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Lipids and Adipokines as Risk Factors for Alzheimer's Disease

Matthew W. Warren¹, Linda S. Hynan¹, Myron F. Weiner¹, and Texas Alzheimer's Research and Care Consortium²

¹University of Texas Southwestern Medical Center at Dallas

Abstract

To determine if measures of adipokines and other blood lipids differentiate between normal controls (NC) and persons with Alzheimer's disease (AD), we examined levels of leptin, adiponectin, total cholesterol, high density lipoproteins (HDL), calculated low density lipoproteins (LDL), triglycerides and apolipoprotein E allele status in 196 early AD subjects and 198 normal controls. We were unable to demonstrate a significant difference between leptin and adiponectin levels between NC and AD subjects. We were able to confirm observations of others of lower HDL and higher LDL cholesterol concentration in AD subjects than in controls. As expected, the presence of the apolipoprotein E4 allele distinguished between the two groups.

Keywords

Cholesterol; Leptin; Adiponectin; Alzheimer's Disease

Introduction

For many years, it has been suspected that Alzheimer's Disease (AD) is a generalized metabolic disorder, but little hard evidence has emerged to confirm this suspicion. In support of this notion, some studies have suggested that being overweight or obese in middle age is a risk for later development of AD [1, 2]. Additionally, a consistent observation is that persons with AD, despite unchanged eating habits, begin to lose weight several years prior to the onset of clinical symptoms, suggesting a link between adipose tissue metabolism and AD [3, 4], although a recent study purports a link between brain atrophy and loss of lean mass [5]. Interestingly, both obesity and underweight have been found coincident with the presence of AD [6].

Leptin is a hormone secreted by adipose tissue that acts to suppress appetite and regulate energy expenditure. Similarly, adiponectin is a hormone secreted by adipose tissue that is

Corresponding author: Myron F. Weiner, M.D., 5323 Harry Hines Blvd., Dallas TX 75390-9129. Phone 214-648-9353, Fax 214-648-2031, Myron.weiner@utsouthwestern.edu.

²Investigators from the Texas Alzheimer's Research and Care Consortium: Baylor College of Medicine: Rachelle Doody, MD, PhD, Susan Rountree, MD, Violeta Capriles, Christie Ballantyne, MD, Eveleen Darby, Tracy Dawson, Aline Hittle, Aisha Khaleeg; Texas Tech University Health Science Center: Sid O'Bryant, PhD, Paula Grammas, PhD, Benjamin Williams, MD, Chuang Kuo Wu, Yan Zhang, Gregory Schrimsher, Andrew Dentino, MD, Parastoo Momeni, PhD, Larry Hill; University of North Texas Health Science Center: Thomas Fairchild, PhD, Janice Knebl, DO, Robert Barber, PhD, Douglas Mains, Lisa Alvarez; University of Texas Southwestern Medical Center: Perrie Adams, PhD, Roger Rosenberg, MD, Joan Reisch, PhD, Ryan Huebinger, PhD, Doris Svetlik, Janet Smith Mechelle Murray, Tomequa Sears; University of Texas Health Science Center – San Antonio: Donald Royall, MD, Helen Hazuda, PhD, Raymond Palmer, PhD Marsha Polk.

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involved with modulation of food intake and glucose and lipid metabolism. It also has anti-inflammatory properties and protects against diabetes and atherosclerosis. Excessive body fat accumulation is associated with increased levels of leptin and reduced adiponectin [7, 8].

There is evidence of a relationship between adipokines and AD. In rodents, leptin modulates production and clearance of beta amyloid (A β) [9, 10]. Mice with leptin receptor disruption show impaired long-term potentiation, synaptic plasticity and spatial learning [11]. When treated with leptin, transgenic mice have shown increase in A β and tau clearance as well as amelioration of AD-like pathology [12]. In humans, recent studies have suggested an association between higher leptin levels and a reduced incidence of dementia and AD [13]. Additionally, the Health ABC study showed leptin to have a modest protective effect against cognitive decline [14]. Conversely, low leptin levels in older adults appear to be associated with the later development of AD and other dementias [13] and are decreased in AD patients with inappropriately low weight, suggesting a malfunction on the hypothalamic level [15]. This has led to the suggestion of leptin as a novel therapeutic strategy for treating AD [16]. Adiponectin has not yet been investigated with regard to its possible effect on cognition [17].

Cholesterol metabolism has also been studied for its effects on AD. The brain contains 23mg of cholesterol (primarily in the form of myelin) per gram of tissue. While virtually no exogenous cholesterol crosses the blood brain barrier [18], it is shed in minute amounts from the brain. This brain-derived cholesterol is transported in the blood stream as 24S-hydroxylcholesterol [19], whose concentration is highly correlated with total cholesterol [20].

Agents that alter cholesterol concentration have also been studied with respect to effects on AD. For example, A β production can be inhibited in hippocampal neurons in vitro by using cholesterol lowering agents [21]. Amyloid precursor protein (APP) transgenic mice show a relationship between hypercholesterolemia and beta-amyloid deposition and plaques [22]. In guinea pigs, simvastatin reduces A β in CSF and brain homogenate [23] while rabbits fed high cholesterol diets show increased A β -like reactivity in the brain [24].

Post mortem human studies suggest that elevated total and LDL cholesterol are associated with neurofibrillary tangles and ApoE4 status, but not plaques [25]. Increased LDL has also been shown to increase white matter change detected by magnetic resonance imaging [26]. Two Finnish studies suggest a relationship between high total cholesterol and the incidence of AD, independent of ApoE4 status [27, 28]. However, in the Framingham study and an additional HMO study, there was no association between total cholesterol and AD [29, 30]. With regard to LDL specifically, in one community study, high LDL was associated with development of dementia with stroke, but not probable AD, and there was no association with HDL or total cholesterol [31]. For HDL, one prospective study suggested high HDL was associated with decreased risk of AD, but so were total and non-HDL cholesterol unless adjusted for vascular risk factors or lipid lowering agents [32].

In this study, individuals with AD and normal controls participating in the Texas Alzheimer's Disease Research and Care Consortium (TARCC) Longitudinal Research Cohort were examined for relationships of lipid metabolism with disease state.

Materials and Methods

Participants included 347 individuals (150 diagnosed with Probable AD and 197 cognitively normal controls; NC) enrolled in the TARCC Longitudinal Research Cohort. The methodology of the TARCC project has been described in detail elsewhere [33]. Of note, this is not a population based study but rather a cross-sectional sample of referred or self-

referred subjects who had presented for evaluation or responded to recruitment advertisement. Briefly, each participant completes an annual examination consisting of a medical examination, interview, blood draw, and neuropsychological testing at one of the five TARCC sites. These data are reviewed by each site's consensus committee and diagnosis is assigned according to National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria with only those meeting criteria for Probable AD included in the study [34]. Controls were judged to be within normal limits on neuropsychological testing by consensus review. Participants with AD were studied at a relatively early stage of the disease and the Clinical Dementia Rating (CDR; Morris, 1993) global scores were as follows: 1=79, 2=53, 3=16 [35]. Subjects thought to have vascular dementia were excluded. The TARCC project received Institutional Review Board approval and all participants and/or caregivers signed written informed consent documents.

Demographic variables collected for the two groups were age, gender, years of education and body mass index (BMI). Laboratory values collected included serum leptin, adiponectin, total cholesterol, high density lipoproteins (HDL), calculated low density lipoproteins (LDL), triglycerides and apolipoprotein E allele status (ApoE4).

Statistical Methods

Categorical measures for the two groups were compared using Chi-squared tests or Fisher Exact tests, as appropriate. Consideration of skewness and kurtosis suggested non-parametric tests were appropriate for leptin, adiponectin, total cholesterol, HDL and triglycerides (data not shown). For this reason, the more conservative Mann-Whitney U test was used in all analyses of continuous data. To determine which variables best predicted disease status (AD versus NC), three separate logistic regression models (demographic values, laboratory values, and demographic and laboratory values combined) were performed for the entire sample, as well as for men alone and women alone. In these analyses the Wald method was used, with a p to enter of 0.15 and a p to remove of 0.20. Since total cholesterol is composed of measures of HDL, LDL and triglycerides, this measure was not included as a factor. IBM SPSS version 19 (IBM, Inc., Chicago, IL) was used for all analyses. Statistical significance was set to $p < 0.05$ except where noted and all statistical tests were 2 sided. The assumptions of normality and equality of variances were examined for the total sample and for the AD and NC groups separately.

Results

The total sample included 347 participants with complete laboratory panels (150 AD subjects and 197 normal controls). Table 1 presents the medians, range and p-values for each demographic and laboratory variable for the two groups. The AD group was significantly older and had higher total cholesterol and LDLs while the NC group had higher education, BMI and HDLs. Leptin, adiponectin and triglycerides were not significantly different between these two groups.

Table 2 provides the results for prediction of disease status (AD vs NC) by logistic regression. The results obtained from demographic or laboratory values alone were well described by the combination of these measures; we report the results for the combination of these measures. When considering the entire sample, factors that predicted membership in the AD group included older age, lower education, lower HDL, higher LDL and having one or more ApoE4 alleles. BMI, leptin, adiponectin and triglycerides were not significant predictors. When considering men only, factors significantly increasing risk of being in the AD group included lower education, lower HDL and having one or more ApoE4 alleles. Age, BMI, leptin, adiponectin, LDL and triglycerides were not significant. Finally, when

considering women only, factors significantly increasing risk of being in the AD group included older age, fewer years of education, lower HDL, higher LDL and the presence of one or more ApoE4 alleles. A trend was found for BMI (p-value = 0.064) with the median for the AD group lower than for the NC group. Leptin, adiponectin and triglycerides were not significant.

Discussion

This study fails to show a robust association between plasma leptin or adiponectin concentration and AD. However, consistent with the findings of others, the leptin levels in ADs were lower than those of the controls [13–16]. Leptin has been shown to decrease in a stepwise fashion with increasing AD severity as measured by the Mini-Mental Status Exam (MMSE [36]) [37]. In a post-hoc analysis, we found no difference in mean leptin among groups of subjects separated by CDR scores (one-way ANOVA, $p=0.299$, see Figure 1). We also separated subjects in AD and NC groups by status of ApoE4 (at least one allele present versus none) while measuring leptin. A one-way ANOVA showed a significant difference among groups ($p=0.034$) while a post-hoc Bonferroni measure showed the group of NCs with an ApoE4 allele present having higher leptin than the NCs with no ApoE4 ($p=0.024$, see Figure 2). The NC group with ApoE4 did not have significantly higher leptin than either AD group with or without ApoE4 ($p=0.121$ and 0.188 , respectively). There was no difference in leptin between NCs without ApoE4 and ADs or among ADs with or without an ApoE4 allele. This may suggest a protective effect for leptin among carriers of ApoE4 who have not developed AD.

AD patients are known to lose weight during the course of the disease and predictably, our AD subjects had a lower BMI compared to controls. Since leptin is produced proportionately to fat, the levels of leptin should be higher in a group with greater BMI. This dependence on adiposity may explain the lack of contribution of leptin in our logistic regression model. Leptin resistance is known to increase with adiposity [38] and factors which modulate resistance increase with age [39, 40]. These effects may be contributing to the observed results.

While adiponectin has not been explicitly studied for its role in cognitive decline, it is known to vary inversely with BMI, which is seen in our subjects. The difference in median however did not show a trend when controlling for other demographic and biochemical variables in the logistic regression models. However, our protocol measures total adiponectin whereas some studies suggest measuring high molecular weight (HMW) adiponectin or a HMW/total adiponectin ratio as a more sensitive measure in relation to cardiovascular risk [17].

Consistent with the literature on cholesterol metabolism, higher HDL appeared to predict lower chance of being in the AD group, while higher LDL appeared to be a risk factor [32]. In addition, median total cholesterol was greater in ADs, consistent with at least one nursing home study [25]. Triglycerides did not differ between NC and AD subjects. LDL cholesterol was not a significant predictor in men when controlling for other demographic and biochemical variables, suggesting differential effect of LDL action in men versus women. If this finding is confirmed, it could lead to change in treating risk factors for AD. That is, while statins may be appropriate in women, men may also need treatment with niacin to elevate HDL. Unfortunately, one recent randomized trial reported no benefit using simvastatin for delaying the progression of AD [41].

BMI was significantly lower in the ADs by about two points. While this did not appear to be a factor predictive of AD for men, it trended towards significance with women ($p=0.064$).

While central obesity in middle age is reportedly predictive of AD, these data were not available in our sample and the results may reflect weight loss after onset of disease. It is possible that other lipid modulators are involved in the genesis of AD, for example, LDL receptors may have a role in amyloid precursor protein catabolism and A β cellular transport [42].

Limitations

In our sample, the AD patients were by median 9.5 years older than normal controls and also had 2 years less education. As age and education are known to be independent predictive factors for cognitive decline [43–45], they may influence some of the other comparisons. For example, our normal controls might be persons who have not yet developed AD. Logistic regressions control for age and education, however, and despite these differences still suggest the effects of cholesterol metabolism.

Because this was a cross-sectional study, we could not determine if leptin and adiponectin levels were risk factors for developing AD. The difference in weight between control and AD groups may have been partly attributable to the difference in age. We do not believe that the difference in mean age between control and AD group affected our results as leptin and adiponectin levels do not vary independently with age [46, 47].

With regard to leptin, some studies have suggested an ultradian rhythm to plasma levels [48]. In this study, blood samples were collected at non-standard times and fasting was not required. This may have affected the data. Additionally, researchers have purported the effects of leptin resistance as more contributory than plasma leptin levels [49]. Leptin resistance was not measured in this study but it would be of interest for a future direction.

Conclusion

We were unable to demonstrate a significant difference between leptin and adiponectin levels between NC and AD subjects. We were able to confirm observations of others of lower HDL and higher total and LDL cholesterol concentration in AD subjects than in controls. With a greater understanding, optimization of cardiovascular and metabolic risk factors for AD may slow, but perhaps not cease, progression of symptoms.

Acknowledgments

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Figure 1. Mean Leptin + SEM by CDR Score. A one-way ANOVA comparing mean leptin among subjects with varying CDR scores showed no significant difference ($p=0.299$).

Figure 2.

Mean Leptin + SEM by Alzheimer's Disease state and ApoE4 allele status. A one-way ANOVA revealed a difference among groups ($p=0.034$) with a post-hoc Bonferroni analysis identifying the group of Normal Controls with ApoE4 presents as higher than the Normal Controls without ApoE4 ($p=0.024$). Differences among other groups were not significant.

Table 1

Mann-Whitney U and Chi-squared tests for similarity between AD group and controls.

Factor	Median (range)		Mann-Whitney
	ADs (n=150)	Controls (n=197)	p-value
Age (years)	79.5 (37)	70 (38)	<0.001
Education (years)	14 (22)	16 (13)	<0.001
BMI	25.0 (25)	26.8 (26)	<0.001
Leptin (ng/ml)	11.00 (114)	16.00 (116)	0.148
Adiponectin (µg/ml)	5.75 (32)	5.1 (18)	0.101
Total Cholesterol (mg/dl)	212 (278)	200 (393)	0.039
HDL (mg/dl)	67 (138)	70.6 (211)	0.020
LDL (mg/dl)	106.8 (219)	88.3 (223)	<0.001
Triglycerides (mg/dl)	172 (608)	165 (516)	0.686
	Percent		Chi-squared p-value
Sex (% female)	70.0	69.0	0.847
ApoE4 (% carrier)	57.3	26.2	<0.001

Table 2

Logistic regression results comparing AD group and controls.

Factor	Total sample (n=347)		Men only (n=103)		Women only (n=241)	
	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value
Age	1.102	<0.001	0.096	0.757	1.131	<0.001
Education	0.862	0.003	0.763	0.002	0.851	0.019
BMI	0.948	0.090	0.033	0.855	0.931	0.064
Leptin	0.076	0.783	0.827	0.363	0.919	0.378
Adiponectin	0.089	0.765	0.025	0.875	0.476	0.490
HDL	0.976	0.001	0.968	0.045	0.980	0.028
LDL	1.017	<0.001	1.143	0.214	1.020	<0.001
Triglycerides	0.059	0.808	0.308	0.579	0.804	0.370
ApoE4 carrier	4.002	<0.001	4.248	0.004	5.188	<0.001