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Statin Users Without an APOE- ϵ 4 Allele have Increased Insulin Resistance

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Abstract

The present study examined the relationships among statin use, APOE genotype, and insulin resistance as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) in healthy older adults. APOE ϵ 4- (i.e., not having an ϵ 4 allele) statin users had higher HOMA-IR values compared with ϵ 4+/statin users ($p = 0.0169$), and with non-users who were ϵ 4- ($p = 0.0003$) or ϵ 4+ ($p = 0.0006$). These results suggest that statin use may modulate insulin levels for individuals without an APOE ϵ 4 allele.

Keywords

Statin; insulin; Alzheimer's disease; dementia; diabetes

Introduction

Alzheimer's disease (AD) has grown in prevalence and is reaching epidemic proportions. Two important risk factors for AD are the presence of the apolipoprotein E (APOE) ϵ 4 allele and insulin resistance (the reduced ability of insulin to dispose of glucose in the periphery). APOE genotype is currently the strongest genetic risk factor for the development of AD[1]. Our work and the work of others has also implicated insulin resistance as a risk factor for AD[2]. Epidemiological studies show an increased risk for AD in people with diabetes or impaired glucose tolerance/insulin resistance [3–5]. Clinical studies also demonstrate increased signs of insulin resistance in patients with AD[6,7]. Our work has demonstrated that patients with AD have lower glucose disposal rates, hyperinsulinemia, and lower cerebrospinal fluid (CSF) to plasma insulin ratios[5,8], and that these characteristics are modulated by APOE genotype [9].

The relationship between insulin resistance and APOE genotype may be related in part to their effects on lipid metabolism. ApoE is a cholesterol transport molecule, and insulin is a primary regulator of lipid metabolism, stimulating lipogenesis and reducing lipolysis. In adipocytes, insulin resistance leads to accelerated lipolysis and increased free fatty acid (FFA) levels. In turn, excess FFA influx into the liver inhibits insulin suppression of hepatic very low-density lipoprotein (VLDL) secretion, an essential process for preventing post-

prandial hyperlipidemia. Acute inhibitory effects of insulin on VLDL production are essential for rapid hepatic adaption to metabolic shifts between fasting and feeding in order to maintain plasma lipids within an optimal physiologic range [10]. Thus, insulin resistant adults have higher and more prolonged post-prandial excursions of VLDL and other deleterious lipids.

The effects of both insulin and APOE genotype in patients with AD may be, in part, lipid related. Hyperlipidemia is associated with increased AD pathology in a transgenic mouse model[11]. Epidemiological studies show increased lipid levels associated with AD[12]. Elevated cholesterol levels in mid-life can lead to a 2 to 3-fold increased risk of AD[13]. This pattern may explain in part the increase in risk associated with APOE ϵ 4 carriage, given that ϵ 4 carriers have higher total and LDL cholesterol levels than do adults without the ϵ 4 allele[14]. Statin lipid-lowering agents (LLAs), HMG-CoA reductase inhibitors that are often used to treat high cholesterol, may reduce the risk of Alzheimer's disease [15,16]. Interestingly, statin use has been shown to affect insulin sensitivity, although the nature and direction of the effects has been inconsistent across studies[17]. Given the interrelationships among insulin, dyslipidemia, and APOE genotype, we sought to determine whether statin use and APOE genotype modulated insulin resistance as indexed by the homeostasis model assessment of insulin resistance (HOMA-IR) in healthy older adults.

Materials and Methods

All studies were approved by the University of Washington Institutional Review Board and the VA Puget Sound Research and Development Committee. All subjects gave written informed consent prior to study participation. Subjects were 251 cognitively intact and 87 memory impaired (30 with AD, 57 with amnesic mild cognitive impairment [MCI]) older adults in good general health who participated from 1997 to 2009 in our research studies exploring the relationship of insulin resistance and memory in aging adults. Exclusionary criteria included diabetes, neurodegenerative disorders other than Alzheimer's disease, head trauma with loss of consciousness > 30 min., large vessel CVA, use of antipsychotic medications and medications known to affect cognition or glucoregulation. As previously described in our work, AD was diagnosed by NINCDS/ADRA criteria[18] and MCI, widely regarded as an AD prodrome, by Petersen's criteria[19]. Subject characteristics are provided in Table 1.

Venous fasting blood was acquired and assayed for insulin by RIA, as previously described[20] and for glucose by the glucose oxidase method (Beckman Instruments, Fullerton, CA) or the HemoCue system (Ängelholm, Sweden). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma insulin (FPI) in μ U/mL times fasting plasma glucose (FPG) in mM/L divided by 22.5 ($\text{HOMA-IR} = [\text{FPI} * \text{FPG}] / 22.5$)[21].

HOMA-IR was analyzed with analysis of covariance (ANCOVA), and pair-wise *t*-tests were conducted. ANCOVA factors were statin-use (no or yes), APOE genotype (ϵ 4 carrier = ϵ 4+ or ϵ 4 non-carrier = ϵ 4-), and memory diagnosis (AD/MCI or intact); covariates included in the model were age, body mass index (BMI), Mattis Dementia Rating Scale[22] (DRS; a continuous measure of cognitive status), and age. Pearson *r* correlations were calculated to examine the relationships among HOMA-IR, FPI, FPG, age, DRS, and BMI.

Results

Memory diagnosis did not contribute significantly to the model and was removed from further analyses. For the remaining variables, the omnibus F-test was significant [$F(7,331) =$

8.86, $p < 0.0001$]. Statin users had significantly higher HOMA-IR values than did non-users, $F(1,337) = 3.95$, $p = 0.0478$ (Figure 1A). Carriers of an APOE $\epsilon 4$ allele ($\epsilon 4+$) had significantly lower HOMA-IR values than did non-carriers ($\epsilon 4-$), $F(1,337) = 5.57$, $p = 0.0188$ (Figure 1B). Statin use moderated the relationship between APOE genotype and HOMA-IR values, $F(1, 337) = 3.96$, $p = 0.0473$ (Figure 1C). Post hoc comparisons revealed higher HOMA-IR values for APOE $\epsilon 4-$ statin users compared with $\epsilon 4+$ /statin users ($p = 0.0169$), and with non-users who were $\epsilon 4-$ ($p = 0.0003$) or $\epsilon 4+$ ($p = 0.0006$).

In exploratory analyses designed to characterize APOE allele-dose effects, we repeated the ANCOVA but substituted a three-level APOE factor (levels = 0, 1, 2 $\epsilon 4$ alleles). As shown in Figure 1D, the pattern of means support an allele-dose effect, but statistical significance was not reached due to insufficient numbers of APOE- $\epsilon 4$ homozygotes.

Across all subjects ($n = 338$), increases in HOMA-IR, indicating increased insulin resistance, were associated with expected increases in FPI ($r = 0.9785$, $p < 0.0001$), FPG ($r = 0.2866$, $p < 0.0001$), and BMI ($r = 0.3011$, $p = 0.0006$), and a higher BMI was associated with increased FPI ($r = 0.2918$, $p = 0.0001$) and statin use ($r = 0.1832$, $p = 0.0007$). Finally, BMI and DRS were not significantly related in the total sample or for $\epsilon 4-$ subjects, but BMI rose as DRS increased in $\epsilon 4+$ subjects ($n = 89$, $r = 0.2625$, $p = 0.093$).

Discussion

This is the first study to suggest that statin users without the APOE- $\epsilon 4$ risk factor have greater insulin resistance as indexed by greater HOMA-IR values than do APOE- $\epsilon 4$ carriers or non-statin users. These results raise the possibility that cognitive benefits associated with statin use for APOE- $\epsilon 4$ carriers but not non-carriers in a recent AD trial[23] may be due in part to improved insulin function. The direction of this effect is interesting because as previously noted $\epsilon 4$ carriers have been found to have both higher total and LDL cholesterol levels than do adults without the $\epsilon 4$ allele and also to demonstrate increased AD pathology in a transgenic mouse model.[11,14] As such, it would not have been surprising to see $\epsilon 4$ carriage as a risk factor that causes increased hyperlipidemia, inflammation, and reduced insulin function, at least as it pertains to a model that does not include statin medications. However, other studies have also shown this inconsistent effect direction when introducing statins into an APOE and insulin model[17].

A massing research body has supported the idea that statin use reduces the likelihood of developing or progressing to dementia. However, researchers have argued both for and against the hypothesized protective effect of statins on AD. For example, a large cohort study found no decreased risk of dementia for statin users[24] and statin users in the Religious Orders Study were also no more likely to develop incident AD nor a drop in cognitive scores.[25] Conversely, a re-examination of the ACT study in 2007 found that statin use at some point in participant's lifetime left to significantly reduced neurofibrillary tangle burden at autopsy.[16]

This controversy may be due in part to the possibility that all statins may not be equal in their proposed neuroprotective effects on dementia. Riekse et al[15] found that simvastatin, a CNS-penetrant, reduced CSF levels of phospho-tau-181 (a bio-marker of AD) in younger, cognitively normal participants. Conversely, Wolozin et al[26] established a lower prevalence of AD in those taking lovastatin and pravastatin, with no effects for simvastatin. However, a recent 2009 analysis of the Rotterdam Study which included 6992 participants found a reduced risk of AD for those taking statin medications, regardless of lipophilicity. [27] The current study did not have enough participants to determine relative effects of lipid soluble vs. non-lipid soluble statins. Additionally, the number of statin users in the current

study was small; as such caution should be exercised in interpretation. However, the results are consistent with differential patterns of insulin function for APOE ϵ 4 carriers. Further prospective studies may elucidate the mechanisms underlying the associations among statin use, insulin activity and APOE genotype.

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D

Figure 1.

Insulin resistance, statin use, and APOE genotype. HOMA-IR values were significantly higher (indicating more insulin resistance) (1A) for statin users than non-users, $p = 0.0478$, and (1B) non-carriers of an APOE $\epsilon 4$ allele ($\epsilon 4^-$) than APOE $\epsilon 4$ carriers ($\epsilon 4^+$), $p = 0.0188$. (1C). Statin use moderated the relationship between APOE genotype and fasting insulin levels, $p = 0.0473$, and (1D) exploratory analyses suggested an allele-dose effect, which did not reach significance.

Table 1

Subject Characteristics.

	Statin Non-Users		Statin Users		p-value
	APOE ε4- (n = 201)	APOE ε4+ (n = 81)	APOE ε4- (n = 39)	APOE 4+ (n = 17)	
Gender (F/M)	95/106	43/38	17/22	7/10	0.5950
Mem imp (MI/intact)	48/153	33/48	3/36	3/14	0.0007
FPG (mmol/L)	5.39±0.82	5.47±0.83	5.67±0.69	5.88±0.46	0.0058
FPI (pmol/L)	84.0±70/8	81.3±60.4	129.9±88.9	80.6±44.4	0.0018
Age (yrs)	73.1±7.1	72.5±7.0	74.9±5.8	73.1±7.5	0.3699
BMI (kg/m ²)	26.3±4.7	25.9±4.4	28.7±4.9	28.2±4.2	0.0071
DRS	136.4±9.1	130.3±15.9	138.5±4.3	137.6±5.1	0.0001
Education (yrs)	15.0±2.7	14.7±2.5	14.7±2.6	14.8±2.5	0.7626

Gender (F/M = female/male) and Mem imp (MI/intact = memory impaired/cognitively intact individuals) are expressed as sample sizes; p-values were derived from χ^2 tests. FPG (fasting plasma glucose; sig. by statin use, $p < .01$), FPI (fasting plasma insulin; sig. by APOE and Statin use and APOE $\times$ Statin use, $p < .05$), Age, BMI (body mass index; sig. by statin use, $p < .01$), DRS (Mattis Dementia Rating Scale; sig. by APOE, $p < .01$ and Statin use, $p < .05$), and Education are expressed as mean±standard deviation; p-values were derived from two-way ANOVAs (statin use by APOE genotype) without covariates. The DRS is a measure of overall cognitive function; test ceiling = 144, suggested dementia cutoff = 123.