemia and the Aging Brain: The Impact of High Cholesterol on Cognitive Decline among the Aging Population

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Abstract

Dementia is a collective term for a number of neurodegenerative diseases characterized by cognitive impairment, memory loss, imparied judgement, and personality changes. There is currently no known cure and current treatment is focused mainly on symptomatic relief. Therefore, an intervention that can reduce the risk of dementia can have a major public health impact. This review aims to examine the current literature on cardiovascular health, specifically hyperlipidemia (HLD), and whether such a condition increases the risk of developing dementia in those ages 65 to 85.

Introduction

Previously explored relationships between total cholesterol and cognitive health:

- apolipoprotein E (ApoE) and its association with LDL cholesterol and development of AD.
- Cholesterol's role in production of β-amyloid peptide (Aβ).
- LDL and its effect on blood brain barrier permeability.
- LDL and HDL and carotid artery atherosclerosis.

This research hopes to clarify the relationship between HLD and subsequent cognitive decline through answering the following research question:

- In the population of those at high risk for developing dementia (age 65-85), does the cardiovascular risk factor of hyperlipidemia increase the risk of cognitive decline? Additionally, does statin therapy decrease the risk?

Methods

Literature Search

➔ Performed in November 2019 using PubMed, ScienceDirect, and Google Scholar.

➔ Search Terms

◆ Coronary artery disease OR atherosclerosis OR hyperlipidemia OR cardiovascular health AND cognitive decline OR dementia OR Alzheimer's disease.

➔ Inclusion Criteria:

- ◆ Written in 1999 or later.
- ◆ Published in a peer-reviewed journal.
- ◆ Written in English.

➔ Exclusion Criteria:

- ◆ Studies that involved individuals < 50 years.
- ◆ Studies in which the direct impact of atherosclerosis on cognitive decline could not be assessed due to the presence of multiple confounding risk factors among participants.
- ◆ Systematic review or meta-analyses.
- ◆ Studies that involved clinical trials with animals.

Results

1. **Cox et al (2015):** RCT examining the potential benefits of curcumin on cognitive functioning in an older adult population. This article was chosen because of curcumin's potential to both improve cognitive function and lower cholesterol. Thus, findings from this study could shed light on the association between high cholesterol and reduced cognitive function.
2. **Kivipelto et al (2002)**: Prospective population-based study of adults examining the relationship between the apolipoprotein E (apoE) allele, high serum total cholesterol, and high systolic blood pressure in midlife with the development of AD in late life. This article was chosen because it specifically included an examination of high cholesterol as a risk factor for Alzheimer's disease (AD).
3. **Simons et al (2002):** RCT examining the potential neuroprotective effects of simvastatin in the brains of individuals with mild and moderate AD. This study was chosen because of its unique exploration of the relationship between cholesterol and development of AD.
4. **Van Oijen et al (2007):** Prospective cohort study examining the relationship between atherosclerosis and increased risk for dementia. This article was chosen because it specifically included an examination of atherosclerosis as a risk factor for Alzheimer's disease (AD).
5. **Vuletic et al (2006):** RCT examining the impact of two different statins on AD brain pathology. This study adds to the literature on cholesterol levels and AD pathogenesis through its examination of the interrelationships between PLTP, apoE and statins in the brain.
6. **Wardle et al (2000):** RCT examining the effects of cholesterol-lowering diets on mood and cognitive function. This study adds to the existing literature through employment of an RCT design that facilitates a more thorough examination of the impact of cholesterol-lowering diets on mood and cognitive functioning.

Table 1: **Comparison of Study Designs**

Study	Design	Total N	Age range (years)	Duration of Intervention	Control	Tx Regimen	Outcome Measures
Cox KH, Pipingas A, Scholey AB	RCT	60	60-85	4 weeks	Placebo 80mg/day x 4 weeks	Curcumin 80mg/day x 4 weeks	Cognitive function (CMPAS), Mood (DASS, Chalder Fatigue Scale), blood sample for total cholesterol, LDL, HDL and AB
Kivipelto M, Helkala E, Laakso M, et al.	Cohort	1449	65-79	21 years	none	N/A	Serum total cholesterol (LB method), apoE allele (PCR), systolic bp (R arm, sitting), DSMIV, ADRDA, NINDS
Simons M, Schwärzler F, Lütjohann D, et al.	RCT	44	59-77	26 weeks	Placebo, 80mg/day x 26 weeks	Simvastatin 80mg/day x 26 weeks	AB40 and AB42 (ELISA), lathosterol, cholesterol and 24-hydroxycholesterol (combination gas chromatography-mass spectrometry), MMSE, AD Assessment Scale-Cognitive Portion
Van Oijen M, De Jong FJ, Witteman JC, et al.	Cohort	6,647	55+	7 years	none	N/A	Carotid IMT and carotid plaques (B-mode ultrasonography), PAD (ankle-brachial index), MMSE, GMSS
Vuletic S, Riekse RG, Marcovina SM, et al.	RCT	24	"Adults"	3 months	none	Pravastatin (80 mg/day) x 3 months or simvastatin (40 mg/day) x 3 months	Plasma apoE (Hitachi automated analyzer), CSF apoE (Dade Behring method), plasma and CSF PLTP (radio assay)
Wardle J, Rogers P, Judd P, et al.	RCT	176	Average age 55	12 weeks	No dietary education sessions x 12 weeks	8 dietary education sessions x 12 weeks	Cognitive function (battery of tests), GHQ, PSS, BDI, PMS subscale, STA inventory

Key: **RCT**: Randomized Control Trial, **CMPAS**: Computerized Mental Performance Assessment System including tasks such as immediate word recall, simple reaction time and rapid visual information processing, **DASS:** Depression, Anxiety and Stress Scales, **LB method**: Leibermann-Burchard method, **DSMIV**: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, **NINDS**: National Institute of Neurological Disorders and Stroke criteria, **ADRDA**: Alzheimer's Disease and Related Disorders Association criteria, **ELISA**: enzyme-linked immunosorbent assay, **MMSE**: Mini-Mental State Exam, **IMT:** carotid intima media thickness, **GMSS**: Geriatric Mental State Schedule, **Battery of tests**: Battery of computer tests assessing free-recall, tapping speed, reaction time and attention, **GHQ**: General Health Questionnaire, **PSS**: Perceived Stress Scale, **BDI:** Beck Depression Inventory, **PMS subscale**: Profile of Mood States depression and anger subscales, **STA inventory**: State-Trait Anger inventory.

Discussion

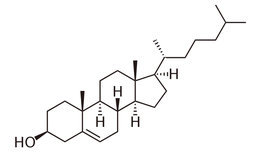
5/6 studies found a significant relationship between high cholesterol and cognitive decline

Strengths

- Primarily RCTs
- Relationships found were statistically significant ($p<.05$)
- Examination through various lenses

Limitations

- Examination through various lenses
- Lack of standardization among independent and dependent variable
- Small sample sizes
- Lack of blinding
- Inclusion of bias (selection, volunteer, recall, reporting, experimenter, and attrition)
- Timeline and Follow-up



Conclusion

Overall, **the studies did not collectively find that lower cholesterol aids in prevention of cognitive decline.**

Given the limitations of the current meta-analysis, **the evidence is insufficient to change current practice.** However, some recommendations can be made. The study fosters support for taking early **heart-healthy actions in the prevention and treatment of AD**. It strengthens support for **clinicians to serve as educators** for their patients on the importance of monitoring their cholesterol.

The current research also paves the way for future studies that aim to delve deeper into the topic and further investigate ways to reduce the burden of disease on the aging population.

Important recommendations for future studies would be to:

➔ Include **larger and more diverse samples** and **longer timeline and follow-up** periods.

➔ Propose the research question among a more cohesive group of studies with more **standardized variables.**

➔ Explore trends across **various demographics**, as such factors often play a role in the development and progression of various disease processes.

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