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Serum Lipids and Hippocampal Volume: The Link to Alzheimer's Disease?

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The association between hippocampal volume (as a presumed index of Alzheimer's disease pathology) with serum total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol was studied in 86 elderly subjects with a range of cognitive functions. High-density lipoprotein cholesterol, but not low-density lipoprotein cholesterol or total cholesterol, was associated with hippocampal volume and dementia. This is compatible with protective effects of high-density lipoprotein cholesterol on hippocampal atrophy and Alzheimer's disease.

Disturbances in brain cholesterol metabolism have been associated with all principal pathological features of Alzheimer's disease (AD): synaptic,[1] amyloid,[2] and tau pathology.[1] Serum cholesterol and brain cholesterol are classically believed to be independent, but experimental,[3] clinical,[4,5] and epidemiological[6] observations suggest the existence of yet unknown signaling or exchange between serum and brain cholesterol.

The hippocampus is particularly vulnerable for AD

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pathology.[7] Macroscopic hippocampal atrophy is already present in the preclinical stages of AD.[8] The hippocampal volume (HcV) as measured by magnetic resonance imaging is a sensitive index of Alzheimer's neurofibrillary changes in demented and nondemented subjects.[9] In light of these findings, the relationship between serum cholesterol and HcV was studied in elderly subjects with a range of cognitive functions.

Subjects and Methods

Subjects aged 75–85 years were recruited to represent a cognitive continuum from normal cognitive function to mild dementia, as previously described.[8] Based on clinical and psychometric methods (for details, see Wolf and colleagues[8]), 26 subjects were cognitively unimpaired, 35 subjects had milder cognitive deficits consistent with modified criteria for mild cognitive impairment, and 25 subjects were mildly demented (clinical dementia rating of 0.5 and 1). They received a diagnosis of Alzheimer-type dementia according to International Classification of Diseases–10 research criteria.

Three-dimensional T1-weighted high-resolution magnetic resonance data sets and T2-weighted magnetic resonance data sets were acquired and processed as previously described.[8] All analyses were performed blind to knowledge of subject identity and clinical status. Total brain volume (BV) and intracranial volume (ICV) were segmented using a previously validated automated region growing procedure.[8] Six hippocampal cross-sections were manually outlined at 3mm intervals in the coronal plane on both hemispheres, and volumes were estimated according to Cavalleri's prinicple (for details and reliability studies see Wolf and colleagues[8]). Left and right HcVs were summed to yield the total HcV estimate. HcVs were normalized to ICV and are reported as percentages of ICV. To yield a severity index of white matter changes, the features were visually assessed periventricular and deep white matter hyperintensities, dilated perivascular spaces, and multiple small lesions on a four-point scale (0, absence; 1, mild; 2, moderate; 3, severe). Lacunar infarcts of 4mm diameter or more were identified and counted (for reliability studies, see Wolf and colleagues[8]). Ratings of periventricular hyperintensities, deep white matter hyperintensities, dilated perivascular spaces, and multiple small lesions were summed to yield the white matter sum score. Infarcts were counted and then categorized (0, absent; 1, one infarct; 2, two infarcts; 3, more than two, ie, "multiple infarcts").

Blood serum was collected using standard sampling tubes. Nonfasting levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using homogenous enzymatic colorimetric in vitro assays (Roche Diagnostics GmbH, Penzberg, Germany). The Apolipoprotein E (ApoE) genotype was analyzed as previously described.[8]

SPSS for Windows (version 10.0.7) was used for statistical analyses. Group comparisons were based on univariate analysis of variance with cognitive group (cognitively unimpaired, mildly cognitively impaired, and demented) and sex as factors or χ^2 tests as appropriate. Correlation analyses were used to assess the association between the three serum cholesterol measures (TC, LDL-C, and HDL-C) and HcV and

BV. To avoid inhomogeneity correlations, partial correlation coefficients between the cholesterol measures and HcV and BV (controlled for ICV) were derived separately for men and women. Using Fisher Z-transforms and Whitehead's standard method for meta-analyses, homogeneous correlations were aggregated to yield common correlation coefficients (r_{aggr}) and their confidence intervals for the whole sample. Linear regression analysis was run with HcV as the independent variable to see whether serum cholesterol measures still independently predicted HcV when a number of samples were considered.

Written informed consent was obtained from all subjects and/or their legal caregivers. The study received approval from the local ethics committee.

Results

The characteristics of the sample are shown in the Table.

Neither TC, LDL-C, nor HDL-C differed between cognitive groups. Women had significantly higher levels of TC (6.4 vs 5.7mmol/L), LDL-C (4.0 vs 3.4mmol/L), and HDL-C (1.5 vs 1.3mmol/L) than men. After transformation into sex-specific Z-scores, having HDL-C in the lowest quartile was associated with a statistically significantly increased relative risk of dementia (relative risk, 1.9; 95% confidence interval [CI], 1.01–3.6). No such risk associations were present for TC and LDL-C (Fig 1).

HDL-C (r_{aggr} = 0.25; 95% CI, 0.04–0.44; p = 0.02), but not LDL-C (r_{aggr} = −0.13; p = 0.2) or TC (r_{aggr} = −0.08; p = 0.5) correlated significantly with HcV (Fig 2). The correlation between HDL-C and BV was also statistically significant (r_{aggr} = 0.29; 95% CI, 0.07–0.47; p = 0.01). There was no statistically sig-

nificant correlation between HDL-C and white matter score (r_{aggr} = −0.128; p = 0.3).

When only nondemented subjects were considered, the statistically significant correlation between HDL-C and HcV remained (r_{aggr} = 0.30; 95% CI, 0.04–0.52; p = 0.02). The correlation between BV and HDL-C was weaker and lost significance (r_{aggr} = 0.19; 95% CI, −0.09–0.43; p = 0.1).

In a linear regression analysis, HDL-C was the only independent predictor (β = 0.258; p = 0.03) of HcV when entered together with LDL-C, age, sex, education, white matter sum score, and infarcts (four multivariate outliers were excluded).

In the sub sample with known ApoE allele status (n = 54), the correlation between HDL-C and HcV had an r value of 0.22 and a p value of 0.1. When the ApoE ε4 allele dose was controlled for, the correlation had an r value of 0.27 and a p value of 0.05. There were no statistically significant group differences in HDL-C between carriers and noncarriers of an ApoE ε4 allele (df 1,52; F = 0.31; p = 0.6).

This result makes it unlikely that possible effects of ApoE allele status on hippocampal volume and serum lipids can solely explain the correlations between HDL-C and HcV.

Discussion

To our knowledge, this is the first study reporting an association between HcV and serum HDL-C in a human in vivo study. In accordance with previous studies,[5,10,11] low HDL-C serum levels were also associated with a higher risk of dementia. However, the associa-

Table. Characteristics of the Sample

Characteristic	NCI (N = 26)	MCI (N = 35)	De (N = 25)	Main Effect of Cognitive Group[a] (p)	Main Effect of Sex[a] (p)
Male (%)	30	32	36	0.70[b]	n/a
Age (yr, SD)	78.5 (3.0)	78.7 (4.1)	77.9 (3.0)	0.63	0.72
Education (yr, SD)	12.2 (2.8)	10.5 (1.8)	11.1 (2.0)	0.34	0.06
MMSE (score, SD)	29.0 (0.7)	26.5 (1.8)	20.6 (4.1)	<0.01	0.10
HcV (% of ICV, SD)	0.21 (0.02)	0.19 (0.03)	0.16 (0.03)	<0.01	0.14
BV (% of ICV, SD)	71 (4)	73 (4)	67 (5)	<0.01	0.21
WML score (sum score, SD)	6.7 (3.1)	7.3 (2.4)	8.2 (3.4)	0.53	0.49
At least one infarct (no. of subjects)	6	10	12	0.13[b]	n/a
TC (mmol/L, SD)	6.1 (1.2)	6.1 (1.3)	6.2 (1.2)	0.81	0.01
LDL-C (mmol/L SD)	3.8 (1.0)	3.7 (1.3)	4.0 (1.0)	0.54	0.04
HDL-C (mmol/L, SD)	1.5 (0.3)	1.5 (0.4)	1.4 (0.4)	0.32	0.04
Casual blood pressure (mean systolic/diastolic)	138/96	137/95	138/92	0.62/0.81	0.79/0.64

[a]Two-way ANOVA with sex and cognitive state as factors if not otherwise stated.
[b]χ^2 test.

NCI = no cognitive impairment; MCI = mild cognitive impairment; De = dementia; SD = standard deviation; MMSE = Mini-Mental State Examination; HcV = hippocampal volume; BV = brain volume; ICV = intracranial volume; WML = white matter lesion; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; n/a = not assessed; ns = nonsignificant.
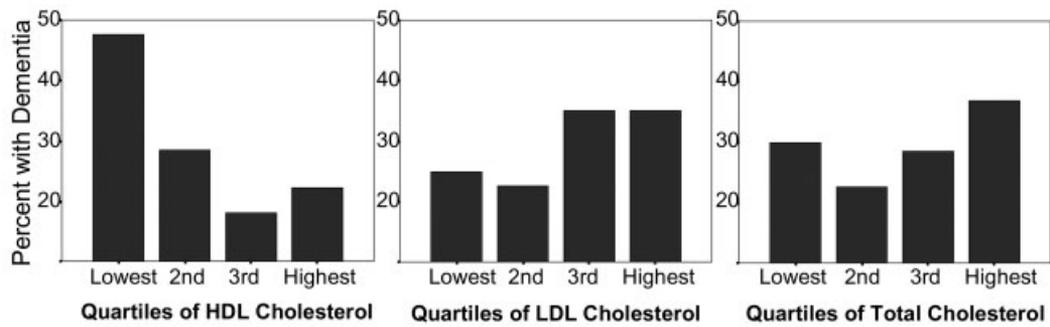
Fig 1. Sex-adjusted quartiles of serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol in relation to the frequency of dementia (n = 86). Having HDL cholesterol in the lowest quartile was associated with a statistically significantly increased relative risk of dementia (relative risk, 1.9; 95% confidence interval, 1.01–3.6). For LDL and total cholesterol, there was no statistically significant association with dementia.

tion between HcV and HDL-C was not due merely to a cluster of patients with AD (having small hippocampi and low HDL-C serum levels) but remained when only nondemented subjects were analyzed. The effects of HDL-C on HcV were small, but they remained statistically significant when controlling for cerebrovascular pathology and ApoE genotype.

The results of this study are compatible with a link between serum HDL-C and HcV, suggesting that high serum HDL-C levels may be protective against hippocampal atrophy. HDL-C in serum and cerebrospinal fluid are highly correlated in humans,[4] adding plausibility to our findings.

These findings could reflect the role of brain lipoproteins and cholesterol to serve the high demands on synaptic plasticity in the hippocampus and other brain regions. Keeping a high level of synaptic plasticity could be protective against AD.[7] Brain lipoproteins exist in the form of HDL-like lipoproteins.[1]

They play a crucial role in cholesterol and apolipoprotein transport. Synaptic growth and regeneration depend greatly on the availability of brain cholesterol.[12] Depletion of cholesterol in tissue cultures inhibits neuritic outgrowth and causes neurodegenerative changes.[1]

Other relevant actions of HDL include the prevention of aggregation and polymerization of amyloid-β protein,[13] antiinflammatory,[14] and antioxidant effects.[15] While our results suggest that the effect of low serum HDL-C levels on HcV was not mediated through macroscopic cerebrovascular lesions, more subtle vascular mechanisms, including temporary or chronic brain hypoperfusion due to systemic atherosclerosis associated with low serum HDL-C levels, cannot be ruled out.

Some obvious limitations need to be addressed. In a cross-sectional design, inversed causation cannot be ruled out: AD or other pathological changes could alter
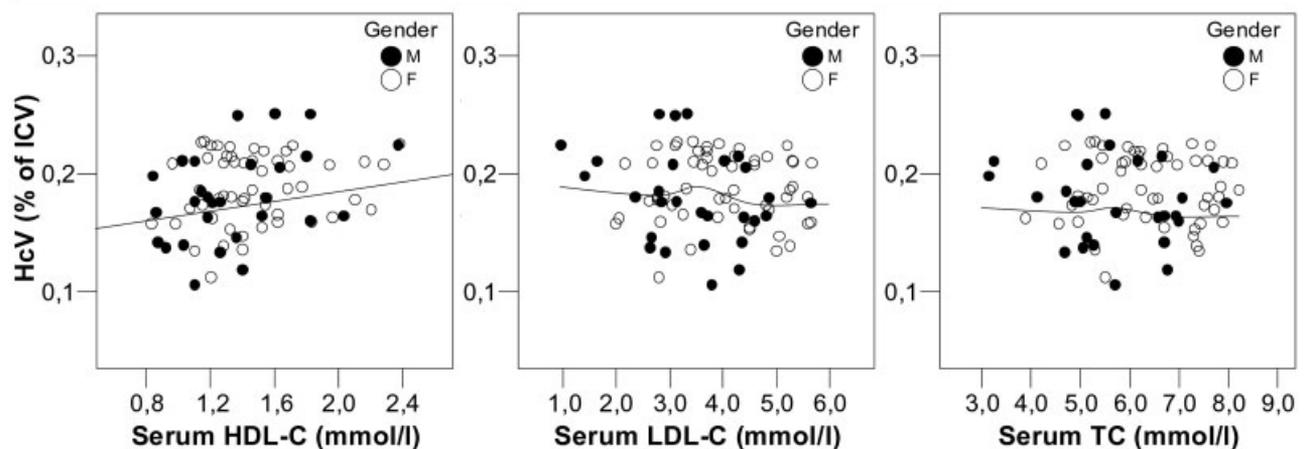

Fig 2. Scatterplot. Serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC) are plotted against hippocampal volume (HcV) in 82 subjects (four outliers were excluded). There was a statistically significant positive correlation between HDL cholesterol and HcV (regression line). No statistically significant correlations were found between HcV and LDL/total cholesterol (locally weighed trend curves). ICV: intracranial volume.

peripheral cholesterol levels. Some possible confounders of serum cholesterol levels and hippocampal volume (eg, physical activities and nutritional factors) were not included. Terminal illness has been associated with alterations in lipid levels, but 3-year mortality in this sample was low (5.8%). Further, it is difficult to estimate how serum cholesterol level changes over time in old-age and dementia disorders could have affected the results. With this regard, the absence of correlations between TC and LDL cholesterol with brain atrophy measures (that would have been indirectly implied by the longitudinal results from epidemiological studies[6]) does not exclude the possibility that hyperlipidemia in midlife is a risk factor for late-life AD and cognitive impairment.

Given these obvious limitations, the results from this study must be regarded as tentative and should be interpreted with caution. Confirmation is mandatory, preferably using longitudinal study designs and larger populations.

Conclusions

In 75- to 85-year-old subjects, high serum HDL cholesterol levels may be protective against hippocampal atrophy, dementia, and possibly AD. These findings could reflect the central role of brain lipoproteins and cholesterol to facilitate synaptic plasticity in the hippocampus and other brain regions. Treatments to increase serum HDL cholesterol could be a promising neuroprotective strategy in AD.

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