Clinical Research and Methods

Cholesterol, Transferrin Saturation, and the Development of Dementia and Alzheimer's Disease: Results From an 18-year Population-based Cohort

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Background and Objectives: *Oxidative stress plays a role in Alzheimer's disease (AD), and iron and cholesterol together have been linked to oxidative stress. This study examined the relationship between transferrin saturation (TS) and cholesterol to see if both are necessary to increase the risk for the subsequent development of AD.* Methods: *We analyzed data from US adults (ages 40–74 years at baseline) followed from baseline in 1971–1974 to 1992 (n=6,558) in the cohort study, the National Health and Nutrition Examination Survey I Epidemiologic Followup Study (NHEFS).* Results: *The unadjusted relative risk of developing AD when both TS and cholesterol were at the 75th percentile was 3.19 (95% CI, 1.31–7.75). In adjusted models when only one marker was elevated, there was no significant increased risk for AD. The risk of AD increased as both markers increased. Even at the 85th percentile, individuals had no significant risk of AD when only having elevated cholesterol (>280 mg/dl) but not elevated TS (39.6%). Findings were similar for individuals with elevated TS but not elevated cholesterol.* Conclusions: *In this population-based cohort, the risk of developing AD when one has both elevated cholesterol and elevated TS is much larger than the risk associated with elevation of either of these factors alone.*

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Free radicals and oxidants are continuously generated within mammalian cells, but they are normally neutralized by the body's antioxidant metabolism. Oxidative stress can, however, damage lipids, proteins, and DNA. Recent evidence has suggested that oxidative stress may play a role in the pathogenesis of Alzheimer's disease (AD).[1]

Iron is a key component in catalyzing the production of reactive radicals and creating oxidative stress. Iron overload, in particular, has been linked to oxidative stress and lipid peroxidation.[2-4] A variety of studies have indicated that metabolism of iron is involved in AD.[5-7] However, these studies have tended to identify the presence of elevated iron in senile plaques, rather than looking at the catalytic role that iron may play in creating oxidative stress in tissue related to AD. It could be that iron does not work alone in the production of senile plaques. This possibility is supported by the evidence that iron supplementation in an undifferentiated pool of patients does not automatically induce oxidative damage.[8] Rather, it may be that iron works in concert with another agent in the production of oxidative stress and/or plaques.

Similar to the evidence concerning iron, a number of studies have found a positive correlation between elevated serum cholesterol at some stage of life and the development of AD.[9-11] Dietary cholesterol has been shown to affect development of amyloid plaques,[12] while statin drugs used to decrease cholesterol levels have been shown to decrease beta-amyloid peptide.[13,14] Some evidence suggests that oxidative stress may be involved in the relationship between cholesterol and AD. Indeed, oxidized low-density lipoprotein seems to play a role in neuronal cell death in AD.[15,16] However, the evidence on whether the presence of iron as a catalyst for potential lipid peroxidation increases the risk of AD development is unclear.

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This study analyzed data from an 18-year cohort representative of US adults. The analysis examined the relationship between transferrin saturation and cholesterol when both were elevated, and when only one was elevated, with the subsequent development of AD.

Methods

This cohort study followed individuals ages 40–74 years at the time of the index interview in the Health and Nutrition Examination Survey I (1971–1974) (NHANES I). The NHANES I baseline data were analyzed with the NHANES I Epidemiologic Followup Studies (1982–1984, 1986, 1987, and 1992) for the same cohort of individuals.

NHANES I was designed to collect extensive demographic, medical history, nutritional, clinical, and laboratory data representative of the noninstitutionalized civilian US population. The survey was a multistage, stratified probability sample of clusters of persons ages 1–74 years. It was conducted from 1971–1975. The NHANES I survey design included oversampling of certain population subgroups, including persons living in poverty areas, women of childbearing age (ages 25–44 years), and persons ages 65 years and over.

The NHANES I Epidemiologic Followup Study (NHEFS) is a national longitudinal dataset that allows investigation of the relationships between clinical, nutritional, and behavioral factors assessed at baseline (NHANES I) and subsequent morbidity, mortality, and institutionalization. More than 98% of the individuals in the initial NHANES I cohort were traced and supplied data in the 1992 NHEFS.

The follow-up information for NHANES was gathered in one of three ways. First, subjects who could be contacted and could participate were interviewed. Surviving subjects were always administered the subject questionnaire. Second, if the subject was alive but incapacitated, a slightly modified version of the subject questionnaire was administered to a proxy respondent. A separate proxy questionnaire was used only when the subject was deceased. Finally, for individuals who had died in the time period between the NHANES I index interview and the follow-up interview, information from death certificates was recorded.

A total of 1,681 proxy respondents were interviewed in the 1992 NHEFS. Of these, 551 responded for an incapacitated subject and were administered a modified version of the subject questionnaire, and 1,130 responded for a deceased subject and thus were administered the proxy questionnaire. Individuals 40 and older who had TS and cholesterol measured at baseline were available for the cohort; those for whom either assessment was unavailable were excluded. These exclusions resulted in an unweighted cohort of 6,558 individuals.

Dependent Variable

Development of Dementia and AD. We chose to measure the general diagnosis of dementia as well as the more specific diagnosis of AD. Using the data supplied in the NHEFS, we identified individuals with dementia and AD through nursing home and hospital records (1982–1984, 1986, 1987, and 1992) as well as death certificates. *International Classification of Diseases, Ninth Edition* (ICD-9) codes representing dementia (290.0 through 290.4, 290.9, 294.1, 331.0, 331.2, and 797) were used to identify individuals who were admitted to a health care facility. The same diagnosis codes were used to identify members of the cohort who died of any of the 20 primary or secondary causes of death. Further, for text descriptions of diagnoses in health care facilities that were captured in the NHEFS, we classified dementia according to the text descriptions of AD, senility, and dementia. For AD only, the ICD-9 code of 331.0 and the text description of AD was used.

Independent Variables

Cholesterol. Total serum cholesterol level was available for analysis from the NHANES I baseline assessment. It is unclear what level of cholesterol is associated with AD risk. Thus, we arbitrarily operationalized elevated serum cholesterol at the 75th percentile for the population (>261 mg/dL). Although other lipids like triglycerides, high-density lipoprotein, low-density lipoprotein, or apolipoprotein e (APOE) might be interesting to explore for oxidized lipoproteins, only total serum cholesterol was available in the NHANES I.

Transferrin Saturation. Transferrin saturation is a well-established marker of body iron stores that may be useful as a predisposition to iron overload and is available in the NHANES I baseline data. As with total serum cholesterol, it is unclear what level of transferrin saturation is associated with AD risk. Thus, we arbitrarily operationalized elevated transferrin saturation initially at the 75th percentile of the population (>34.9%).

Control Variables

To reduce the effects of confounding and examine the independent relationships between transferrin saturation/cholesterol and dementia or AD, we included in multivariate analyses several variables that had been shown in past studies to be associated with the risk of AD. Age, gender, race, education, exercise, being overweight or obese, previously diagnosed diabetes, previously diagnosed hypertension, and high vitamin C intake have all been associated with AD and were included.[17-19] High dietary intake of vitamin C was determined according to a 24-hour dietary history and was operationalized as the 75th percentile (121.9 mg/day), which is similar to the levels used in a previous study in The Netherlands focusing on vitamin C and AD risk.[17]

Data Analysis

We classified the population into four groups based on low and high transferrin saturation and low and high total serum cholesterol levels. Because of the exploratory nature of the examination of the relationship between transferrin saturation and cholesterol with the development of dementia or AD, we began, as noted, by classifying high and low levels at the 75th percentile. Since it is unknown what level of transferrin saturation and cholesterol together connote risk of dementia or AD, after the initial analyses at the 75th percentile for elevated levels we performed analyses at other levels for each marker in an effort to see if increased dementia or AD risk was associated at lower and higher levels. Specifically, we examined elevated transferrin saturation and cholesterol at the 50th, 80th, and 85th percentiles. We could not conduct analyses at the 90th percentile because less than 1% of the population fell in the combined marker elevated group, which was too few individuals to make a reliable population estimate for the survival analysis.

For the analysis of the NHEFS we used sampling weights to calculate prevalence estimates for the civilian noninstitutionalized US population. Because of the complex sampling design of the survey, we performed all analyses with SUDAAN (SUDAAN Statistical Software Center, Research Triangle Park, NC). Using the population estimates generated by SUDAAN, we graphically show the unadjusted relationship between AD and low and high serum transferrin saturation and low and high cholesterol. We performed Cox proportional hazards analysis with time to development of dementia or AD for each group controlling for age, gender, race, education, exercise, body mass index, previously diagnosed diabetes, previously diagnosed hypertension, and vitamin C intake. In these forced inclusion models, time to dementia or AD development was a continuous variable measured in 1-year increments up to 18 years from the baseline. Schoenfeld test of residuals for the pro-

Table 1

Demographics of Adults Ages 40 and Older in NHANES I Baseline Population (1971–1974) With High Transferrin Saturation and Cholesterol Representing >75th Percentile

	TS ≤ 34.9% Cholesterol ≤ 261 mg/dl	*TS ≤ 34.9% Cholesterol > 261 mg/dl*	*TS > 34.9% Cholesterol ≤ 261 mg/dl*	*TS >34.9% Cholesterol > 261 mg/dl*
Total	*n=33,906,115*	*n=12,237,469*	*n=12,122,311*	*n=3,381,975*
Age group (%)				
40–52	47.65	35.97	46.05	31.06
53–69	45.22	54.16	46.34	56.80
≥ 70	7.13	9.87	7.61	12.14
Gender (%)				
Male	47.48	36.63	55.03	44.05
Female	52.52	63.37	44.97	55.95
Race (%)				
White	90.05	90.10	92.24	94.44
Black and other	9.95	9.90	7.76	5.56
Education (%)				
Less than high school	45.39	46.92	43.54	41.41
High school or more	54.61	53.08	56.46	58.59
Exercise (%)				
Much exercise	17.11	18.00	18.65	14.30
Moderate exercise	35.49	33.85	40.26	39.95
Little or no exercise	47.41	48.15	41.08	45.75
Body mass index (%)				
≤ 30	81.29	77.56	90.56	90.44
> 30	18.71	22.44	9.44	9.56
Diabetes (%)				
Yes	4.44	5.48	3.62	2.75
No	95.56	94.52	96.38	97.25
Hypertension (%)				
Yes	18.70	21.81	13.70	16.52
No	81.30	78.19	86.30	83.48
Vitamin C intake (%)				
Low	76.53	72.51	73.87	73.39
High	23.47	27.49	26.13	26.61

TS—transferrin saturation

portionality of hazards assumption within the models was also computed.[20]

Results

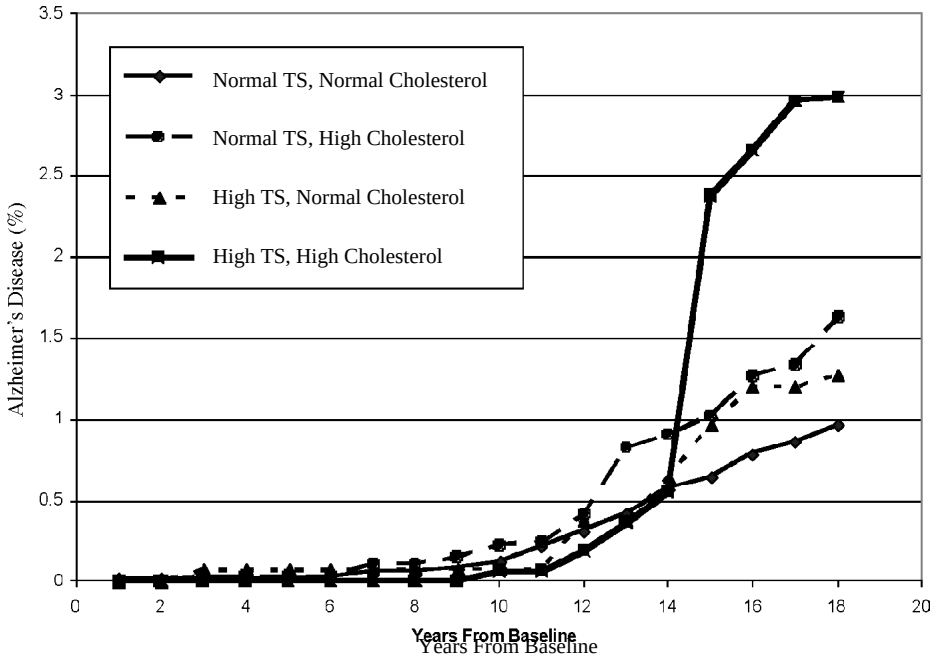
Table 1 shows the demographic characteristics of the population with elevated transferrin saturation (>34.9%) and elevated total serum cholesterol (>261 mg/dl), defined at the 75th percentile level at the NHANES I baseline. Transferrin saturation and total cholesterol were not correlated (r=0.01). At the 75th percentile for both variables, only 5.5% of the adult population (>40 years) had high levels of both transferrin saturation and cholesterol. When the population was defined with elevated markers at the 50th percentile, 24.6% of the population had both elevated transferrin saturation (27.6%) and cholesterol (227 mg/dl).

The unadjusted relationships between development of AD and transferrin saturation and total cholesterol when elevated markers were defined as the 75th percentile are shown in Figure 1. The curves suggest similar risks for the two intermediate groups and greater risk when individuals have both high transferrin saturation and high total cholesterol. Among individuals with elevated transferrin saturation and cholesterol at the 75th percentile, 3.0% developed AD, while 4.7% developed AD at the 80th percentile and 5.3% at the 85th percentile.

When the combined marker groups were analyzed in Cox regressions controlling for potential confounding variables, the group with both high cholesterol and high transferrin saturation levels consistently had the highest risk of developing AD compared to a reference group having low cholesterol and low transferrin saturation (Table 2). Using the cut-off of the 50th percentile for the two risk factors, the risks for transferrin saturation and cholesterol were similar to each other and similar to the risks for the combined elevated group. As the levels increased, the risk for AD for the combined elevated group continued to increase, but the risk for the one-marker groups did not (Table 3). Having only high cholesterol or only high transferrin saturation, with the other of these levels normal, did not increase risk for AD as the levels increased. For dementia, although not as profound as in the case of AD, the combined elevated markers exhibited a pattern of increased risk. However, having elevated cholesterol without elevated transferrin saturation had a consistent adjusted relative risk of dementia of approximately 1.5 from cholesterol levels of 227 mg/dl to 268 mg/dl. The Schoenfeld test for the proportionality of hazards assumption indicated that the assumption was satisfied in the models.

Figure 1

Unadjusted Relation of Alzheimer's Disease With Elevated Cholesterol and Elevated Transferrin Saturation Markers Defined at the 75th Percentile



Years From Baseline

Discussion

In this population-based cohort of adults, our results show that the risk of developing AD when one has both elevated serum cholesterol and elevated transferrin saturation level is much larger than the risk associated with elevation of either of these factors alone. As levels increased, the risk of AD increased only for individuals who were high on both. This demonstration of an increased risk of AD from a combined marker is a novel finding.

Our results are consistent with and also extend previous findings of the risk of elevated serum cholesterol or iron and AD, including studies linking the genetic mutation associated with hemochromatosis, an iron overload disease, to AD.[21,22] Our study

Table 2

Unadjusted Relationships Between Transferrin Saturation and Cholesterol With the Development of Dementia and Alzheimer's Disease

	Dementia HR (95% CI)		*Alzheimer's Disease* HR (95% CI)	
Individual markers based on elevated as >75th percentile				
Normal TS (≤ 34.9%)	1.00	(1.00–1.00)	1.00	(1.00–1.00)
Elevated TS (> 34.9%)	1.11	(0.79–1.56)	1.47	(0.82–2.63)
Normal cholesterol (≤ 261 mg/dl)	1.00	(1.00–1.00)	1.00	(1.00–1.00)
Elevated cholesterol (> 261 mg/dl)	2.06	(1.51–2.81)	1.91	(1.09–3.33)
TS—cholesterol groups				
85th percentile as elevated				
TS ≤ 39.6%—cholesterol ≤ 280 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 39.6%—cholesterol > 280 mg/dl	1.74	(1.16–2.61)	2.00	(1.00–3.99)
TS > 39.6%—cholesterol ≤ 280 mg/dl	1.04	(0.65–1.66)	1.14	(0.49–2.67)
TS > 39.6%—cholesterol > 280 mg/dl	2.97	(1.39–6.33)	4.99	(1.65–15.12)
80th percentile as elevated				
TS ≤ 37.0%—cholesterol ≤ 268 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 37.0%—cholesterol > 268 mg/dl	2.19	(1.53–3.15)	2.09	(1.09–3.99)
TS > 37.0%—cholesterol ≤ 268 mg/dl	1.00	(0.64–1.57)	1.03	(0.45–2.36)
TS > 37.0%—cholesterol > 268 mg/dl	3.21	(1.78–5.80)	4.67	(1.93–11.33)
75th percentile as elevated				
TS ≤ 34.9%—cholesterol ≤ 261 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 34.9%—cholesterol > 261 mg/dl	2.09	(1.46–3.00)	1.78	(0.92–3.44)
TS > 34.9%—cholesterol ≤ 261 mg/dl	1.17	(0.78–1.75)	1.36	(0.66–2.81)
TS > 34.9%—cholesterol > 261 mg/dl	2.34	(1.33–4.14)	3.19	(1.31–7.75)
50th percentile as elevated				
TS ≤ 27.6%—cholesterol ≤ 227 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 27.6%—cholesterol > 227 mg/dl	2.03	(1.32–3.14)	2.69	(1.18–6.14)
TS > 27.6%—cholesterol ≤ 227 mg/dl	1.06	(0.66–1.69)	2.23	(0.97–5.15)
TS > 27.6%—cholesterol > 227 mg/dl	2.09	(1.36–3.21)	2.93	(1.31–6.59)

HR—hazard ratio
TS—transferrin saturation

brings together two separate areas of inquiry, cholesterol and iron in relation to AD, to consider the influence of both factors. Both need to be elevated to increase risk of AD, and the risk increases as the levels increase. Since transferrin saturation and cholesterol were uncorrelated, the present results may suggest the importance of iron as a catalyst for oxidative stress with lipids and the corresponding deleterious outcome of AD. Although we could not measure oxidative stress directly, the results from this population-based cohort appear consistent with that hypothesis.

Limitations

Several limitations to this study must be considered when interpreting our findings. First, our definition of AD was dependent not on autopsies but on nursing home records, hospital records, and death certificates, so some misclassification may have occurred. Our use of both a general diagnosis of dementia and a more specific diagnosis of AD helps in addressing the potential misclassification, but misclassification may still have occurred due to the prevalence of vascular dementia following strokes. When we investigated how many individuals at baseline had reported having had a stroke by their likelihood of developing AD, however, only three individuals fit that criteria.

Second, baseline levels of transferrin saturation and cholesterol may not have remained stable during the period under investigation. Since the transferrin saturation percentages under investigation were all less than levels normally associated with iron overload, it would be unlikely that any intervention would be undertaken to lower those levels. Cholesterol levels may have been modified by interventions. However, the risk for de-

Table 3

Adjusted Cox Regression Using Transferrin Saturation and Total Cholesterol to Predict Time to the Occurrence of Dementia and Alzheimer's Disease*

	Dementia HR (95% CI)		*Alzheimer's Disease HR (95% CI)*	
TS—cholesterol groups				
85th percentile as elevated				
TS ≤ 39.6%—cholesterol ≤ 280 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 39.6%—cholesterol > 280 mg/dl	1.21	(0.82–1.80)	1.50	(0.77–2.93)
TS > 39.6%—cholesterol ≤ 280 mg/dl	1.06	(0.66–1.70)	1.16	(0.49–2.74)
TS > 39.6%—cholesterol > 280 mg/dl	1.96	(0.91–4.19)	3.71	(1.17–11.73)
80th percentile as elevated				
TS ≤ 37.0%—cholesterol ≤ 268 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 37.0%—cholesterol > 268 mg/dl	1.52	(1.08–2.16)	1.56	(0.82–2.95)
TS > 37.0%—cholesterol ≤ 268 mg/dl	1.01	(0.65–1.57)	1.03	(0.45–2.36)
TS > 37.0%—cholesterol > 268 mg/dl	2.07	(1.16–3.72)	3.16	(1.34–7.48)
75th percentile as elevated				
TS ≤ 34.9%—cholesterol ≤ 261 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 34.9%—cholesterol > 261 mg/dl	1.48	(1.04–2.10)	1.32	(0.69–2.52)
TS > 34.9%—cholesterol ≤ 261 mg/dl	1.19	(0.79–1.79)	1.37	(0.65–2.89)
TS > 34.9%—cholesterol > 261 mg/dl	1.55	(0.88–2.73)	2.23	(0.93–5.36)
50th percentile as elevated				
TS ≤ 27.6%—cholesterol ≤ 227 mg/dl	1.00	(1.00–1.00)	1.00	(1.00–1.00)
TS ≤ 27.6%—cholesterol > 227 mg/dl	1.51	(0.98–2.33)	2.09	(0.90–4.86)
TS > 27.6%—cholesterol ≤ 227 mg/dl	0.95	(0.60–1.53)	2.03	(0.86–4.81)
TS > 27.6%—cholesterol > 227 mg/dl	1.28	(0.83–1.99)	1.96	(0.85–4.52)

* Adjusted for age, gender, race, education, body mass index, exercise, diagnosed diabetes, diagnosed hypertension, vitamin C intake

veloping AD is still substantial even if cholesterol was reduced.

Conclusions

In summary, a large proportion of the adult population is at risk for developing AD based on the combined presence of two markers. The implications of the results of this study are far reaching.

Millions of individuals worldwide suffer from AD. However, the results indicate that the synergistic effect of having both markers elevated seems to apply more to AD than to the more generalized construct of dementia. This could be because of the effect of lipid peroxidation on the development of senile plaques, which is important in the pathology of AD but not for other types of dementia. In fact, elevated cholesterol levels without elevated transferrin saturation yielded a consistent significant risk for dementia at a variety of increasing levels. The findings of risk for dementia but not AD with elevated cholesterol but not elevated transferrin saturation seems consistent with the classification of both vascular dementia and AD within the dementia category.

By lowering transferrin saturation through a technique like phlebotomy or by lowering cholesterol, perhaps oxidative stress could be decreased. If oxidative stress is the mechanism by which these two combined markers yield this increased risk, decreasing oxidative stress may prevent the formation of plaques and may alleviate or prevent the destruction of the brain seen in AD.

Slowing the disease progression by decreasing amyloid plaque formations may not only extend the life of an AD patient but also the quality of life. Prevention of AD may benefit from a focus on both cholesterol and transferrin saturation. Future research should focus on the potential production of oxidative stress and deleterious outcomes associated with elevated iron and lipids.

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