Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

An Atherosclerosis Indicator Hyaluronic Acid: Can Plasma Hyaluronic Acid Be Useful in Diagnosing Alzheimer's Disease?

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SUMMARY

Background: **The aim is to compare the plasma levels of hyaluronic acid (HA) which is closely related to inflammation and vascular changes and arterial stiffness (AS) related values in patients with Alzheimer's disease (AD), amnestic type mild cognitive impairment (aMCI), and normal cognitive functions (NCF).**
Methods: **Ninety participants were categorized into three groups, patients with AD, MCI, and NCF. Arterial stiffness measurement in the nephrology outpatient clinic, and storage and analysis of plasma samples in the biochemistry laboratory.**
Results: **Of the 90 patients, 32 had NCF, 32 had aMCI, and 26 had AD. Between groups, there was no difference in HA, pulse wave velocity, and augmentation index. The HA level had no statistically significant correlation with any of the other variables.**
Conclusions: **Plasma HA levels will not be useful in the diagnosis of AD. More comprehensive studies with larger number of patients are needed.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2023.230734)

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Manuscript accepted September 6, 2023

KEYWORDS

Alzheimer's disease, arterial stiffness, hyaluronic acid

INTRODUCTION

Endothelial cells are enveloped by proteoglycan complexes called the endothelial glycocalyx. The endothelial glycocalyx provides barrier integrity between the endothelial surface and the blood flow, limiting extravasation of salt, water, and proteins, preventing direct interaction of cytokines and proteins with the endothelium. It inhibits coagulation by diminishing leukocyte and platelet adherence to the endothelium [1,2]. The endothelial gycocalyx also preserves the cytoskeleton and regulates nitric oxide-mediated vasodilation [3,4]. Due to the functions of the endothelial glycocalyx, the dis-

ruption of endothelial glycocalyx structure is associated with atherosclerosis and cardiovascular events [5,6]. One of the endothelial glycocalyx members is hyaluronic acid (HA). It is produced in numerous cells, especially in skin and soft tissue. It is known as the cornerstone of the perineuronal network in the brain [7,8]. While HA is a regulator of endothelial proliferation and vascular functions, it plays an important role in the development of atherosclerosis together with other adhesion molecules [9,10].

Arterial stiffness (AS) is characterized by a decline in pressure-varying arterial volume caused by diminished vascular elasticity and compliance [11]. It reduces the dilatation capacity of the arteries and their adaptation to blood ejection in systole. In this condition, more pulsatile pressure is supplied to the microcirculation of the organ systems. Therefore, AS poses a risk for health outcomes including dementia, hypertension, diabetes, chronic kidney disease, and cardiovascular diseases [12]. There are indicators that reflect arterial stiffness. Pulse wave velocity (PWV) and augmentation index (AI) are calculated from the properties of the pulse waves, and their rise raises cardiovascular risk [13].

Alzheimer's disease (AD) is a disorder with specific neuropathological findings, characterized by impaired cognitive function, increasing the need for care and leading to death [14]. In recent years, it has been demonstrated that vascular pathologies have effects on amyloid formation, neurodegeneration, and cognitive function. It has been determined that AD is associated with chronic diseases that cause vascular changes such as atherosclerosis, diabetes, and hypertension [15,16]. With age, HA, and AS which promote atherosclerosis, cause damage to the central nervous system. In AD patients, HA levels have been reported to rise in a variety of brain regions [17].

There are very few studies in the literature between plasma HA level and cognitive function. The aim of the present study is to compare the plasma level of HA, which is closely related to inflammation and vascular changes, and AS related values in patients with AD, amnestic type mild cognitive impairment (aMCI), and normal cognitive functions (NCF).

MATERIALS AND METHODS

Participants

The study included participants who were admitted to a university hospital's geriatric outpatient clinic. Comprehensive geriatric assessment (CGA) and cognitive assessment scales were performed in the geriatric medicine outpatient clinic, AS measurement in the nephrology outpatient clinic, and storage and analysis of plasma samples in the biochemistry laboratory. Patients who agreed to participate in the study and could cooperate with the tests were included in the study. Participants were categorized into three groups, patients with AD, aMCI, and NCF. Only AD patients with mild dementia according to functional assessment staging (FAST) were included.

Exclusion criteria were determined mostly by considering the conditions that may affect the HA level:

1) Uncontrolled diabetes (HbA1c > 8)
2) Liver dysfunction (alanine transaminase > 50 Unit (U)/Liter (L), aspartate aminotransferase > 50 U/L, gamma-glutamyl transferase > 55 U/L)
3) Inflammatory disease (acute or chronic)
4) Hypoalbuminemia (plasma albumin < 3 mg/dL)
5) Malignancy
6) Clinical hypervolemia
7) Moderate, moderately severe, and severe dementia

Besides plasma HA level and AS values, sociodemographic, clinical, and laboratory values were also recorded.

Comprehensive geriatric assessment

To perform an objective CGA, various screening and assessment tests were used. To assess patients' independence in activities of daily living, Katz activities of daily living (ADL) score [18] and Lawton-Brody instrumental activities of daily living (IADL) score [19] were used. The Mini Nutritional Assessment-Short Form (MNA-SF) was performed to evaluate nutritional status [20] and the Yesavage Geriatric Depression Scale (GDS) to evaluate mood [21]. The clinical frailty scale (CFS) was applied to determine frailty status [22]. All of the tests mentioned have Turkish validity and reliability.

Cognitive assessment

In order to evaluate the cognitive functions of the patients, after clinical assessment including anamnesis from the patient and their relatives, cognitive screening tests were performed. The Mini-Mental State Examination (MMSE) [23] and Quick Mild Cognitive Impairment Screen (QMCI) [24,25], a rapid test that gives more accurate results in distinguishing aMCI and subjective cognitive complaints, were performed. The MMSE is a 30-point test that assesses patients' orientation, registration, attention, calculation, delayed recall, language, motor function, and copying capacities. The QMCI includes questions for orientation, registration, clock drawing, delayed recall, verbal fluency, and logical memory. It is scored between zero and one hundred points [24]. For the diagnosis of aMCI, Petersen's criteria were used [26]. After CGA and cognitive assessment, diagnosis of probable AD was established based on DSM-V diagnostic criteria [27]. The FAST scale was used to assess the severity of cognitive impairment [28].

Arterial stiffness measurement

Variables related to AS were measured on the day the blood samples were taken, over the brachial artery, using a standard cuff appropriate for arm diameters, using the Mobil-O-Graph device (IEM, Germany) in the Department of Nephrology. With the measurements made

by this blood pressure device, PWV and AI were obtained.

Hyaluronic acid measurement

Blood samples were stored at -80°C after centrifugation. The plasma levels of hyaluronic acid were analyzed by enzyme-linked immunosorbent assay (ELISA) using a kit (Human Hyaluronic Acid ELISA Kit Cloud Clone-USCN-CEA182Ge) according to the manufacturer's instructions.

Ethical approval

Hacettepe University Faculty of Medicine Non-Interventional Ethics Committee reviewed and approved the study protocol (Ethics committee approval number: GO 20/1110). All of the patients provided informed consent.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 24.0 was used for analysis. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean and standard deviation or median and interquartile range values according to the normal distribution. Comparisons between the AD group, aMCI group, and NCF group were performed with the Kruskal-Wallis test for continuous variables, and with the chi-squared test for categorical variables. The correlation of HA with age, cognitive tests, and components of CGA were evaluated with Spearman's Rho test. $p < 0.05$ was accepted statistically significant.

RESULTS

Of the 90 patients included in the study, 32 had NCF, 32 had aMCI, and 26 had AD. The median age was 71.0 (IQR: 67.0 - 74.0), 50% (n = 45) of the patients were female. The number of patients with five or less years of education was 54 (60%). Multimorbidity was present in 62 (68.9%) patients. The results obtained after CGA were as follows: the Katz ADL median was 6.0 (min: 3.0, max: 6.0), the Lawton-Brody IADL median was 8.0 (min: 2.0, max: 8.0), the MNA-SF median was 14.0 (IQR: 12.0 - 14.0), the Yesavage GDS median was 2.0 (IQR: 1.0 - 6.0), and the CFS median was 3.0. (IQR: 3.0 - 5.0). Forty-one (45.6%) patients were living with frailty. In cognitive assessment, the median MMSE score was 27.0 (IQR: 24.0 - 29.0), and the median QMCI score was 51.0 (38.0 - 61.0). The median of HA was 13.9 nanogram (ng)/milliliter (mL) (IQR: 11.1 - 24.5). Of the AS variables, the median of PWV was 10.1 meters (m)/second (s) (IQR: 9.2 - 11.2), while the median of AI was 24.0% (IQR: 15.0 - 34.0) (Table 1).

Between groups, there were statistically significant differences in age ($p = 0.003$), education ($p = 0.003$), Lawton-Brody IADL ($p < 0.001$), MNA-SF ($p = 0.004$), Yesavage GDS ($p < 0.001$), CFS ($p < 0.001$), living with frailty ($p < 0.001$), MMSE ($p < 0.001$), and QMCI ($p < 0.001$). There was no difference in gender, smoking, multimorbidity, Katz ADL, HA, PWV, and AI (Table 1). Although higher HA levels were measured in NCF and aMCI groups compared to AD, it was not statistically significant ($p = 0.55$) (Figure 1).

The correlations of HA level with various variables were examined in Table 2. The HA level had no statistically significant correlation with any of the other variables. A weak negative correlation was detected with MNA-SF in the NCF group (rho = -0.40, $p = 0.02$), and with Katz ADL in the AD group (rho = -0.40, $p = 0.04$).

DISCUSSION

The present study investigated the difference in plasma HA levels between NCF, aMCI, and AD groups. In addition, AS-related variables were also measured and compared between the groups. No difference was found in HA levels and AS values in patients with AD compared to other groups. Furthermore, there was no correlation between HA levels and AS values.

Alzheimer's disease is often diagnosed using neuropsychiatric tests, clinical evaluation, application of diagnostic criteria, and exclusion of other causes of cognitive impairment. The progression of the disease and the worsening of symptoms support the diagnosis. However, definitive diagnosis is made by observing characteristic pathological brain lesions, amyloid plaques, and neurofibrillary tangles in biopsy/autopsy. Although the progression of the disease can be partially slowed down with early treatment, there is currently no treatment that provides a satisfactory cure or improves the symptoms of the disease. Clarifying the pathogenetic processes more clearly will guide the development of new treatment strategies. This clinical necessity has led to the exploration of numerous biomarkers in the early detection of Alzheimer's disease, its separation from other dementia etiologies and elucidation of its pathogenesis [29, 30].

One of the researched biomarkers is HA. While HA regulates endothelial proliferation and vascular function, it also plays a crucial role in the development of atherosclerosis in cooperation with other adhesion molecules. With aging, HA accumulates in the central nervous system. Although HA levels have been shown to climb in various areas of the brain in AD patients [31-33], they have not been reported to increase in cerebrospinal fluid (CSF) samples. Nagga et al. showed that HA in CSF was higher than the control group in vascular dementia patients, but there was no difference in AD patients compared to the control group [34]. In a study conducted in Sweden examining the difference of HA levels in CSF according to gender in AD and dementia with Lewy bodies patients, HA levels in CSF in AD patients were not higher than the control group [35]. Although data exists on CSF levels, there is little research on the effect of HA levels in peripheral blood in AD. In the present study, plasma HA levels were not higher in AD patients than in other groups. In the study conducted by

Table 1. Demographic and clinical characteristics of patients.

	Total (n = 90)	Normal (n = 32, 35.6%)	MCI (n = 32, 35.6%)	AD (n = 26, 28.9%)	p
Age, years (median, IQR)	71.0 (67.0 - 74.0)	68.0 (66.0 - 71.0)	72.0 (67.0 - 73.5)	74.5 (69.0 - 79.0)	0.003
Gender, female (n, %)	45 (50.0)	14 (43.8)	16 (50.0)	15 (57.7)	0.57
Education (≤ 5 years) (n, %)	54 (60.0)	12 (37.5)	21 (65.6)	21 (80.8)	0.003
Smoking	29 (32.2)	10 (34.5)	11 (37.9)	8 (27.6)	0.95
Multimorbidity (≥ 2 diseases)	62 (68.9)	22 (68.8)	22 (68.8)	18 (69.2)	1.0
Katz ADL (median, min-max)	6.0 (3.0 - 6.0)	6.0 (5.0 - 6.0)	6.0 (5.0 - 6.0)	6.0 (3.0 - 6.0)	0.51
Lawton-Brody IADL (median, min-max)	8.0 (2.0 - 8.0)	8.0 (8.0 - 8.0)	8.0 (6.0 - 8.0)	6.5 (2.0 - 6.0)	< 0.001
MNA-SF (median, IQR)	14.0 (12.0 - 14.0)	14.0 (14.0 - 14.0)	13.0 (12.0 - 14.0)	13.0 (12.0 - 14.0)	0.004
Yesavage GDS (median, IQR)	2.0 (1.0 - 6.0)	1.0 (0.0 - 2.0)	6.0 (1.0 - 7.5)	3.0 (2.0 - 6.0)	< 0.001
CFS (median, IQR)	3.0 (3.0 - 5.0)	3.0 (2.0 - 3.0)	3.0 (3.0 - 4.0)	5.0 (5.0 - 6.0)	< 0.001
CFS (≥ 4) (n, %)	41 (45.6)	1 (3.1)	14 (43.8)	26 (100.0)	< 0.001
MMSE (median, IQR)	27.0 (24.0 - 29.0)	29.0 (27.0 - 30.0)	26.5 (25.0 - 28.0)	21.0 (20.0 - 24.0)	< 0.001
QMCI (median, IQR)	51.0 (38.0 - 61.0)	62.5 (52.5 - 66.5)	51.5 (43.0 - 56.0)	28.5 (19.0 - 46.0)	< 0.001
Hyaluronic acid (ng/mL) (median, IQR)	13.9 (11.1 - 24.5)	14.0 (12.3 - 20.2)	14.3 (11.0 - 31.1)	12.7 (9.9 - 22.4)	0.55
Pulse wave velocity (m/s) (median, IQR)	10.1 (9.2 - 11.2)	9.9 (9.3 - 10.6)	10.1 (9.4 - 11.2)	10.1 (9.0 - 12.0)	0.87
Augmentation index (%) (median, IQR)	24.0 (15.0 - 34.0)	24.0 (15.5 - 33.5)	23.0 (18.0 - 35.0)	25.0 (12.0 - 36.0)	0.75

N - Number, MCI - Mild cognitive impairment, AD - Alzheimer's disease, IQR - Interquartile range, min - minimum, max - maximum, ADL - Activities of Daily Living, IADL - Instrumental Activities of Daily Living, MNA-SF - Mini Nutritional Assessment Short Form, GDS - Geriatric Depression Scale, MMSE - Minimental State Examination, QMCI - Quick Mild Cognitive Impairment, CFS - Clinical Frailty Scale, ng - nanogram, mL - milliliter, m - meter, s - second.

Nielsen et al., there was no difference between plasma HA levels in patients with AD compared to the control groups. In fact, similar to our findings, a modest decline was detected in the AD group [35]. These results suggest that plasma HA levels are less likely to be utilized to diagnose AD.

Arterial stiffness is a significant risk factor for dementia as it causes cerebral small vessel disease, stroke, and brain aging [36]. In particular, with a rise in amyloid accumulation, it increases the risk of AD [37]. In a review study, assessment of PWV was discovered to be associated with cognitive deficits, including MCI [38]. Arterial stiffness was revealed to raise the risk of dementia 1.27 times over a 15-year median follow-up of Framingham Heart Study participants [12]. There was no difference in AS between patients with AD and the other groups in the present study. This may be due to the small sample size of the study.

An answer to the question of whether HA plays a role in the development of AS has been sought in the literature. In mice, increased arterial stiffness and thinning of the elastic membrane were observed after the deposition of hyaluronic acid in the tunica media layer [39]. In the present study, no relationship was detected between plasma HA levels and AS.

There are several limitations of this present study. First of all, because it is a cross-sectional study, a causal relationship cannot be established. The number of patients is relatively small and it is difficult to conclude whether the results are generalizable. Almost one hour after waking up, plasma HA levels reach their peak. It is hypothesized that this is because HA accumulates in the tissues at night and goes into the circulation with movement after waking up, particularly from muscle tissue [40]. Although blood samples were obtained in the morning, the effect of participants' sleep patterns on HA levels could not be fully controlled. In addition, it is not known how much the participants moved until they ar-

Table 2. Correlation between hyaluronic acid levels and other variables.

	Total		Normal		MCI		AD	
	rho	p	rho	p	rho	p	rho	p
Age	-0.11	0.32	0.19	0.29	-0.18	0.32	0.03	0.89
Katz ADL	-0.13	0.24	-0.22	0.23	0.15	0.40	-0.40	0.04
MNA-SF	-0.15	0.16	-0.40	0.02	-0.18	0.34	0.01	0.98
Yesavage GDS	0.01	0.93	-0.05	0.80	0.03	0.87	0.05	0.82
CFS	-0.10	0.33	0.17	0.35	-0.19	0.30	0.39	0.05
MMSE	0.03	0.80	0.06	0.76	-0.23	0.22	-0.07	0.74
QMCI	0.05	0.62	0.21	0.25	0.01	0.94	-0.27	0.19
Pulse wave velocity	0.08	0.47	0.06	0.73	0.16	0.37	-0.03	0.90
Augmentation index	0.11	0.31	0.31	0.08	0.26	0.15	-0.18	0.39

ADL - Activities of Daily Living, IADL - Instrumental Activities of Daily Living, MNA-SF - Mini Nutritional Assessment Short Form, GDS - Geriatric Depression Scale, MMSE - Minimental State Examination, QMCI - Quick Mild Cognitive Impairment, CFS - Clinical Frailty Scale.

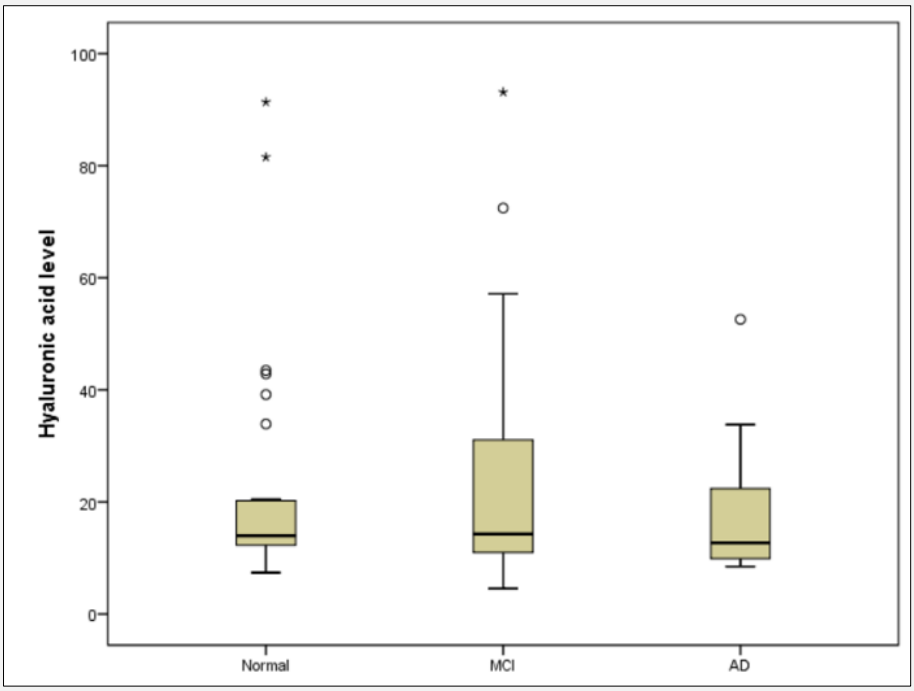

Figure 1. Box plot graph showing the distribution of serum hyaluronic acid levels of the patient groups.

Values of serum hyaluronic acid levels were 14.0 (IQR: 12.3 - 20.2), 14.3 (IQR: 11.0 - 31.1), and 12.7 (IQR: 9.9 - 22.4) ng/mL for the normal, MCI, and AD groups, respectively (p = 0.55). MCI - mild cognitive impairment, AD - Alzheimer disease.

rived at the hospital. The amount of movement may have influenced the HA level.

In conclusion, there is no difference in plasma HA levels in older adults between NCF, aMCI, and AD groups. Similar to plasma HA levels, no difference was found between the groups in arterial stiffness. The present

study shows results that plasma HA levels will not be useful in the diagnosis of AD, despite the limited number of patients. More comprehensive studies with larger number of patients are needed.

Declaration of Interest:
None.

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