Research Article

Diagnostic accuracy of salivary biomarkers in Alzheimer's disease: A systematic review

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Abstract: Background: Alzheimer's disease causes cognitive decline and neuronal death due to amyloid-beta plaques and neurofibrillary tangles. Current diagnostic methods are intrusive, expensive, and few, but early diagnosis improves patient outcomes. Due to its oral-brain axis relationship to the central nervous system, saliva may be a viable source of non-invasive Alzheimer's biomarkers. This systematic review aimed to assess the diagnostic potential of salivary biomarkers for Alzheimer's disease by carefully reviewing the existing data. Methodology: Studies published between January 1, 2008, and September 30, 2023, were the subject of a thorough literature search in the PubMed, Scopus, and Web of Science databases. Relevant data were extracted after studies were evaluated according to predetermined inclusion and exclusion criteria. The Oxford Centre for Evidence-Based Medicine criteria were implemented to evaluate the quality of the studies that were incorporated. Results: A total of 36 studies were included in the systematic review, as they met the inclusion criteria. Alzheimer's disease patients exhibited significantly elevated salivary levels of beta-amyloid- 42 and p-tau in comparison to healthy controls. Patients with Alzheimer's disease exhibited non-significant trends in salivary t-tau and lactoferrin. Conclusion: The levels of beta-amyloid-42 and p-tau in the saliva of patients with Alzheimer's disease are significantly altered. Beta-amyloid-42 regard as a best marker in early diagnosis by salivary sample. These findings emphasize the prospect of saliva as a non-invasive source of biomarkers for the diagnosis of Alzheimer's disease. Nevertheless, salivary tests must undergo additional validation in larger, well-characterized cohorts and standardization of methodologies before they can be implemented in clinical practice.

Keywords: Alzheimer's disease, Salivary biomarkers, Systematic review, saliva proteomics.

Introduction

Alzheimer's disease (AD) is a severe neurological disease that gradually deprives persons of their memories, cognitive functions, and finally, their identity. Globally, Alzheimer's disease (AD) is the primary underlying factor contributing to the development of dementia. Hence, Alzheimer's disease imposes a significant burden not only on the individuals affected by it, but also on their family members and the

broader community[1,2]. Despite ongoing efforts utilizing advanced technologies, existing diagnostic procedures are unable to detect the early stages of the disease, hence reducing the effectiveness of treatment. Therefore, the primary objective that clinicians should undertake is to promptly diagnose the disease [3].

AD is caused by a complicated and multifaceted pathophysiology that involves the buildup of beta-amyloid (Aβ) plaques, the presence of phosphorylated tau (p tau) in the brain, damage to synapses, loss of neurons, oxidative stress, neuroinflammation, and impaired metabolism of mitochondria [4–6]. The accumulation of degenerative processes results in brain atrophy and the manifestation of dementia symptoms, including memory loss, apathy, and impaired ability to carry out everyday activities [7]. The diagnosis of Alzheimer's disease (AD) should rely on the assessment of molecular indicators and clinical symptoms. Standard diagnostic techniques, such as cerebrospinal fluid biomarkers, together with imaging procedures like magnetic resonance imaging (MRI) and positron emission tomography (PET), are used to assess regions of brain shrinkage, impaired metabolism, and aberrant buildup of chemicals [8–10]. However, these procedures are invasive and expensive, and a significant number of individuals are unable to utilize them, prompting the exploration of alternative approaches. Several theories have been proposed to explain the emergence of salivary biomarkers related to AD. One theory suggests that neurons may leak biomarkers into the salivary glands because they are near the central nervous system [11]. Saliva, being a readily accessible and non-invasive bodily fluid, has demonstrated potential in indicating a range of pathophysiological states, such as gastrointestinal, thyroid, oncological, autoimmune, cardiovascular diseases, and neurological disorders. The oral-brain axis, which involves many routes linking the oral cavity and the central nervous system, presents an opportunity to identify signs of Alzheimer's disease in saliva [12–16].

The primary question that governs this systematic review is: "Is it feasible to employ salivary biomarkers for the diagnosis of Alzheimer's disease with a high degree of reliability?" This review explores the current state of reported evidence to provide a comprehensive report on the most promising salivary biomarkers for AD, their diagnostic capabilities, and the challenges and opportunities that practitioners encounter in this rapidly evolving field. Finally, we aim to expand the boundaries of technology by promoting non-invasive and accessible diagnostic methods to aid in early diagnosis. This, in turn, can be beneficial for treatment and alleviate the significant burden of this disease on the individual, family, and society.

Search Strategy and Data Extraction

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) provide a framework to conduct these systematic reviews [17] . We conducted a search in the databases of PubMed, Scopus, and Web of Science, specifically looking at the references published between 01/01/2008 and 30/09/2023. In addition, we have executed search strategies. The search terms used were meticulously designed to capture pertinent material.

The Boolean operators utilize the following combinations:

- For PubMed: (saliva) AND (marker OR biomarker OR enzyme OR metabolite OR hormone) AND (Alzheimer).
- For Scopus: (saliva) AND (marker OR biomarker OR enzyme OR metabolite OR hormone) AND (Alzheimer).

- For Web of Science: (saliva) AND (marker OR biomarker OR enzyme OR metabolite OR hormone) AND (Alzheimer).

The search results were then manually refined to exclusively encompass journal articles published on or after January 1st, 2008. It is crucial to emphasize that the search method is organized to encompass topics related to AD. This review being reviewed by two authors and in case of any discrepancies or disagreement the third author would solve these discrepancies. During the systematic screening procedure, two distinct reviewers conducted searches for pertinent publications based on their titles, abstracts, and full texts. Only studies that met the pre-established criteria based on the PICO framework, which stands for Population, Intervention, Comparison and Outcomes were included in this study.

Materials and Methods

Inclusion and exclusion criteria

Population: Ensured that both genders were represented, and the participants were from all age categories, in this instance, the decision is to preserve the statistical robustness of a randomized controlled trial (RCT) by enrolling a minimum of 15 patients, and preferably more. The studies that had a sample size of less than 15 patients or controls were excluded.

Intervention: The primary objective of the systematic review was to address Alzheimer's disease. Excluded studies that examined other diseases, such as Mild Cognitive Impairment (MCI), in order to preserve the specificity of our research inquiry.

Comparison: The presence of a non-demented control group was a critical component of the inclusion criteria for the purpose of comparison. Research that did not include a non-demented control group was considered ineligible for inclusion.

Results: The primary focus of our review was the alterations in the levels of salivary markers. Excluded studies that examined changes in markers from other biological samples, such as serum, or that investigated the microbiota, as they were not within the scope of the research question.

Study design: Incorporated case-control, cohort, and cross-sectional studies to guarantee a comprehensive and robust analysis. Nevertheless, literature reviews, case reports, expert opinions, letters to the editor, and conference reports were excluded.
Furthermore, to guarantee that the most pertinent and recent literature was incorporated, the search was limited to studies published after January 1, 2008. Additionally, this systematic review exclusively analyzed studies that were published in the English language.

This systematic review endeavored to maintain a high level of scientific integrity and relevance by conducting a comprehensive and rigorous analysis of the changes in salivary markers for the diagnosis of Alzheimer's disease in accordance with these well-defined inclusion and exclusion criteria.

Assessment of the quality of study: This systematic review utilizes a rigorous evaluation of the quality and reliability of evidence from the studies included. It employs the evidence classification scheme developed by the Oxford Centre for Evidence-Based Medicine (OCEBM)[18] which is widely recognized and

respected in the field. The purpose of this five-level scale is to evaluate the accuracy of diagnostic investigations and determine their reliability. Higher levels on the scale indicate stronger and more dependable evidence.

Quality Assessment and Critical Appraisal for the Systematic Review of Included Studies

The quality of studies involved in the systematic review was given a score of 0 to 9 using the Newcastle-Ottawa Scale (NOS) [19]. The final score was converted into categories of good (7 to 9), fair (4 to 6), and poor (0 to 3) according to the Agency for Healthcare Research and Quality standards (AHRQ).

Results

Literature search

Identification Phase: A total of 1,307 records were obtained from the initial search across three databases (PubMed, Scopus, and Web of Science). PubMed recorded 346 records, Scopus recorded 521 records, and Web of Science recorded 440 records. After the removal of duplicate records, there were 549 unique records.

Screening Phase: The titles and abstracts of the 758 remaining records were considered during the screening process. Following this screening process, 616 records were eliminated leaving 142 reports that were submitted for retrieval.

Eligibility Phase: One report out of the 142 report was unable to be retrieved. Consequently, 141 reports were evaluated for eligibility according to the predetermined inclusion and exclusion criteria.

During this audit, a total of 105 reports were eliminated due to the following reasons:

A total of 63 reports were deemed irrelevant to the review.

There were 36 reports specifically related to Parkinson's disease were excluded.

4 reports had a sample size smaller than 15 ($n < 15$).

Two reports were categorized as other articles, such as literature reviews and case reports.

Inclusion Phase: Following a thorough screening and assessment process, 36 reports of eligible research were selected for further analysis and synthesis in the systematic review as shown in PRISMA chart in figure 1.

Quality of the included studies

Upon careful examination of the studies evaluated, it can be determined that all included studies were in the third or fourth level of evidence, as per the OCEBM standards. These levels pertain to case-control studies, which are observational studies that include comparing a group of persons with a certain disease (cases) to a group without the disease (controls). (Table 1)

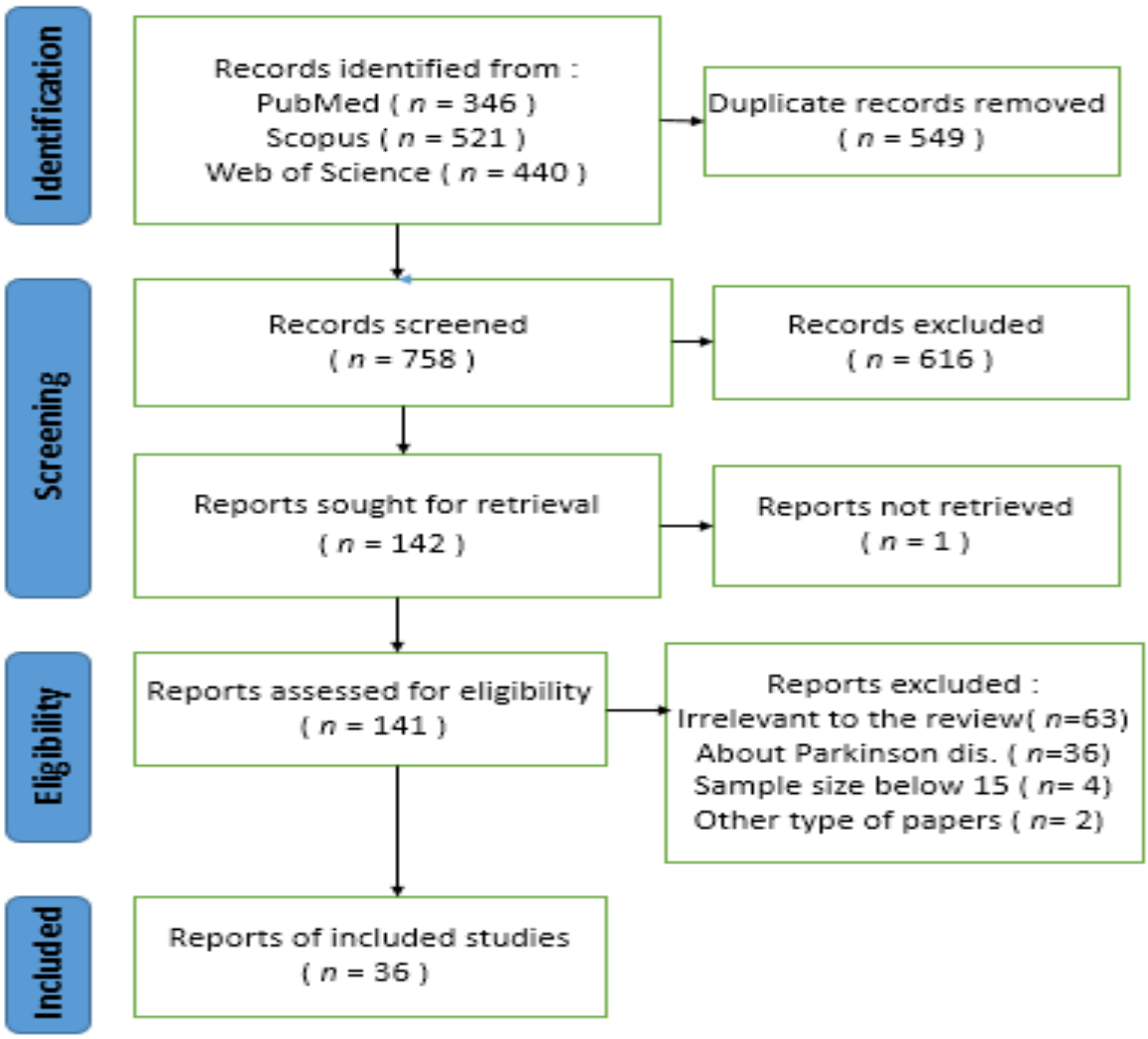

Figure 1: PRISMA chart of the included studies

Assessing Risk of bias

The assessment of the quality of studies using the NOS is shown in Tables 2 and 3. Four studies received a full score. Twenty (56%) of the studies fell into the good category, whereas sixteen (44%) of the studies were fair. The non-respondent rate in cross-sectional and case-control studies received the lowest scores.

Characteristics of the studies

The extensive data obtained from our team's research was carefully filtered according to the inclusion criteria. This table presents the salivary biomarkers for Alzheimer's disease (AD) and provides readers with a comprehensive summary of the current research on salivary biomarkers for AD. The table not only provides a summary of the key features of each study, such as the year of publication, geographical location, and demographics, but also includes important methodological details. Peña-Bautista et al., 2020 studied the minimum number, 14 AD patients [20]. While, Carro et al., 2017 studied the maximum number,80 AD patients [21]. The studies classified according to the continents as (10) from Asia, (15) from Europe, (7) from North America, (2) from South America, (2) from Australia. Most of studies found a significant increase of salivary Aβ42 in AD patients [7,22–25] so, we can regard Aβ42 as a best marker in early AD

diagnosis by salivary sample. Most of studies used enzyme-linked immunosorbent assay (ELISA) as a method of markers determination[21–34] so, it is considered as a better method. These details are essential for evaluating and comparing the results of different studies as shown below in Table 4.

Table 1: Results of Oxford Centre for Evidence-Based Medicine

Study	Year	Level
Ashton et al [11]	2018	3b
Peña-Bautista et al [20]	2019	4
Carro et al [21]	2017	3b
Bermejo-Pareja et al [22]	2010	4
Santos et al [23]	2020	4
Katsipis et al [24]	2021	3b
Zalewska et al [25]	2021	3b
Lau et al [26]	2017	4
lee et al [27]	2017	3b
McGeer et al [28]	2018	4
Pukhalskaia et al [29]	2020	4
González-Sánchez et al [30]	2020	3b
Gleerup et al [31]	2021	3b
McNicholas et al [32]	2022	4
Sabaei et al [33]	2023	3b
Huan et al [34]	2018	3b
Peña-Bautista et al[35]	2020	4
Lau et al [36]	2015	3b
Shi et al [37]	2023	3b
Bakhtiari et al [38]	2017	3b
Yilmaz et al [39]	2017	3b
Sabbagh et al [40]	2018	3b
Tvarijonaviciute et al [41]	2020	3b
Boschi et al [42]	2022	3b
Eldem et al [43]	2022	3b
Marksteiner et al [44]	2022	3b
Boston et al [45]	2008	4
Souza-Talarico et al [46]	2008	4
Kim et al [47]	2014	4
Liang et al [48]	2015	4
Ahmadi-Motamayel et al [49]	2019	4
Pekeles et al [50]	2019	4
François et al [51]	2021	4
Cui et al [52]	2022	4
Ryu et al [53]	2023	4
Contini et al [54]	2023	4

Table 2: Assessment of case control studies involved in the systematic review using Newcastle – Ottawa quality scale.

	Year	Selection				Compa-rability		Outcome		Total
		Is the case definition ade-quate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls based on the design	Ascertainment of exposure	Same method of ascertain-ment for cases and controls	Non-Response rate	
Peña-Bautista et al [20]	2019	*	*	*	*	*	*	*		7
Bermejo-Pareja et al[22]	2010	*	*	*	*	**	*	*	*	9
Santos et al [23]	2020	*	*	*	*	*	*	*		7
Lau et al [26]	2017	*	*	*	*	*	*	*	*	8
McGeer et al [28]	2018	*	*	*	*	*	*	*		7
Pukhalskaia et al [29]	2020	*	*	*	*	*	*	*		7
McNicholas et al [32]	2022	*	*	*	*	*	*	*		7
Peña-Bautista et al [35]	2020	*	*	*	*	*	*	*		7
Boston et al [45]	2008	*	*	*	*	*	*	*	*	8
Souza-Talarico et al [46]	2008	*	*	*	*	*	*	*		7
Kim et al [47]	2014	*	*	*	*	*	*	*	*	8
Liang et al [48]	2015	*	*	*	*	*	*	*		7
Ahmadi-Mota-mayel et al [49]	2019	*	*	*	*	*	*	*	*	8
Pekeles et al[50]	2019	*	*	*	*	*	*	*	*	9
François et al [51]	2021	*	*	*	*	**	*	*	*	9
Cui et al [52]	2022	*	*	*	*	**	*	*	*	9
Ryu et al [53]	2023	*	*	*	*	*	*	*	*	8
Contini et al [54]	2023	*	*	*	*	*	*	*	*	8

Newcastle-Ottawa scale adapted for (case control) studies; good studies: 7- 9; fair: 4-6 points; poor: 0-3 points, each category with selection and outcome can be awarded up to one star, comparability can be awarded up to two stars.

Table 3: Assessment of case studies involved in the systematic review using Newcastle – Ottawa quality scale.

Study	Year	Selection				Comparability	Outcome		Total
		Representativeness of the cases	Sample size	Non-Response rate	Ascertainment of the screening/surveillance	The potential confounders were investigated by subgroup analysis or multivariable analysis.	Assessment of the outcome	Statistical test:	
Ashton et al [11]	2018	*			*	*	*	*	5
Carro et al [21]	2017	*	*		*	*	*	*	6
Katsipis et al [24]	2021	*	*		*	*	*	*	6
Zalewska et al [25]	2021	*	*		*	*	*	*	6
lee et al [27]	2015	*	*	*	*	*	*	*	7
González-Sánchez et al [30]	2020	*	*		*	*	*	*	6
Gleerup et al [31]	2021	*	*		*	*	*	*	6
Sabaei et al [33]	2023	*	*		*	*	*	*	6
Huan et al [34]	2018	*	*		*	*	*	*	6
Lau et al [36]	2015	*	*		*	*	*	*	6
Bakhtiari et al [38]	2017	*	*		*	*	*	*	6
Yilmaz et al [39]	2017	*	*		*	*	*	*	6
Sabbagh et al [40]	2018	*	*		*	*	*	*	6
Tvari-jonaviciute et al [41]	2020	*	*		*	*	*	*	6
Boschi et al [42]	2022	*			*	*	*	*	5
Eldem et al [43]	2022	*	*	*	*	*	*	*	7
Marksteiner et al [44]	2022	*	*		*	*	*	*	6
Shi et al [55]	2011	*	*		*	*	*	*	6

Newcastle-Ottawa scale adapted for cross-sectional studies; good studies: 7- 9; fair: 4-6 points; poor: 0-3 points

Table 4: Characteristics of included studies

Author, Year	Study Group (F/M), Age (year)	Control Group, (F/M), Age (year)	Method of Marker Determination	Salivary Biomarkers
Ashton et al., 2018 [11]	AD: 53 (30/23), (81.4 ± 6.6); MCI: 68 (35/33), (79.8 ± 6.4)	160 (94/66), (78.0 ± 6.7)	SIMOA	t-tau (NS)
Peña-Bautista et al 2019 [20]	mild AD: 50 (29/21), 70(68-74); MCI-AD: 47 (30/17), 71(69-74)	41 (16/25), 66 (62-69)	UPLC-MS/MS	cortisol (NS)
Carro et al., 2017 [21]	AD: 80 (49/31), (76.2 ± 5.33) ; MCI: 44 (25/19), (75.16 ± 5.13)	91 (59/32), (73.7 ± 6.88)	ELISA	lactoferrin
Bermejo-Pareja et 2010 [22]	AD: 70 (49/21), 77.20(60-91)	56 (39/17), 74.35(64-85)	ELISA	Aβ42, Aβ40 (NS) (beta-amyloid)
Santos et al., 2020 [23]	AD: 60 (NR), NR	60 (NR), NR	ELISA	Aβ42, t-tau
Katsipis et al., 2021 [24]	AD: 20 (9/11), (75 ± 5.5); MCI: 20 (12/8), (75 ± 7.2)	20 (11/9), (79 ± 4.7)	ELISA, Dot Blot, Western Blot	GFAP, p-tau, IL-1β, IL-6, TNF-α, caspase-8, COX-2, Aβ42
Zalewska et al., 2021 [25]	AD: 25 (15/10), (81.19 ± 6.77)	25 (15/10), (82.1 ± 6.67)	colorimetric, spectrofluorimetric, spectrophotometric methods, thioflavin T fluorescence, ELISA	Aβ, lactoferrin, IL-1β, SOD, CAT, GPx, UA (NS), GSH, TAC (NS), TOS, AGE, AOPP, MDA, NO, peroxynitrite, nitrotyrosine
Lau et al., 2017 [26]	AD: 28, (76.4±1.8)	17, (63.4±1.6)	EG-IDFET biosensor	Trehalose
Lee et al., 2017 [27	AD: 28, (77.3±1.3)	17, (67.8±1.4)	ELISA	Aβ42
McGeer et al., 2018 [28]	AD: 27, (83.0±1.5)	28, (68.0±1.3)	ELISA	Aβ42
Pukhalskaia et al., 2020 [29]	AD: 64 (NR), elderly (63.0 ± 2.4), senile (82.0 ± 2.3)	58 (NR), NR	ELISA	SIRT1, SIRT3, SIRT5 (NS), SIRT6
González-Sánchez al., 2020 [30]	AD-PET+: 25 (12/13), (67.2 ± 9.2), MCI-PET+: 21 (8/13), (68.8 ± 7.5)	Control-PET-: 48 (33/15), 66.9 ± 5.9; control-PET+: 4 (2/2), (75.9 ± 3.6)	ELISA	lactoferrin
Gleerup et al., 2021 [31]	AD: 71 (41/30), (72.1 ± 7.3); MCI: 56 (27/29), (70.4 ± 8.2)	20 (8/12), (65.7 ± 10.1)	ELISA	lactoferrin
McNicholas et al., 2022 [32]	AD: 16 (6/10), (79 ± 6); MCI: 15 (8/7), (76 ± 6)	29 (14/15), (74 ± 8)	ELISA	cystatin-C, IL-1 receptor antagonist, stratifin, haptoglobin, matrix metalloproteinase 9
Sabaei et al., 2023[33]	AD: 24 (10/14), (73.5 ± 9.8)	22 (13/9), (64.1 ± 9.2)	ELISA	Aβ 1--42, p-tau, α-synuclein
Huan et al., 2018[34]	AD: 22 (16/6), (77.09 ± 11.20); MCI: 25 (15/10), (70.40 ± 3.38)	35 (22/13), (69.94 ± 3.80); 10 (5/5), (71.40 ± 2.84)	LC-MS	metabolomics
Peña-Bautista et al 2020 [35]	mild AD: 14 (NR), NR; MCI-AD: 17 (NR), NR	12 (NR), NR	UPLC-MS/MS	aspartic acid (NS), glutamic acid (NS), glutamine, GABA (NS), creatine, taurine, N-acetyl aspartate (NS), myoinositol, acetylcholine
Lau et al., 2015 [36]	AD: 20 (12/8), (72.5 ± 7.68)	20 (15/5), (66.1 ± 7.79)	ELISA, EG-ISFET	Aβ42 (not detected), p-tau (NS), t-tau (NS), trehalose
Bakhtiari et al., 2017 [38]	AD: 15 (6/9), 78.4 (64-90)	15 (8/7), 71 (61-85)	Ellman colorimetric method	AChE (NS)

Yilmaz et al., 2017 [39]	AD: 22, (70.5±1.8)	35, (69.7±1.2)	Proton NMR spectroscopy	Propionate
Sabbagh et al., 2018[40]	AD: 15, (77.8±1.8)	7, (70.4±3.5)	ELISA	Aβ42
Tvarijonaviciute et al., 2020 [41]	AD: 69 (NR), NR	83 (NR), NR	MILLIPLEX MAP, automated spectrophotometric method	FRAP (NS), ADA (NS), ChE (NS), Hp (NS), Aβ42, Aβ40 (NS), t-tau (NS), p-tau (NS), CRP (NS), PEDF (NS), SAP (NS), MIP-4 (NS), CC4, α1 antitrypsin (NS)
Boschi et al., 2022 [42]	AD: 18 (10/8), (72.13 ± 5.45)	18 (11/7), (65.67 ± 12.02)	ELISA	Aβ42
Eldem et al., 2022 [43]	AD: 17 (9/8), (72 ± 1.36); MCI: 21 (16/5), (73 ± 1.51)	19 (13/6), (64 ± 2.63)	LC-MS/MS, Western Blot, FASP	proteomics, t-tau (NS), transthyretin
Marksteiner et al., 2022 [44]	AD: 44 (25/19), (79 ± 1); MCI: 45 (25/20), (74 ± 1)	27 (14/13), (71 ± 1)	HPLC-EC, robotic-automated enzymatic Lumipulse assay	norepinephrine, p-tau (NS), t-tau, Aβ40 and Aβ42 (not detected in cases)
Boston et al., 2008 [45]	AD: 15, (77.6±6.6)	13, (68.8±9.1)	Ellman's colorimetric method	AchE activity
Souza-Talarico et al., 2008 [46]	AD:40 (27/13), (80.1 ± 6.0)	40 (35/5), (72.2 ± 6.3)	Radioimmunoassay	Cortisol
Kim et al., 2014 [47]	AD: 28, (66-88)	17, (65-87)	Immunoassay with nanobeads	Aβ42, Aβ40
Liang et al., 2015 [48]	AD: 256 (NR)	218 (NR)	FUPLC-MS	metabolomics
Ahmadi-Motamay et al., 2019 [49]	AD: 30 (NR), (70.57±6.317)	30 (NR), (66.50±8.046)	Ellman colorimetric method	AChE, PChE (Pseudo-cholineesterase)
Pekeles et al., 2019 [50]	AD: 46 (22/24), (80 ±9); MCI: 55 (32/23), (78 ±14)	47 (32/15), (73 ±6)	Western Blot, tau antibodies	p-tau (T181 (NS), S396, S404, S400, T403, T404)
François et al., 2021 [51]	AD: 20 (8/12), 78.0; MCI: 20 (11/9), 77.8	40 (19/21), 75.3	GC-MS, LC-MS	proteomics, metabolomics
Cui et al., 2022 [52]	AD: 30 (NR), NR	30 (NR), NR	-	Aβ42, Aβ40 (NS)
Ryu et al., 2023 [53]	AD: 27 (12/15), (72.59 ± 6.90)	13 (11/2), (75.46 ± 6.58)	qPCR	miRNA-485-3p
Contini et al., 2023 [54]	AD: 35 (23/12), (80 ± 6)	36 (18/18), (78 ± 6)	RP-HPLC-LR-ESI-MS	proteomics
Shi et al., 2011 [55]	AD: 21 (11/10)	38 (19/19)	Luminex assays, IP/MS	t-tau, p-tau, Aβ42 (not detected)

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's Disease; ChE, cholinesterase; COX-2, cyclooxygenase 2; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillar acidic protein; LF, lactoferrin; MCI, mild cognitive impairment; NO, nitric oxide; NR, not reported; ns, not significant; OSI, oxidative stress index; p-tau, phosphorylated tau; qPCR, quantitative real-time polymerase chain reaction; SOD, superoxide dismutase; t-tau, total tau

Discussion

Based on the comprehensive analysis of this subject, it can be seen that some biomarkers have the ability to be identified in the saliva of individuals with Alzheimer's disease. This systematic review revealed a significant increase in beta-amyloid42 and phosphorylated tau (p Tau) levels in people with Alzheimer's disease compared to healthy individuals [1]. However, there was a slight decrease in total tau and lactoferrin levels, but this difference did not achieve statistical significance [56]. Moreover, the histopathological features of AD such as beta-amyloid plaques and hyperphosphorylated tau tangles are found to be in individual brain samples. Saliva contains the primary indicators for Alzheimer's disease (AD), suggesting that the development of non-invasive diagnostic procedures has great promise.

Beta-amyloid

The peptide which is mainly found in neurons and that can be present in pathological plaques which can be characterized as hallmark of AD is called beta-amyloid (Aβ) [57].

Many studies were in line with a significant increase of salivary Aβ42 in AD patients, [22–25,33,42] while others did not find such alteration [36,44]. Bermejo-Pareja et al. (2010) discovered that individuals with mild Alzheimer's disease (AD) had significantly elevated levels of salivary Aβ42 compared to the control group. They also observed a similar but non-significant trend in patients with moderate and severe AD [22]. The levels of Aβ42 showed a correlation with sex, whereas Aβ40 did not exhibit such correlation. In their study, Santos et al. (2020) found that there was a little increase in salivary Aβ42 levels in patients with Alzheimer's disease, however this increase was not statistically significant [23]. Cui et al. (2022) discovered a notable rise in Aβ42 levels, but not Aβ40 levels, in the saliva of individuals with Alzheimer's disease (AD). However, neither of these biomarkers alone demonstrated predictive capability [52]. Katsipis et al. (2021) and Boschi et al. (2022) found that individuals with Alzheimer's disease (AD) had noticeably higher levels of salivary Aβ42 compared to individuals without AD. This increase was observed regardless of gender or MMSE score [24,42]. Salivary Aβ42 had good diagnostic performance (AUC 0.806) With a cut-off value of 92.5 pg/mL, sensitivity and specificity are 0.84 and 0.68, respectively in Boschi et al. (2022) study.[42] In another study, Sabaei et al. (2023) found that individuals with Alzheimer's disease (AD) had significantly elevated levels of salivary Aβ1-42, even after accounting for age differences, Salivary Aβ 1–42 level at a 60.3 pg/ml cutoff point revealed an excellent performance for diagnosing AD (AUC: 0.81) [33]. Contrarily, Tvarijonaviciute et al. (2020) discovered a reduction in salivary Aβ42 levels in people with Alzheimer's disease (AD) when compared to individuals without the condition. This decrease was observed regardless of the stage of the disease, and no correlation was established between Aβ42 levels and the progression of the disease [41]. Zalewska et al. (2021) used thioflavin T fluorescence to evaluate the β-amyloid formation (The intensity of the amyloid associated with thioflavin T fluorescence was measured at 385/485 nm wavelength) and found significantly higher salivary Aβ in AD (AUC 0.949) [25]. Nevertheless, Lau et al. (2015), Marksteiner et al. (2022), and Shi et al. (2011) were unable to identify the presence of salivary Aβ40 or Aβ42 in individuals with Alzheimer's disease using ELISA, automated enzymatic tests, or Luminex technology [36,44,55,58].

Lactoferrin

Lactoferrin is an iron-binding protein with potential neuroprotective effects in AD [59]. Lactoferrin, a protein with neuroprotective effects and serving as a biomarker, has recently shown potential as a compelling candidate warranting additional investigation [59]. Most studies found significantly decreased salivary lactoferrin in AD and MCI patients compared to controls, [21,25,30] although one study found no difference [31]. Carro et al. (2017) reported significantly lower salivary lactoferrin in AD and MCI compared to controls, correlating with disease severity and MMSE scores. Lactoferrin had perfect diagnostic accuracy (AUC 1.0) [21]. González-Sánchez et al. (2020) found decreased lactoferrin in MCI and AD patients with positive amyloid PET scans versus controls (AUC 0.952) using the Youden's index, found that the optimal cut-off point to differentiate salivary Lactoferrin from MCI/AD-PET+patients and control-PET group was 5.63mg/ml [30]. Zalewska et al. (2021) also observed significantly reduced salivary lactoferrin in AD (AUC 0.690) [25]. However, Gleerup et al. (2021) found no significant difference and a non-significant trend for increased lactoferrin in AD saliva, possibly due to including milder, more heterogeneous cases [31].

Acetylcholinesterase and Related Enzyme

Acetylcholinesterase (AChE) breaks down the neurotransmitter acetylcholine and is a key AD treatment target [60,61]. Two studies reported conflicting results on salivary AChE activity in AD [38,49]. Pseudocholinesterase and general cholinesterase activity findings were also mixed [41,49]. Ahmadi-Motamayel et al. (2019) found significantly increased AChE and pseudocholinesterase activity in AD saliva, more so in males [49]. However, Bakhtiari et al. (2017) reported non-significantly decreased AChE activity in AD patients on memantine therapy [38]. Tvarijonaviciute et al. (2020) observed a non-significant trend for increased cholinesterase in AD saliva [41].

Tau Protein

Tau proteins stabilize neuronal microtubules but can become hyperphosphorylated and aggregate in AD, impairing synaptic function [62,63]. Studies found mixed results for salivary total tau (t-tau) and phosphorylated tau (p-tau) in AD. Shi et al. (2011) reported non-significantly decreased salivary t-tau and increased p-tau in AD, with a significantly higher p-tau/t-tau ratio [55].

Lau et al. (2015) detected p-tau and t-tau but found no differences between AD and controls [36]. Ashton et al. (2018) found a non-significant trend for increased salivary t-tau in AD, correlating with poorer cognition [11]. Cui et al. (2022) observed no relationship between p-tau and t-tau, but the p-tau/t-tau ratio was significantly higher in AD, Combining p-tau, t-tau, Aβ40 and Aβ42 had excellent diagnostic value (AUC 0.921) [52]. Santos et al. (2020) and Marksteiner et al. (2022) both reported significantly decreased salivary t-tau in AD patients [23,44]. However, Eldem et al. (2022) found no difference in t-tau levels between AD, MCI and controls using Western blot.[43]Marksteiner et al. (2022), and Sabaei et al. (2023) found significantly increased salivary p-tau in AD compared to controls, with good diagnostic performance [33,44]. Marksteiner et al. (2022) found laboratory diagnosis with a cut-off of ≥18 pg/mg protein pTau181 (for MCI) and ≤ 300 pg/mg protein tau (for AD) with an accuracy of 71.4% [44]. Sabaei et al. (2023) found the cut-off point of p-tau in AD patients equel to 5.1 pg/ml with (AUC: 0.78) [33]. Pekeles et al. (2019) reported significantly higher p-tau/t-tau ratios at specific phosphorylation sites in AD saliva.[50]However, Tvarijonaviciute et al. (2020) found no significant differences in salivary p-tau or t-tau between AD and controls [41].

Inflammation and Oxidative Stress Markers

AD involves chronic inflammation and oxidative damage [4,64]. Studies found altered levels of various salivary inflammatory and oxidative stress biomarkers in AD, such as haptoglobin, interleukins, TNF-alpha, antioxidant enzymes, and oxidative damage products [24,32,41].

Tvarijonaviciute et al. (2020) observed decreased haptoglobin, adenosine deaminase, and ferric-reducing ability of plasma, and increased macrophage inflammatory protein-4, α1-antitrypsin, complement C4, and pigment epithelium-derived protein in AD saliva, with only complement C4 being significant [41. Katsipis et al. (2021) found significantly decreased glial fibrillary acidic protein (GFAP), COX-2, and caspase-8, and increased IL-1β, IL-6, and TNF-α in AD saliva compared to MCI and controls. These markers had excellent diagnostic accuracy (AUC up to 1.0) and correlated with each other and MMSE scores. The proposed ELISA cut-off values, determined using the J indexes for various thresholds, are as follows: for cognitively healthy individuals, [GFAP] levels exceed 10.0 ng/mg; for MCI patients, [GFAP] levels range between 4.0 and 10.0 ng/mg (J index = 0.95, 95% sensitivity, and 100% specificity); and for AD patients, [GFAP] levels fall below 4.0 ng/mg of total protein (J index = 0.75, 75% sensitivity, and 100% specificity [24]. Zalewska et

al. (2021) reported significantly reduced antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase) and glutathione, and increased oxidative damage markers(nitric oxide, protein oxidation products, lipid peroxidation, interleukin-1β) in stimulated AD saliva. Many had good diagnostic performance like nitric oxide (AUC 0.672) with cut-off value > 0.1961 ng/mg [25]. McNicholas et al. (2022) found altered levels of cystatin-C, IL-1 receptor antagonist, stratifin, haptoglobin and matrix metalloproteinase 9 in AD and MCI saliva. Panels combining age, sex, APOE status and some of these markers adjusted for total protein had excellent accuracy to distinguish AD and MCI from controls (AUC 0.97) [32].

Cortisol

Cortisol is a stress hormone that may contribute to AD pathology [27,65]. One study found increased salivary cortisol in mild AD,[46]while another found no significant difference [20,66]. De Souza-Talarico et al. (2008) reported significantly higher salivary cortisol in mild AD patients compared to controls, with a non-significant trend correlating with worse working memory [46]. However, Peña-Bautista et al. (2019) found no significant association between AD and salivary cortisol despite a non-significant increase.

Amino Acids and Derivatives

Altered levels of amino acids and derivatives in AD saliva may reflect impaired neurotransmission. [67,68] Peña-Bautista et al. (2020) found significantly increased acetylcholine in mild AD, and decreased creatine and myoinositol in AD saliva compared to controls [35]. These correlated with cognitive scores and combining them had good diagnostic accuracy (AUC 0.806). Marksteiner et al. (2022) reported significantly decreased salivary norepinephrine in AD patients [44].

miRNAs and Sirtuins

MicroRNAs regulate gene expression and sirtuins are neuroprotective enzymes [69,70]. Ryu et al. (2023) found significantly increased salivary exosomal miRNA-485-3p in AD, with good diagnostic accuracy (AUC 0.895) and correlation to amyloid PET [53]. Pukhalskaia et al. (2020) reported significantly decreased salivary sirtuins 1, 3 and 6 in AD compared to controls, especially in older subjects [71].

Trehalose

Trehalose is a disaccharide with potential neuroprotective effects [72]. Lau et al. (2017) found increased salivary trehalose in AD using a novel biosensor method [26].

Metabolomics and Proteomics

Metabolomic and proteomic approaches can identify disease biomarker panels [73]. Huan et al. (2018) developed salivary metabolite panels that distinguished AD from controls and MCI with excellent accuracy (AUC >0.99) [34]. François et al. (2021) identified 79 salivary metabolites and 346 proteins significantly altered in AD versus control [51].

Limitations

This systematic review had certain limitations, such as the presence of variability among the included papers regarding diagnostic methodologies, inclusion/exclusion criteria, and the specific biomarkers ex-

amined. There is a requirement for standardized techniques to be established for the collection and processing of saliva in order to minimize variability. Given the relatively small sample sizes in most of the researches [26,32,34,35,39,42,46,48,53,54] it is necessary to validate the findings in bigger cohorts that are well-characterized.

Conclusion

This systematic review indicated that AD patients have changed salivary biomarkers, namely beta-amyloid42, tau proteins, and lactoferrin. AD was associated with increased salivary beta-amyloid42 and phosphorylated tau, while decreased total tau and lactoferrin were not significant. Most of studies found a significant increase of salivary Aβ42 in AD patients. so, we can regard Aβ42 as a best marker in early AD diagnosis by salivary sample. However, salivary testing for early AD diagnosis requires high-quality research to validate these findings in bigger cohorts and standardize techniques. Biomarker panels and potential indicators such microRNAs, metabolites, and inflammatory mediators may also be beneficial. This review shows saliva's promising potential as a non-invasive AD biomarker source, despite its limits and need for more study. Salivary tests may help diagnose this terrible neurological illness earlier and more easily with current study. These tests can help track disease development and assess new disease-modifying medications. The use of salivary biomarkers in AD diagnosis may improve early detection and treatment.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Conceptualization: NHA & AMA; Design of the study: AAM & AMA; Data Collection: AAM & NHA; Data Analysis: AAM & NHA; Critical Review: NHA &AMA; Drafting the paper: AMA & NHA

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Informed consent

NA

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الدقة التشخيصية للمؤشرات الحيوية اللعابية في مرض الزهايمر: مراجعة منهجية

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المستخلص:

خلفيه :يتسبب مرض الزهايمر في التدهور المعرفي وموت الخلايا العصبية بسبب لويحات أميلويد بيتا والتشابك الليفي العصبي. طرق التشخيص الحالية تدخلية ومكلفة وقليلة ، لكن التشخيص المبكر يحسن نتائج المرضى. نظرا لعلاقة محور الفم والدماغ بالجهاز العصبي المركزي ، قد يكون اللعاب مصدرا قابلا للتطبيق للمؤشرات الحيوية لمرض الزهايمر غير التداخلي. تهدف هذه المراجعة المنهجية إلى تقييم الإمكانات التشخيصية للمؤشرات الحيوية اللعابية لمرض الزهايمر من خلال مراجعة البيانات الموجودة بعناية. ألمنهجيه : كانت الدراسات المنشورة بين 1 يناير 2008 و 30 سبتمبر 2023 موضوع بحث شامل في الأدبيات في مجلات, سكوبوس و شبكة العلوم وقواعد البيانات. تم استخراج البيانات ذات الصلة بعد تقييم الدراسات وفقا لمعايير التضمين والاستبعاد المحددة مسبقا. تم تنفيذ معايير مركز أكسفورد للطب القائم على الأدلة لتقييم جودة الدراسات التي تم دمجها. ألنتائج : تم تضمين ما مجموعه 36 دراسة في المراجعة المنهجية ، لأنها استوفت معايير الإدماج. أظهر مرضى الزهايمر مستويات لعاب مرتفعة بشكل ملحوظ من بيتا اميلويد 42 و p-Tau بالمقارنة مع الضوابط الصحية. أظهر المرضى الذين يعانون من مرض الزهايمر اتجاهات غير مهمة في اللعاب **T-Tau** واللاكتوفيرين. ألخاتمة : تغير في مستويات بيتا اميلويد 42 و p-Tau في لعاب المرضى الذين يعانون من مرض الزهايمر بشكل كبير. تؤكد هذه النتائج على احتمال اللعاب كمصدر غير جراحي للمؤشرات الحيوية لتشخيص مرض الزهايمر. ومع ذلك ، يجب أن تخضع اختبارات اللعاب للتحقق الإضافي في مجموعات أكبر وذات خصائص جيدة وتوحيد المنهجيات قبل أن يتم تنفيذها في الممارسة السريرية.