ADAM10 plasma levels predict worsening in cognition of older adults: a 3-year follow-up study

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Research

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Abstract

Background: Blood-based biomarkers for Alzheimer's disease (AD) are highly needed in clinic practice. So far, the gold standards for AD diagnosis are brain neuroimaging and beta-amyloid peptide, total tau and phosphorylated tau in cerebrospinal fluid (CSF), however, they are not attractive for large-scale screening. Blood-based biomarkers will allow an initial large-scale screening of patients under suspicion that could later be tested for the already established CSF biomarkers. To this regard, we and other research groups have already described that the plasma and platelet levels of ADAM10 are higher or lower, respectively, in patients with AD, compared to those cognitively healthy.

Methods: This was a three-year longitudinal cohort study that included 219 community-dwelling older adults. Sociodemographic, clinical, lifestyle, depressive symptoms (GDS) and cognitive data (Mini-Mental State Examination, MMSE; Clock Drawing test, CDT) were gathered. The measurement of ADAM10 plasma levels was performed using a sandwich ELISA kit. Bivariate comparisons between groups were performed using Wilcoxon-Mann-Whitney for continuous data and Pearson's chi-square tests with Yates continuity correction, for categorical data. Longitudinal analyzes of changes in the MMSE score were performed using Linear Mixed-Effects modeling.

Results: Baseline MMSE score and ADAM10 values were significantly associated with MMSE score values on the follow-up assessment. When analyzing the interaction with time, having a normal MMSE at baseline and ADAM10 plasma levels presented a significant and independent negative association with MMSE score values on the follow-up assessment. The analyses also showed that the effect of ADAM10 plasma levels on decreasing MMSE score values on follow-up seems to be more pronounced in those with normal MMSE at baseline. Taken together, these results provide the first direct evidence that changes in ADAM10 plasma levels are predictors of cognitive worsening in older adults.

Conclusions: Considering that ADAM10 increase in plasma is detected as soon as in mild cognitive impairment (MCI) patients, the results presented here may support the complementary clinical use of this biomarker, in addition to the classical AD biomarkers. Moreover, this work can shed light on the study of blood biomarkers for AD and contribute to the advancement of the area.

Background

Alzheimer's disease (AD) is the most common type of dementia affecting older adults worldwide, and is considered an important public health problem (1). The amyloidogenic pathway of amyloid precursor protein (APP) cleavage results in the formation of β-amyloid (βA) peptide and its extracellular accumulation and aggregation in the brain is one of the causes of AD; this is known as the amyloid hypothesis of AD (2). On the other hand, the non-amyloidogenic cleavage of APP, carried out by α and γ-secretases, avoids the βA formation.

The amyloidogenic and non-amyloidogenic cleavages of APP are the basis for detecting of the cerebrospinal fluid (CSF) βA marker which, together with total tau (t-tau) and phosphorylated tau (p-tau), as well as neuroimaging analyses, are considered gold standards to identify the underlying pathophysiology at the earliest stages of AD. However, they do not have the scalability needed for population screening (3, 4). On the other hand, blood-based AD biomarkers are advantageous over the CSF markers due to several aspects, including, but not restricted to, their non-invasive and cost-effective screening tool characteristics (5).

As the damage to blood vessels is the initial insult in the blood-brain barrier (BBB) that leads to neuronal injury and Aβ accumulation in the AD brain (6), the traffic of molecules from the central nervous system towards the periphery, and vice versa, is associated with neurodegeneration and allows the blood-based AD biomarker evaluation (6–8). Even in non-disease situations, the exchange of molecules and proteins between CSF and blood is well reported, despite the limitation imposed by BBB (9). In this regard, several blood-based AD biomarker candidates have been described, including the α-secretase ADAM10 (10).

ADAM10 is the main α-secretase participating in the non-amyloidogenic cleavage of APP in neurons, thus having a potential protective function against AD development (11). As a membrane-bound protein, ADAM10 acts as a sheddase cleaving different substrates on the plasma membrane, including APP in neurons; hence, avoiding the production, accumulation and aggregation of neurotoxic βA peptide (12, 13). Platelet ADAM10 levels were demonstrated to be decreased in AD patients, compared to the levels of cognitively healthy controls (14–18), whereas its plasma levels were increased in MCI and AD (19). These results are in line with most postmortem data that reveal an overall decrease of ADAM10 mRNA, protein, and/or activity in central nervous tissue of AD patients compared to age-matched controls (20).

Considering that plasma is even easier to collect compared to platelets, as obtaining it requires a single centrifugation step, in this study we evaluated whether plasmatic ADAM10 would be a predictor of declined cognition in community-dwelling older adults after a 3-year period follow up.

Methods

Study design, participants and setting

This was a longitudinal cohort study that used data from older adults in two time-points (2015 and 2018). A convenience sample of 219 adults aged 60 years or older were recruited from a community health center in São Carlos, São Paulo, Brazil. Only complete cases were analyzed. All recruited subjects gave their written informed consent prior to their inclusion in this study. The study was conducted according to the guidelines

established in the Declaration of Helsinki and all procedures involving human subjects were approved by the Federal University of Sao Carlos' Research Ethics Committee (Number: 36167914.9.0000.5504).

Study assessments and variables

The following sociodemographic, clinical, lifestyle and education level data were assessed from the participants who met the inclusion criteria: sex (male, female), age (years), schooling (years), cigarette smoking (yes/no) and alcohol consumption (yes/no). Metabolic syndrome was defined considering the presence of any three of the five following metabolic impairments: elevated waist circumference, elevated triglycerides, reduced HDL-C, hypertension and elevated fasting glucose (21).

Depression and cognitive performance

Depression was assessed by the Geriatric Depression Scale (GDS), short version [21]. The Mini Mental State Examination (22) was used to evaluate global cognitive performance. The clock-drawing test (CDT) was applied as a more specific screening for cognitive impairment [23]. As the Brazilian population in general has a low education background, the scholarly cut-offs proposed by Brucki et al. (23) were adopted. Therefore, participants with MMSE values < 20 for illiterates; <25 for 1–4 years of education; <26 for 5–8 years; <28 for 9–11 years and < 29 for more than 11 years of formal education were considered as altered MMSE scores. Considering that mean rate of progression of cognitive impairment is approximately 2 to 4 points per year in the MMSE [25], we chose a 3-year follow-up period to assure enough time for cognitive deterioration.

ADAM10 measurements

In the morning after an overnight fast, venous blood was drawn in tubes containing sodium citrate (3.8%) and glucose (136 mM) and centrifuged at 2400 rpm for 10 minutes to obtain plasma. The plasma was stored at -80°C until use. The measurement of ADAM10 levels in the plasma was performed using a sandwich ELISA kit (Cloud-Clone Corp., Houston, TX, USA) that contained adhered anti-human ADAM10 antibodies, which reacted with the ADAM10 present in the samples. Secondary antibodies conjugated to the alkaline phosphatase enzyme, supplied by the kit, were used to bind to the adhered proteins and, after adding substrate to the enzyme, the absorbance reading of the plates was performed on a plate reader at 450 nm wavelength (Labtec LT4000). The minimum concentration detectable by the kit is 28 pg/mL, with a detection range between 78 and 5000 pg/mL and an intra-assay coefficient of variation below 10% and interassay below 12%.

Statistical analysis

Continuous data are presented as the mean (standard deviation) according to the Shapiro-Wilk test of normality. Categorical variables are presented as counts and percentages. Comparisons between groups were performed using the Wilcoxon-Mann-Whitney test for continuous variables, and Pearson's Chi-squared test with Yates' continuity correction for categorical variables.

As the primary study outcome (MMSE score) was ascertained through two clinical assessments, patients had varying scores of MMSE captured at different times. Therefore, the longitudinal analyses of MMSE score changes over time were performed using Linear Mixed-Effects Modeling, considering the MMSE score values on follow-up, and incorporating the existing variability of each individual in the models (random effect). The model included age (years), sex (female, male), ADAM10 values, baseline MMSE score values, baseline grouping and the interactions of baseline grouping and ADAM10 with the time of assessment, and of baseline grouping with ADAM10 as fixed effects.

Statistical significance was assessed at a two-sided p value < 0.05. All analyses were conducted using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria) in R-Studio 1.1.463 (RStudio Inc., Boston, USA).

Results

The characteristics of the participants are presented in Table 1. Only complete cases were analyzed. A total of 219 individuals were included in the study. From the 151 (68.9%) participants who had normal MMSE scores at the baseline, 23 (33.8%) progressed to altered values in the follow-up. Overall, individuals with altered MMSE were predominantly female (60.3%; p = 0.7) and had a mean age of 70 ± 7.81 years, as compared to those with normal MMSE (p = 0.4). As expected, individuals with normal MMSE performed significantly better than individuals with altered MMSE both in the baseline (p < 0.001), as well as in the follow-up evaluations (p < 0.001) (see Table 1).

Table 1
Baseline and follow-up clinical and demographic parameters of the study population.

Variable	Overall (N = 219)	Normal (n = 151)	Altered (n = 68)	*p*
Age, years				0.4
Baseline	69.59 ± 7.07	69.22 ± 6.71	70.43 ± 7.81	
Follow-up	72.62 ± 7.11	72.30 ± 6.85	73.31 ± 7.67	
Female sex	127 (58.0)	86 (57.0)	41 (60.3)	0.7
Schooling				0.5
Illiterate	68 (31.1)	51 (33.8)	17 (25.0)	
1–4 years	117 (53.4)	78 (51.7)	39 (57.4)	
5–8 years	28 (12.8)	18 (11.9)	10 (14.7)	
9 + years	6 (2.7)	4 (2.6)	2 (2.9)	
Cigarette smoking, yes				0.3
Baseline	122 (55.7)	81 (53.6)	41 (60.3)	
Follow-up	119 (54.3)	79 (52.3)	40 (58.8)	
Alcohol consumption, yes				
Baseline	30 (13.7)	20 (13.2)	10 (14.7)	0.8
Follow-up	33 (15.1)	25 (16.6)	8 (11.8)	0.4
Metabolic Syndrome, yes				
Baseline	96 (43.8)	65 (43.0)	31 (45.6)	0.5
Follow-up	89 (40.6)	58 (38.4)	31 (45.6)	0.1
Depression, yes				
Baseline	59 (26.9)	37 (24.5)	22 (32.4)	0.2
Follow-up	61 (27.9)	41 (27.2)	20 (29.4)	0.7
Clock-Drawing test				
Baseline				0.1
Correct	19 (8.7)	17 (11.3)	2 (2.9)	
Minimal errors	39 (17.8)	27 (17.9)	12 (17.6)	
Major errors	161 (73.5)	107 (70.9)	54 (79.4)	
Follow-up				0.1
Correct	28 (12.8)	24 (15.9)	4 (5.9)	
Minimal errors	32 (14.6)	22 (14.6)	10 (14.7)	
Major errors	159 (72.6)	105 (69.5)	54 (79.4)	
MMSE				< 0.001
Baseline	22.21 ± 4.22	24.00 ± 3.12	18.22 ± 3.56	
Follow-up	21.68 ± 4.91	22.80 ± 4.20	19.18 ± 5.44	
ADAM10, pg/mL				
Baseline	1973.34 ± 1025.88	2021.36 ± 1069.04	1875.10 ± 931.55	0.4
Follow-up	2541.31 ± 2088.53	2494.11 ± 2058.67	2637.15 ± 2160.94	0.5

Continuous data are presented as mean ± standard deviation or median [interquartile range]. Categorical variables are presented as counts (percentage); MMSE, Mini-Mental State Examination.

Longitudinal analyses of changes in the MMSE scores over time were performed using the linear mixed-effects model considering the values of the MMSE score in the follow-up and incorporating the existing variability in each individual on the models. Taking as a reference the model with a random effect on the intercept, it was decided to adjust different models in relation to the response variable and the number of variables included in the model. Table 2 shows that in the first model, having an altered MMSE and ADAM10 was significantly associated with MMSE score values in the follow-up assessment ($p < 0.001$ and 0.03, respectively). The same occurred when introducing the variable age and sex in the model (Model 2). However, Model 3 shows that when adjusting for baseline MMSE score values, having an altered MMSE and sex lost their significance. On the other hand, it corrected intercept variability.

Table 2
Estimates of the fixed and random parts of the models with random effect on the intercept, using MMSE score values on follow-up as the dependent variable.

	Model 1			Model 2			Model 3		
Fixed effects	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
Intercept	24.09	0.38	< 0.001	37.73	2.33	< 0.001	10.19	1.73	< 0.001
Age, years	-	-	-	-0.20	0.03	< 0.001	-0.11	0.01	< 0.001
Male Sex	-	-	-	0.94	0.46	0.04	0.18	0.25	0.4
Altered MMSE	-5.04	0.54	< 0.001	-4.79	0.49	< 0.001	0.60	0.35	0.08
ADAM10, pg/mL	-0.0002	0.0001	0.03	-0.0002	0.0001	0.02	-0.0002	0.00007	0.003
Baseline MMSE score	-	-	-	-	-	-	0.90	0.03	< 0.001
Random effects	**Variance**	**SD**		**Variance**	**SD**		**Variance**	**SD**	
Individuals (Intercept)	9.38	3.06		7.21	2.69		0.0	0.0	
Residuals	7.01	2.65		7.01	2.65		6.02	2.45	
Bayesian Information Criterion	2175			2148			1871		

SE, Standard error; SD, Standard deviation; MMSE, Mini-Mental State Examination.

The interaction of the baseline grouping and ADAM10 levels with time was also investigated - which in this case is the time of assessment (Table 3). The interaction term between the grouping variable and time was statistically significant, that is, the effect of each baseline grouping on the MMSE score values on follow-up varies with time. The same occurred with ADAM10. Looking at the estimates of having a normal MMSE and the ADAM10 plasma levels, it can be observed that both have a significant and independent negative association with MMSE score values on the follow-up assessment. The impact of age and sex is shown in both models 5 and 7.

Table 3
Estimates of the fixed and random parts of the models with interactions and random effect on the intercept, using MMSE score values on follow-up as the dependent variable.

	Model 4			Model 5			Model 6			Model 7		
Fixed effects	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
Intercept	1.09	0.79	0.1	10.21	1.57	< 0.001	0.57	1.00	0.5	10.01	1.72	< 0.001
Age, years	-	-	-	-0.11	0.01	< 0.001	-	-	-	-0.11	0.01	< 0.001
Male Sex	-	-	-	0.18	0.24	0.4	-	-	-	0.18	0.24	0.3
Altered MMSE: Follow-up assessment	1.02	0.44	0.02	1.03	0.42	0.01	-	-	-	-	-	-
Normal MMSE: Follow-up assessment	-0.88	0.45	0.05	-0.66	0.43	0.1	-	-	-	-	-	-
ADAM10: Follow-up assessment	-	-	-	-	-	-	-0.0002	0.00007	0.003	-0.0002	0.00007	0.001
Altered MMSE	-	-	-	-	-	-	0.85	0.36	0.02	0.63	0.35	0.07
ADAM10, pg/mL	-0.0001	0.00007	0.01	-0.0002	0.00007	0.005	-	-	-	-	-	-
Baseline MMSE score	0.95	0.03	< 0.001	0.90	0.03	< 0.001	0.96	0.03	< 0.001	0.90	0.03	< 0.001
Random effects	**Variance**	**SD**		**Variance**	**SD**		**Variance**	**SD**		**Variance**	**SD**	
Individuals (Intercept)	0.0	0.0		0.0	0.0		0.0	0.0		0.0	0.0	
Residuals	6.35	2.52		5.74	2.39		6.57	2.56		5.95	2.44	
Bayesian Information Criterion	1893			1862			1901			1871		

SE, Standard error; SD, Standard deviation; MMSE, Mini-Mental State Examination.

Finally, we investigated further if there was an interaction of the baseline grouping with ADAM10, adjusting it for the time of assessment. Table 4 shows that the interaction term between the baseline grouping and ADAM10 plasma levels was statistically significant, that is, the effect of ADAM10 plasma levels on decreasing MMSE score values on follow-up varies with the baseline grouping, and it seems to be more pronounced in those with normal MMSE at baseline.

Table 4
Estimates of the fixed and random parts of the models with interaction of the baseline grouping with ADAM10, and random effect on the intercept, using MMSE score values on follow-up as the dependent variable.

	Model 8			Model 9		
Fixed effects	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
Intercept	1.87	0.82	0.02	11.06	1.59	< 0.001
Age, years	-	-	-	-0.11	0.01	< 0.001
Male Sex	-	-	-	0.17	0.25	0.4
Altered MMSE: ADAM10	-0.00006	0.0001	0.5	-0.00008	0.0001	0.4
Normal MMSE: ADAM10	-0.0002	0.00008	0.005	-0.0002	0.00008	0.002
Baseline MMSE score	0.93	0.03	< 0.001	0.88	0.03	< 0.001
Follow-up assessment	-0.46	0.26	0.08	-0.44	0.25	0.07
Random effects	**Variance**	**SD**		**Variance**	**SD**	
Individuals (Intercept)	0.0	0.0		0.0	0.0	
Residuals	6.64	2.58		6.0	2.45	
Bayesian Information Criterion	1905			1875		

SE, Standard error; SD, Standard deviation; MMSE, Mini-Mental State Examination.

Discussion

Biomarkers for AD are highly needed in clinic, especially those based on samples of easy collection, such as blood (5, 10). Currently, validated AD biomarkers are represented by neuroimage measures and quantification of the βA peptide, t-tau and p-tau derived from CSF, both requiring specific equipment or invasive procedures, respectively. Attempts to validate the CSF biomarkers were also made in blood, although demanding high-performance analytical tools for their detection (24). The interassay variability and inconsistency of βA measurements in plasma are main factors that impair the interpretation of results and represent major obstacles to their clinical use (25). However, recently promising results have demonstrated that blood p-tau181 is capable to predict tau and βA pathologies and to differentiate AD from other neurodegenerative disorders (26), hence supporting this tissue as a useful source for AD biomarker investigations, aiming to develop simple, accessible, and scalable tests for screening and diagnosis of AD.

In previous studies, we and others have shown that levels of membrane-bound ADAM10 are reduced in platelets of patients with AD compared to cognitively healthy individuals (15, 16, 18) and that this reduction correlated with patients' cognitive performance, as measured by the CDT (27) or MMSE (14) scores. Moreover, levels and platelet ADAM10 activity were shown to be increased throughout cognitively healthy aging, pointing to the possibility that ADAM10 might contribute to or is a prerequisite for cognitively healthy aging (28). On the other hand, ADAM plasma levels were found to be increased as early as in patients with mild cognitive impairment (MCI), as well as in AD, compared to healthy controls (19). We hypothesized that these higher plasmatic ADAM10 levels found in MCI and AD patients represent less active protein bound at the platelet's membrane exerting the sheddase activity. This could also be the case of neuronal ADAM10, where inactive forms can be cleaved from the membrane and released in the CSF by other proteins.

In agreement with this hypothesis, ADAM10 itself can undergo shedding and be extracellularly released by other proteins from the ADAM family, ADAM9 and 15 (29), which can be the source of the plasmatic detection of this protein. In addition, recent findings of our group have demonstrated that in plasma and CSF samples of both healthy and AD patients, ADAM10 is unable to cleave a fluorogenic substrate, whereas in whole lysates of platelets and SH-SY5Y neuroblastoma cells, the protein is active (19).

The requirement of a membrane-bound form for ADAM10 activity was further highly supported by findings of a study showing that only the active form of this metalloproteinase is expressed at the surface of different cell types, including leukocytes derived from peripheral blood (30). Moreover, the negatively charged phospholipid phosphatidylserine (PS) translocation to the outer membrane leaflet is pivotal for ADAM10 to exert its sheddase function (31).

In previous studies, we demonstrated that the levels of ADAM10 in platelets had sensitivity and specificity of 80 and 91% respectively, to identify AD patients versus controls matched by sex and age. (14). These experiments were performed in platelets, where we have shown that the protein is

active, as it is bound to the membrane. When considering plasmatic ADAM10, the protein achieved 72% sensitivity and 100% specificity, at the cut-off > 1765 pg/mL, to correctly differentiate among healthy controls *versus* MCI and AD patients (19).

Here, we used different models to investigate whether the plasmatic levels of ADAM10 would be efficient to predict cognitive declines in older adults after a 3-year follow-up period. We showed that the increase in ADAM10 plasma levels influences the decrease of the MMSE score values in the follow-up, and this seems to be more significant in those with normal MMSE at baseline, therefore proving that ADAM10 plasma levels can be a predictor of cognitive decline.

A systematic review and meta-analysis found six blood-based AD candidate biomarkers from different proteomic studies that exhibited a consistent pattern of regulation in three or more independent cohorts, namely alpha-2-macroglobulin (α2M), pancreatic polypeptide (PP), apolipoprotein A-1 (ApoA-1), afamin, insulin growth factor binding protein-2 (IGFBP-2) and fibrinogen-γ-chain (8). Most of these biomarkers are related to systemic inflammatory responses rather than with AD pathophysiology itself. This can bring into question the fact that inflammation *per se* is a response already found in several age-related diseases, common throughout aging.

It is important to highlight that MMSE is a screening tool for cognitive impairment that detects losses in the evolutionary follow-up of dementias (22). However, in some populations, individuals with lower educational levels perform worse than individuals from countries with high levels of education, but still have no cognitive decline. Regarding this, MMSE cut-offs were validated for each population, including the Brazilian one (23, 32). Hence, the results found here may not represent the general population and should be adapted for different specificities, such as the education level.

Other limitations of this work include the evaluation of a single AD blood biomarker candidate, instead of a panel or a signature that would be more representative of the longitudinal changes in cognition. Moreover, a lack of a complete battery including the application of a diverse set of instruments does not allow a detailed cognitive evaluation of the participants. Yet, this is the first longitudinal study investigating the effects of plasmatic ADAM10 level changes on cognition.

Conclusions

The results presented here provide the first direct evidence that changes in ADAM10 plasma levels can predict cognitive worsening in older adults, supporting its complementary clinical use for the AD diagnosis, in addition to the classical CSF-based biomarkers. This work can shed light on the study of blood-based AD biomarkers, open up new possibilities for investigations and contribute to the advancement of the field.

Abbreviations

α2M: alpha-2-macroglobulin; bA: b-amyloid peptide; AD: Alzheimer's disease; ADAM10: a disintegrin and metalloproteinase; ApoA-1: apolipoprotein A-1; APP: amyloid precursor protein; BBB: blood-brain barrier; CDT: Clock Drawing test; CSF: cerebrospinal fluid; ELISA: Enzyme-linked immunoassay; GDS: geriatric depression scale; IGFBP-2: insulin growth factor binding protein-2; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; p-tau: phosphorylated tau; PP: pancreatic polypeptide; PS: phosphatidylserine; t-tau: total tau

Declarations

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Authors' contributions

MPAOM, DSMSO, PRM, CMCN, AASA, GAOG, FSO: participated in data collection and analysis. MSZ: participated and data collection and analysis and funding acquisition. HPJ: performed statistical analyses, interpreted the data and was a major contributor in writing the manuscript. MRC: participated and data collection and analysis, interpreted the data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was performed according to the ethical principles of the Declaration of Helsinki and was approved by the Federal University of Sao Carlos' ethics committee. Written informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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