HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2019 February 22.

Published in final edited form as:

J Alzheimers Dis. 2019 ; 67(1): 257–263. doi:10.3233/JAD-180682.

Retinol Binding Protein 4 Levels Are Not Altered in Preclinical Alzheimer's Disease and Not Associated with Cognitive Decline or Incident Dementia

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Abstract

Accumulating evidence suggests that disparate pathways from systemic metabolism to retinoic acid/vitamin A signaling can contribute to Alzheimer's disease (AD) pathobiology. Retinol binding protein 4 (RBP4) is an adipocyte-secreted hormone (adipokine) that regulates insulin signaling and is also a key transporter of retinoic acid and its derivatives. While earlier studies found alterations in the brain and cerebrospinal fluid (CSF) levels of RBP4 in later stages of AD, it is not known if circulating RBP4 is altered in preclinical AD or if it can be a useful biomarker for cognitive decline and dementia. In this study, we used ELISA to measure plasma RBP4 levels in cognitively normal individuals (Clinical Dementia Rating, CDR 0). Subjects with preclinical AD were identified by previously established CSF criteria (preclinical AD: 20 men, 18 women; control: 45 men, 73 women). Plasma RBP4 levels were similar between preclinical AD and control subjects in men (preclinical AD: 30.0 ± 7.4 μg/mL; control: 30.0 ± 8.7 μg/mL; $p = 0.97$) and women (preclinical AD 30.9 ± 7.9 μg/mL; control: 31.7 ± 8.5 μg/mL; $p = 0.72$). Additionally, RBP4 levels were not related to body mass index or CSF AD biomarkers levels of amyloid-β_{42}, tau, or phosphorylated tau. Baseline plasma RBP4 levels were not associated with the incidence of CDR ≥ 0.5, all-cause dementia, or AD diagnosis. Collectively, these results do not support peripheral RBP4 as a clinical biomarker or therapeutic target in the early stages of AD.

Keywords

Alzheimer's disease; amyloid beta-peptides; enzyme-linked immunosorbent assay; metabolism; plasma; retinol binding proteins

INTRODUCTION

Recent clinical trial failures suggest that targeting Alzheimer's disease (AD) during the earliest stages provide the best opportunity for developing effective disease modifying therapies [1]. Therefore, it is critical to understand the underlying pathological processes

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Handling Associate Editor: Michelle Mielke

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0682r2).

during the preclinical stage of AD, where neuropathological abnormalities like amyloid- β (Aβ) and tau can accumulate several years to decades before any significant cognitive decline [2]. The exact pathogenesis of AD remains elusive and is likely multi-factorial. Accumulating evidence suggests that dysfunction in disparate pathways from systemic metabolism to retinoic acid signaling can all contribute to AD pathobiology. For example, insulin resistance and late life weight loss have been associated with AD pathology [3], while retinoic acid and its derivative vitamin A can modulate Aβ plaque formation and hippocampal function [4, 5]. However, it is unclear if these two pathways share a common neurobiological process especially early in AD.

Retinol binding protein 4 (RBP4) is a secreted protein that has been associated with both the regulation of systemic metabolism and retinoic acid signaling. RBP4 is expressed in adipocytes and can circulate as an adipocyte-derived hormone or adipokine [6]. In animal models, high levels of RBP4 are associated with insulin resistance and could impair insulin signaling in liver and muscle [6]. In human studies, adipose-derived RBP4 is associated with insulin resistance and cardiovascular risk factors and in many, but not all, studies with body mass index (BMI) [6–8]. In addition to its role as an adipokine, RBP4 is a major transporter of vitamin A [9]. Therefore, RBP4 plays a critical role in vitamin A signaling. RBP4 can also bind to transthyretin, which can act as a carrier protein that is believed to modulate Aβ levels by transporting Aβ from brain to the periphery resulting in lower amounts of toxic Aβ in the brain [10]. Collectively, these studies suggest that RBP4 may be involved in critical pathways related to AD pathobiology.

A few human studies have investigated the potential link between RBP4 and AD. A postmortem brain study with a limited number of subjects found that brain RBP4 levels were increased in AD subjects compared to non-AD control subjects [11]. In another small study, the cerebrospinal fluid (CSF) RBP4 levels were decreased in AD subjects compared to control subjects [12]. A more recent study found CSF RBP4 levels to decrease gradually from normal controls to mild cognitive impairment (MCI) and eventually be very low or absent in the more severe cases of AD [13]. These early studies suggest that RBP4 may be a biomarker of AD progression; however, whether alterations in RBP4 can be detected in the blood at the earliest stages of AD and the relation, if any, of peripheral RBP4 levels to the cognitive decline in AD are not known. Therefore, in this study, we sought to determine if RBP4 levels in plasma are altered in cognitively normal subjects with CSF biomarker-defined preclinical AD compared to CSF biomarker negative controls, and if plasma RBP4 levels are associated with cognitive decline and incident dementia and AD diagnosis in these subjects.

MATERIALS AND METHODS

Study participants

Participants were community-dwelling volunteers enrolled in longitudinal studies of healthy aging and dementia through the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University School of Medicine in St. Louis [14]. Study participants were in good general health, with no other known medical illness that could contribute to dementia. All participants had baseline body weight and BMI recorded, and underwent

cognitive testing in the form of the Mini-Mental State Examination (MMSE). Additionally, baseline fasting plasma and CSF samples were obtained from all subjects. CSF samples were analyzed for $A\beta_{42}$, total tau, and tau phosphorylated at threonine 181 (p-tau181) by ELISA (INNOTEST; Innogenetics) as previously described [14]. Apolipoprotein E (APOE) genotypes were obtained from all participants as previously described [14].

Inclusion criteria for our analysis of these cohorts were: 1) normal cognition at study entry (defined as having a Clinical Dementia Rating (CDR) of 0); 2) BMI less than 30 to exclude obese subjects; 3) and availability of baseline fasting CSF and plasma samples. For longitudinal studies, the median follow-up time was 5.2 years (range, 0.5–9.7 years) for men and 5.9 years (range, 0.8–10.9 years) for women. The diagnosis of dementia or AD was made clinically, as previously described [14].

This study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis. Written informed consent was obtained from all participants and their informants.

Preclinical Alzheimer's disease status

Preclinical AD was defined as a CSF $A\beta_{42}$ level <459 pg/mL, a previously established CSF criterion of preclinical AD for this cohort [14]. Controls were all subjects who were amyloid-negative, defined as a CSF $A\beta_{42}$ level ≥459 pg/mL.

Plasma collection and processing for RBP4 levels

Fasting plasma samples were collected at baseline from all eligible study participants and were stored in frozen aliquots at –80○C at Washington University School of Medicine in St. Louis. For this analysis, de-identified aliquots were sent to Weill Cornell Medicine, where plasma levels of RBP4 were measured by enzyme-linked immunosorbent assays (ELISA) that have been validated for human plasma and serum following the manufacturer's protocol (Catalog Number DRB400; R&D Systems, Minneapolis, MN, USA). All plasma samples were diluted 1000 fold before running the ELISA. The linear range for the ELISA was 1.56 to 100 ng/mL. The mean minimum detectable dose of RBP4 was 0.224 ng/mL. The mean intra-assay and inter-assay coefficient of variation were 6.9% and 7.2% respectively. Five samples were discarded due to being out of the linear range or having significant visible precipitation. All samples were run in duplicates, and mean values were used.

Statistical analysis

The estimated sample size needed for a two-sample means test was calculated based on a previously published study on RBP4 levels and AD [12]. 30 total subjects or 15 control and 15 AD subjects would be needed for alpha of 0.05 and power of 0.9. All analyses were stratified by sex due to probable sex differences in adipokine levels and function [15, 16]. Variables were summarized as mean (standard deviation) and compared between groups using two tailed *t*-tests. Linear regression was used to examine correlations between BMI and plasma RBP4 levels. Associations between plasma RBP4 and the individual CSF AD biomarker levels as continuous measures were examined by linear regression. As a significant difference in age was seen between male preclinical and control groups, all of the

multiple linear regression analyses were adjusted for age. Subgroup analyses were conducted to determine the effects of the interaction of APOE genotype (E4 carriers compared to non-E4 carriers) or age on the individual AD CSF biomarkers in relation to plasma RBP4 levels. Cox regression models were used to examine the association between baseline RBP4 levels and the incidence of CDR ≥ 0.5, diagnosis of dementia, and diagnosis of AD after confirming that the assumption of proportionality of hazards was met. Cox regression model analyses were also adjusted for age. All tests were two-sided, and the threshold of statistical significance was defined as $p < 0.05$. Statistical analyses were performed using Stata version 13.1 (StataCorp, TX).

RESULTS

Demographic characteristics of study participants

A total of 161 subjects (70 men and 91 women) met all study criteria. Samples from 5 male subjects had to be discarded due to poor quality of the plasma sample including levels below the detection threshold of the ELISA assays or grossly visible precipitation in the sample. Using previously defined CSF criteria for preclinical AD [14], 20 male and 18 female subjects were categorized as being in the preclinical stage of AD, and 45 male and 73 female subjects were categorized as amyloid-negative controls. Compared to control subjects, male preclinical AD subjects had significantly lower CSF $A\beta_{42}$ levels and higher CSF tau and p-tau levels; however, females had significantly lower CSF $A\beta_{42}$ levels, but CSF tau and p-tau levels were not significantly different compared to control subjects (Table 1). Baseline MMSE scores were all within the normal range with no significant differences between preclinical AD and control subjects among men or women (Table 1). In male subjects, the preclinical AD group was older and had lower BMI than biomarker negative controls (Table 1). Both male and female preclinical AD groups had increased percentage of subjects with at least one copy of the APOE ε4 allele compared to their respective control groups (Table 1). Otherwise, the rest of the demographic characteristics were similar between preclinical AD and control groups in men and women.

Plasma RBP4 levels are similar between male and female subjects

Since circulating adipokine levels often display sex differences [15, 16], we examined if plasma RBP4 levels were different between men and women regardless of preclinical AD status. In our cohort, despite male subjects having on average higher BMI than female subjects (men 25.8 ± 2.0 kg/m^2 versus women 23.8 ± 3.1 kg/m^2; $p < 0.001$), the plasma RBP4 levels were not statistically different between male and female subjects (men 30.0 ± 7.7 μg/mL versus women 31.1 ± 8.0 μg/mL; $p = 0.39$). Next, we examined if RBP4 levels correlated with BMI and found no significant correlation in male or female subjects after adjustment for age (men: beta coefficient, 0.077; $p = 0.56$; women: beta coefficient 0.0097, $p = 0.93$).

Plasma RBP4 levels are not altered in preclinical AD and are not associated with CSF AD biomarker levels

We then examined whether plasma RBP4 levels were different between preclinical AD and control subjects in men and women. In both male and female subjects, the plasma RBP4

levels were not statistically different between preclinical AD and control subjects (Table 1). Additionally, plasma RBP4 levels were not associated with CSF AD biomarker levels of $A\beta_{42}$, p-tau, or tau (Table 2). Subgroup analyses were conducted to determine the effects of APOE genotype and age. In both male and female subjects, APOE genotype did not interact significantly with the individual CSF AD biomarkers (i.e., $A\beta_{42}$, p-tau, or tau) in relation to plasma RBP4 levels (Table 2). There was also no significant interaction between age and the individual CSF AD biomarkers in relation to plasma RBP4 levels for both male and female subjects (all $p > 0.05$).

Plasma RBP4 levels are not associated with development of cognitive decline, incident dementia, and AD

Finally, we examined the relation between baseline plasma RBP4 levels and decline in cognitive function over time and incident all-cause dementia and AD. For the 65 male subjects, during a median follow-up time of 5.2 years (range, 0.5–9.7 years), 25 subjects converted to CDR ≥ 0.5, 25 had incident all-cause dementia, and 15 were diagnosed with AD. For the 91 female subjects, during a median follow-up time of 5.9 years (range, 0.8–10.9 years), 14 subjects converted to CDR ≥ 0.5, 12 had incident all-cause dementia, and 6 were diagnosed with AD. For both male and female subjects, plasma RBP4 levels were not associated with change in CDR ≥ 0.5, incident all-cause dementia or AD diagnosis (Table 3).

DISCUSSION

In this study of cognitively normal community dwelling volunteers, baseline plasma RBP4 levels were not significantly different between those subjects with or without CSF Aβ pathology consistent with preclinical AD. Additional analyses revealed that baseline plasma RBP4 levels were not associated with baseline CSF AD biomarkers. In longitudinal studies, baseline plasma RBP4 levels were not associated with change in CDR ≥ 0.5 and incident all-cause dementia or AD. The overall findings suggest that plasma RBP4 levels are unlikely to play a significant role in the early stages of AD. Furthermore, this study does not support plasma RBP4 levels as a potential biomarker of AD progression or in the prediction of cognitive decline in clinical practice.

In our study, plasma RBP4 levels were similar between male and female subjects despite males having significantly higher BMI. Importantly, plasma RBP4 levels were not related to BMI in both males and females, suggesting that in our cohort RBP4 is not related to body adiposity. Interestingly, in at least one study of healthy elderly subjects, RBP4 levels were associated with insulin resistance in only the obese group and not in the non-obese group [17]. The mechanism for this possible discrepancy between obese and non-obese elderly subjects is not known. Since anyone with a BMI ≥30 was excluded from our study, it is possible that RBP4 levels do not reflect insulin signaling in our cohort. Therefore, additional studies investigating insulin signaling and related metabolic factors are needed.

To our knowledge, this is the first study that investigated circulating RBP4 levels in biomarker-defined preclinical AD. These results differ from earlier human studies in AD that found significantly altered brain or CSF levels of RBP4. In one report of 4 patients with

neuropathologically confirmed AD and 3 control patients, postmortem brain analysis by ELISA found that RBP4 levels were increased in AD subjects compared to non-AD control subjects [11]. In another small study that used two-dimensional gel electrophoresis and mass spectroscopy to analyze CSF of 7 patients with clinically diagnosed AD and 7 healthy controls, the CSF RBP4 levels were decreased in AD subjects compared to control subjects [12]. Together, these studies with limited number of subjects suggest that in later stages of AD there is an increase in brain RBP4 levels but a decrease in CSF RBP4 levels, which is similar to what is seen with Aβ in AD. A more recent cross-sectional study did investigate earlier stages of AD including MCI and found a gradual decrease in CSF RBP4 levels with worse disease progression [13]. However, this study relied on clinical diagnosis of AD, which may have led to misdiagnosis and misclassification of some study subjects. Despite the limitations of these earlier studies, it is possible that in early stages of AD that the RBP4 levels in the brain or CSF are altered, but circulating levels of RBP4 in the periphery are unaffected. Future studies investigating RBP4 levels in the CSF of preclinical AD subjects are needed to address any differences between central and peripheral RBP4 levels in the early stages of AD.

Based on our studies, it appears unlikely that RBP4 would have any significant role in the early pathogenesis of AD. However, this may not be the case in other neurodegenerative diseases, as a recent study found that serum RBP4 levels were associated with risk for and prognosis of amyotrophic lateral sclerosis [18]. Also, these results do not exclude other adipokines that are directly related to BMI and body adiposity such as leptin playing a critical role in early stages of AD [19, 20]. Finally, a role for vitamin A signaling cannot be excluded, as vitamin A levels were not measured directly in our subjects. Moreover, studies suggest that RBP4-independent pathways such as by chylomicrons and other lipoproteins may play a major role in vitamin A signaling [21]. Therefore, future studies that measure levels of vitamin A, RBP4, and additional retinol signaling molecules in the same subjects are needed to obtain a comprehensive analysis of vitamin A signaling in early stages of AD.

A major strength of our study is the use of a well-characterized study cohort of community dwelling healthy volunteers with CSF biomarker defined preclinical AD. Defining subjects by CSF AD biomarkers leads to a more accurate categorization of the pathological state of the subjects than relying solely on clinical diagnosis. A limitation of this study is the relatively modest number of preclinical AD subjects and the small number of subjects that converted to AD particularly in the female subjects. The study cohort is also racially homogenous with high education levels. Therefore, the negative results should be taken with some caution until additional studies in larger more diverse cohorts with longer follow-up times are available.

In summary, plasma RBP4 levels were not significantly different between CSF biomarker defined preclinical AD and control subjects. Furthermore, baseline plasma RBP4 levels were not associated with cognitive decline or incident all-cause dementia or AD diagnosis. Alterations in RBP4 levels, if any, may be restricted to the brain and CSF or in later stages of AD. Therefore, our results do not support plasma RBP4 as a clinical biomarker or peripheral RBP4 as a therapeutic target in the early stages of AD. Further studies

investigating additional adipokines in a similar fashion will help elucidate whether these other adipokines play a key role in early AD pathobiology.

ACKNOWLEDGMENTS

We would like to thank especially all the volunteers for participating in the study. We gratefully acknowledge the contributions of Drs. Anne Fagan, Betsy Grant, Krista Moulder, John Morris, and David Holtzman, the Clinical, Psychometrics, Biomarker, and Biostatistics cores of The Charles F. and Joanne Knight Alzheimer's Disease Research Center (P50 AG05681), Healthy Aging and Senile Dementia (P01 AG03991), and Adult Children Study (P01 AG026276) for providing biospecimens and associated clinical, biomarker, and psychometrics data. We thank Mr. Matthew McGuire, Ms. Laurie Pham, and Ms. Abigail Hiller for providing technical and administrative assistance. This study was funded by the BrightFocus Foundation (A2015485S) and NIH (K08AG051179, K23NS082367, and R01NS37853).

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Table 1

Demographic characteristics, cerebrospinal fluid biomarkers, body weight, and plasma RBP4 levels

	Male			Female		
	Control (*n* = 45)	**Preclinical AD (*n* = 20)**	***p***	**Control (*n* = 73)**	**Preclinical AD (*n* = 18)**	***p***
Age at baseline lumbar puncture mean (SD), y	69.7 (7.0)	76.4 (5.9)	***	66.0(7.8)	68.8(8.3)	0.17
Caucasian (%)	44 (98)	20 (100)		71 (97)	18 (100)	
CSF $A\beta_{42}$, mean (SD), pg/mL	786.4 (253.9)	340.0 (77.3)	***	773.9 (227.2)	372.4 (68.3)	***
CSF tau, mean (SD), pg/mL	281.8 (142.6)	530.5 (271.3)	***	293.5 (178.6)	368.5 (246.6)	0.14
CSF p-tau181, mean (SD), pg/mL	65.3 (33.7)	83.7 (35.4)	0.049	58.5 (29.3)	69.7 (37.5)	0.17
APOE genotype	0	0		0	0	
ε2/ε2 (%)						
ε2/ε3 (%)	4 (9)	0		8 (11)	1 (6)	
ε3/ε3 (%)	27 (60)	7 (35)		48 (66)	7 (39)	
ε2/ε4 (%)	0	0		2 (3)	0	
ε3/ε4 (%)	14 (31)	12 (60)		14 (19)	5 (28)	
ε4/ε4 (%)	0	1 (5)		1 (1)	5 (28)	
ε4 isoform (%)	14 (31)	13 (65)		17 (23)	10 (56)	
Education, mean (SD), y	16.5 (2.4)	16.1 (2.8)	0.51	15.8 (2.5)	15.3 (2.7)	0.41
MMSE, mean (SD), score	29.0 (1.3)	28.5 (1.5)	0.18	29.5 (0.8)	29.1 (1.1)	0.11
BMI, mean (SD), kg/m^2	26.2 (1.8)	24.9 (2.2)	0.016	24.0 (3.0)	23.4 (3.5)	0.47
Plasma RBP4, mean (SD), μg/mL	30.0 (7.4)	30.0 (8.7)	0.97	30.9 (7.9)	31.7 (8.5)	0.72

*** denotes $p<0.001$; SD, standard deviation.

Table 2

Association of plasma RBP4 levels with CSF AD biomarkers

	Male			Female		
	APOE genotype	Beta coefficient	*p*	APOE genotype	Beta coefficient	*p*
CSF $A\beta_{42}$ levels	All	0.16	0.16	All	0.057	0.59
	E4 carrier	0.32	0.64	E4 carrier	–0.040	0.48
	Non-E4 carrier	0.13		Non-E4 carrier	0.14	
CSF tau levels	All	–0.054	0.64	All	0.043	0.65
	E4 carrier	–0.14	0.78	E4 carrier	–0.16	0.57
	Non-E4 carrier	–0.0084		Non-E4 carrier	0.099	
CSF p-tau levels	All	–0.019	0.88	All	–0.0051	0.96
	E4 carrier	–0.19	0.41	E4 carrier	0.00092	0.96
	Non-E4 carrier	0.069		Non-E4 carrier	–0.033	

All were adjusted for age.

J Alzheimers Dis. Author manuscript; available in PMC 2019 February 22.

Table 3

Association of plasma RBP4 levels with incidence of Clinical Dementia Rating (CDR) ≥0.5, all-cause dementia, and Alzheimer's disease (AD)

	Male		Female	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
CDR ≥0.5	0.97 (0.92–1.02)	0.27	1.02 (0.95–1.08)	0.63
All-cause dementia	0.97 (0.92–1.02)	0.32	1.01 (0.94–1.08)	0.80
AD	0.99 (0.92–1.05)	0.68	0.97 (0.87–1.09)	0.65

All were adjusted for age. HR, hazard ratio; CI, confidence intervals.

J Alzheimers Dis. Author manuscript; available in PMC 2019 February 22.