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Salivary biomarkers of Alzheimer's disease as a diagnostic strategy in primary health care: potential and challenges for vulnerable regions of Brazil

Biomarcadores salivares da doença de Alzheimer como estratégia diagnóstica na atenção primária: potencial e desafios para regiões vulnerabilizadas do Brasil

Biomarcadores salivales de la enfermedad de Alzheimer como estrategia diagnóstica en la atención primaria: potencial y desafíos para las regiones vulnerables de Brasil

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ABSTRACT

Alzheimer's disease (AD) is the leading form of dementia worldwide, affecting an estimated 55 million people, with projections exceeding 150 million by 2050. In Brazil, only 20% of cases are formally diagnosed, with even lower rates in the North and Northeast regions, where specialized neurological services remain scarce. Reference diagnostic methods present structural access barriers that limit their use in low-resource settings. In this context, saliva emerges as a non-invasive, low-cost, easily collected alternative biofluid. This study conducted a literature review on salivary biomarkers for AD diagnosis with searches in PubMed/ MEDLINE, SciELO, and LILACS databases, including 22 primary studies. Findings were organized into five thematic axes: classical protein biomarkers ($A\beta_{42}$ and tau); indirect and inflammatory biomarkers (lactoferrin, AChE, cytokines); emerging multi-omic approaches; pre-analytical standardization challenges; and implications for primary health care in Brazil. Salivary $A\beta_{42}$ shows moderate-to-good diagnostic accuracy (AUC=0.803) and lactoferrin demonstrates potential as a low-cost screening tool. Pre-analytical standardization remains the main bottleneck for clinical validation. The capillarity of oral health teams within Brazil's Family Health Strategy positions the dental surgeon as a strategic agent for integrating saliva-based cognitive screening, representing a possible health equity response.

Keywords: Salivary biomarkers. Alzheimer's disease. Primary health care.

RESUMO

A doença de Alzheimer (DA) é a principal forma de demência no mundo, com estimativa de 55 milhões de pessoas afetadas e projeção acima de 150 milhões até 2050. No Brasil, apenas 20% dos casos estão devidamente diagnosticados, com subdiagnóstico ainda mais acentuado nas regiões Norte e Nordeste, onde a oferta de serviços médicos especializados é insuficiente. Os métodos diagnósticos de referência apresentam limitações estruturais de acesso que os tornam inviáveis em contextos de baixa complexidade tecnológica. Nesse cenário, a saliva surge como biofluido alternativo não invasivo, de baixo custo e de fácil coleta. O presente estudo realizou uma revisão da literatura sobre biomarcadores salivares no diagnóstico da DA, com buscas nas bases PubMed/MEDLINE, SciELO e LILACS, incluindo 22 estudos primários. Os achados foram organizados em cinco eixos temáticos: biomarcadores proteicos clássicos ($A\beta_{42}$ e tau); biomarcadores

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indiretos e inflamatórios (lactoferrina, AChE, citocinas); abordagens multi-ômicas emergentes; desafios de padronização pré-analítica; e implicações para a atenção primária à saúde no Brasil. A $A\beta_{42}$ salivar apresenta acurácia diagnóstica moderada a boa (AUC=0,803) e a lactoferrina mostra potencial de triagem de baixo custo. A padronização pré-analítica é o principal gargalo para validação clínica. A capilaridade das equipes de Saúde Bucal na Estratégia Saúde da Família posiciona o cirurgião-dentista como agente estratégico para integração de rastreio cognitivo baseado em saliva, configurando uma resposta possível de equidade em saúde.

Palavras-chave: Biomarcadores salivares. Doença de Alzheimer. Atenção primária à saúde.

RESUMEN

La enfermedad de Alzheimer (EA) es la principal forma de demencia en el mundo, con una estimación de 55 millones de personas afectadas y una proyección superior a 150 millones para 2050. En Brasil, solo el 20 % de los casos están debidamente diagnosticados, con un infradiagnóstico aún más pronunciado en las regiones Norte y Nordeste, donde la disponibilidad de servicios médicos especializados es insuficiente. Los métodos diagnósticos de referencia presentan limitaciones estructurales de acceso que los hacen inviables en contextos de baja complejidad tecnológica. En este escenario, la saliva surge como un biofluido alternativo, no invasivo, de bajo costo y fácil recolección. El presente estudio realizó una revisión de la literatura sobre biomarcadores salivales para el diagnóstico de la EA, mediante búsquedas en las bases de datos PubMed/ MEDLINE, SciELO y LILACS, que incluyeron 22 estudios primarios. Los hallazgos se organizaron en cinco ejes temáticos: biomarcadores proteicos clásicos (Aβ42 y tau); biomarcadores indirectos e inflamatorios (lactoferrina, AChE y citocinas); enfoques multi-ómicos emergentes; desafíos de estandarización preanalítica; e implicaciones para la atención primaria de salud en Brasil. La Aβ42 salival presenta una precisión diagnóstica de moderada a buena (AUC = 0,803), mientras que la lactoferrina muestra potencial como herramienta de cribado de bajo costo. La estandarización preanalítica constituye el principal obstáculo para la validación clínica. La amplia cobertura territorial de los equipos de Salud Bucal en la Estrategia de Salud de la Familia sitúa al cirujano dentista como un agente estratégico para la integración del cribado cognitivo basado en saliva, lo que configura una posible respuesta orientada a la equidad en salud.

Palabras clave: Biomarcadores salivales. Enfermedad de Alzheimer. Atención primaria de salud.

INTRODUCTION

Population ageing should not be treated as a future concern, it is a current, concrete, and irreversible reality. In Brazil, an individual is classified as elderly from the age of 60. The country currently has just over 17% of its population in this age bracket, representing exponential growth when compared to figures from previous years (Instituto Brasileiro de Geografia e Estatística [IBGE], 2025). Ageing is a heterogeneous process, highly influenced by social determinants, resulting in a later life characterized by varying levels of autonomy and independence (Ministério da Saúde, 2023).

In this context, the proportion of older persons affected by chronic and neurodegenerative diseases is growing significantly, with repercussions across all aspects of society. Alzheimer's disease (AD) is the leading form of dementia, accounting for approximately 60 to 80% of cases. Widely recognized for its effects on memory, it also

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affects communication, behaviour, spatial orientation, judgement, and, in advanced stages, mobility, speech, and swallowing (Alzheimer's Association, 2025).

The diagnosis of AD remains a challenge, particularly in resource-limited settings. The inclusion of plasma biomarkers, cerebrospinal fluid (CSF) analysis, and imaging in the diagnostic process has advanced considerably; however, given the associated costs, the proportion of individuals who access these techniques remains low (Jack Jr. *et al.*, 2024). The use of these biomarkers undoubtedly represents an advance in AD diagnosis, yet making them more accessible is an exercise in democratic healthcare that remains to be carried out.

In this context, saliva presents itself as a potential diagnostic medium that is easy to collect and relatively low in cost. In 2024, the first guidelines for the standardization of variables in studies on salivary biomarkers for AD were published (Ng *et al.*, 2025), given that one of the main obstacles to their clinical use is the lack of uniformity in collection and processing techniques.

The present study therefore aims to conduct a literature review on salivary biomarkers in AD diagnosis and to discuss the potential for applying this approach in Primary Health Care (PHC) settings characterized by low technological complexity.

METHODOLOGICAL PATHWAY

Study design

This is a literature review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020), adapted for integrative reviews.

Research Question

The review was structured around the following question, formulated according to the PICO model: in older adults with suspected Alzheimer's disease (P), which salivary biomarkers (I) present evidence of diagnostic accuracy compared with reference methods (CSF analysis, amyloid PET, and NIA-AA 2024 criteria) (C), and what is their potential for application in primary health care settings of low technological complexity (O)?

Search Strategy

Searches were conducted in the following databases: PubMed/MEDLINE, SciELO, and LILACS. The searches were carried out between December 2025 and June 2026.

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For PubMed/MEDLINE, the following search string was used with MeSH terms and free text: ("Alzheimer Disease"[MeSH] OR "Alzheimer's disease"[tiab] OR "Alzheimer disease"[tiab] OR "cognitive decline"[tiab] OR "dementia"[MeSH] OR "neurodegenerative disease"[tiab]) AND ("Saliva"[MeSH] OR "saliva"[tiab] OR "salivary"[tiab] OR "oral fluid"[tiab] OR "whole saliva"[tiab] OR "parotid saliva"[tiab] OR "submandibular"[tiab]) AND ("Biomarkers"[MeSH] OR "biomarker*"[tiab] OR "amyloid beta"[tiab] OR "amyloid-beta"[tiab] OR "Abeta42"[tiab] OR "Aβ42"[tiab] OR "tau protein*"[tiab] OR "phosphorylated tau"[tiab] OR "p-tau"[tiab] OR "lactoferrin"[tiab] OR "acetylcholinesterase"[tiab] OR "neuroinflammation"[tiab] OR "cytokine*"[tiab] OR "early detection"[tiab] OR "early diagnosis"[tiab]).

Equivalent strategies using DeCS descriptors were applied to SciELO and LILACS, using a more concise search string: ("Alzheimer disease" OR "Alzheimer's disease" OR "doença de Alzheimer" OR dementia OR demência) AND (saliva OR salivary OR saliva) AND (biomarker* OR biomarcador* OR "amyloid beta" OR "tau" OR "p-tau" OR lactoferrin OR lactoferrina). The coverage period encompassed publications from 2010 to 2026, excluding reviews. Studies prior to 2010 were included on the grounds of historical relevance, with explicit justification.

Box 1 - Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Studies investigating salivary biomarkers in humans with AD, with any methodological design, except reviews.	Studies exclusively in animal models or in vitro without discussed clinical translation.
Studies reporting data on diagnostic accuracy and/or salivary collection methodology.	Studies that do not specify a diagnostic criterion for AD.
Relevant institutional documents: guidelines, protocols, and reports on dementia in Brazilian primary health care.	Letters to the editor, editorials, and opinion texts without primary or secondary data.
Published in English, Portuguese, or Spanish (2010–2026).	Studies on other forms of dementia without comparative analysis with AD.

Source: Developed by the authors (2026).

Study selection occurred in four stages: identification of records in the databases, removal of duplicates, title and abstract screening, and full-text reading.

Data synthesis and analysis

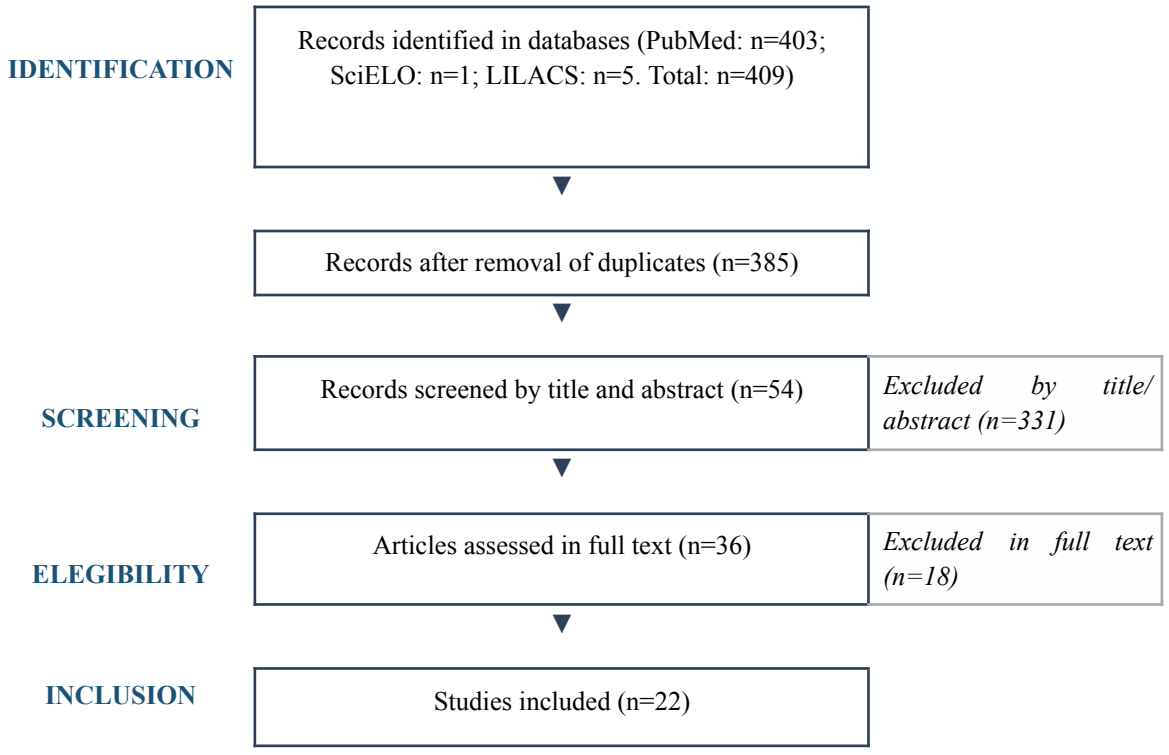
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The synthesis was thematic and interpretative, organized into five axes that emerged from the reading of the included studies: (1) classical protein biomarkers; (2) indirect and inflammatory biomarkers; (3) emerging multi-omic approaches; (4) pre-analytical standardization challenges; and (5) implications for Brazilian primary health care and health equity. Prior to this, information on the characterization of AD, epidemiological data, reference diagnostic methods, and the use of saliva as a potential diagnostic medium will be presented.

Selection and characterization of included studies

The study selection process is represented in the PRISMA flowchart (Figure 1) and the included studies are systematized in Table 2.

Figure 1 - Flowchart of the article selection process for the review.



Source: Developed by the authors (2026).

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Box 2 - Categorization of primary data articles included in the review.

Author / Year	Study design	Biomarker Investigated	Detection Method	N	Mean Age	AD Diagnostic Criterion	Main Finding
Bermejo-Pareja *et al.*, 2010	Case-control	Aβ1-42, Aβ1-40	ELISA	n=32 (16 AD; 16 CTL)	≥65	NINCDS-ADRDA	Salivary Aβ1-42 detectable; association with AD suggested
Shi *et al.*, 2011	Case-control	Total Tau	ELISA	n=35	≥60	DSM-IV / NINCDS	Immunoreactive tau present in saliva; association with AD
Kim *et al.*, 2014	Case-control	Aβ42 / Aβ40	Immunoassay with magnetic nanoparticles (IMR)	n=45 (17 CTL; 28 MCI/ AD)	NR	NR (clinical assessment)	Salivary Aβ42 increased in MCI and AD vs. CTL
Carro *et al.*, 2017	Case-control	Lactoferrin	ELISA	n=126	≥65	NIA-AA 2011	Lactoferrin reduced in AD and MCI vs. controls
Huan *et al.*, 2018	Case-control	Metabolomic panel	LC-MS / NMR	n=76	≥60	NIA-AA 2011	Novel salivary metabolites associated with AD identified
Markstein er; Defrances-co; Humpel, 2022	Case-control	p-tau181	Lumipulse	n=52	≥65	NIA-AA 2011	Salivary p-tau181 detectable; partial correlation with CSF
François *et al.*, 2024	Case-control	Proteomics + metabolomics + microbiome	LC-MS / 16S rRNA	n=80	≥60	NIA-AA	Multi-omic signatures correlated with plasma p-tau181
Lee *et al.*, 2017	Case-control	Aβ42	ELISA (Aurin Biotech kit)	NR (AD and CTL groups)	NR	NR (clinical criteria)	Salivary Aβ42 approximately 2 to 3 times higher in AD vs. controls
Peña-Bautista *et al.*, 2020	Case-control	Amino acids and neurotransmission derivatives (myo-inositol, creatine, acetylcholine, glutamine)	LC-MS/MS	N=43 (17 early AD; 14 moderate AD; 12 CTL)	≥60	NIA-AA (clinicopathological criteria)	Significant differences in myo-inositol, creatine, and acetylcholine in AD saliva vs. CTL. Diagnostic model with AUC=0.806 (sens. 61%; spec. 92%)

González-Sánchez *et al.*, 2020	Case-control	Lactoferrin (LF)	ELISA	Cohort 1=116 (CTL; MCI; AD; FTD) Cohort 2=142 (CTL; MCI)	≥60	Amyloid PET + NIA-AA	Salivary LF reduced exclusively in PET+ (AD and amyloid-positive MCI); LF showed high specificity for AD (vs. FTD)
Q. Liang *et al.*, 2015	Case-control	Metabolomic panel (6 metabolites: sphinganine-1-phosphate, ornithine, phenylacetic acid, inosine, 3-dehydrocarnitine, hypoxanthine)	FUPLC-MS + multivariate PCA	n=474 (256 AD; 218 CTL)	≥70	NINCDS-ADRDA	6 salivary metabolites with significant differences between AD and CTL. Sphinganine-1-phosphate (increased in AD) as main marker (AUC=0.998, sensitivity 99.4%, specificity 98.2%)
Lau *et al.*, 2015	Case-control	Salivary trehalose	EG-ISFET cellular biosensor	n=60 (20 AD; 20 PD; 20 CTL)	≥59	NR	EG-ISFET biosensor significantly distinguished salivary trehalose in AD vs. PD and CTL
Katsipis *et al.*, 2021	Case-control	Salivary GFAP	Dot Blot + ELISA + Western Blot	N=60 (20 MCI; 20 AD; 20 CTL)	NR	Clinical criteria (single-domain amnestic MCI)	Salivary GFAP reduced in MCI and AD vs. CTL ($p<0.05$). Correlation with Aβ42, p-tau, caspase-8, IL-1β, IL-6, TNFα, and COX-2 in saliva
Contini *et al.*, 2022	Case-control	Salivary proteomic panel	RP-HPLC-ESI-IT-MS and MS/MS	70 (35 adult CTL; 34 elderly CTL; 35 AD)	≥40	Clinical criteria	AD with higher levels of α-defensins, thymosin β4, cystatin B, S100A8, and A9. Reduction of anti-inflammatory, antioxidant, and antimicrobial proteins in AD, suggesting impaired innate defences
Ryu *et al.*, 2023	Case-control	miRNA-485-3p	qRT-PCR + amyloid PET (correlation)	40 (27 AD and 13 CTL)	≥65	Amyloid PET (Aβ-PET+ vs. PET−) + NIA-AA	Salivary EE-EV miRNA-485-3p increased in AD vs. CTL

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						clinical criteria	($p<0.0001$) and in Aβ-PET+ vs. PET− (AUC=0.9217). Correlation with cerebral Aβ deposition
McGeer *et al.*, 2020	Case-control	Aβ42 + CRP + TNF	ELISA + IHC	NR (AD, cancer, and coronary disease cases vs. healthy CTL)	12–90	NR (clinicopathological diagnoses)	Aβ42, CRP, and TNF present in saliva of CTL and increased in AD, cancer, and coronary disease. Suggests saliva may predict disease before symptom onset
Bakhtiari *et al.*, 2017	Case-control	AChE	Ellman's method	n=30 (15 AD; 15 CTL)	61–85	NR (clinical criteria)	Salivary AChE assessed as a potential diagnostic biomarker. Non-conclusive results; limited by small sample size
Pekeles *et al.*, 2019	Case-control	p-tau / t-tau (S396, S404, T181, S400, T403, T404)	Western Blot	148 (46 AD; 55 MCI; 47 CTL)	≥65	NIA-AA 2011 / NINCDS-ADRDA	p-tau/t-tau ratio at site S396 increased in AD. Site T181 did not differentiate groups. No correlation with CSF or hippocampus. High intragroup variability
Yilmaz *et al.*, 2017	Case-control	Metabolomic panel (22 metabolites)	^{1}H NMR	n=29 (12 CTL; 8 MCI; 9 AD)	≥65	NR (neuropsychological assessment)	22 metabolites with altered concentrations in MCI and AD vs. CTL
Sabbagh *et al.*, 2018	Case-control	Aβ42	ELISA	n=23 (15 AD; 8 CTL)	AD: ≥75; CTL: ≥56	Clinical criteria + MMSE	Salivary Aβ42 2.45× higher in AD vs. CTL
Zalewska *et al.*, 2021	Case-control	LF + oxidative stress markers (NO, AOPP, MDA, IL-1β)	ELISA + spectrophotometry	50 (25 AD; 25 CTL)	66–90	NIA-AA	Salivary LF reduced in AD (AUC=0.6896). NO, AOPP, MDA, and IL-1β increased in AD
Sabaei *et al.*, 2023	Case-control	p-tau / Aβ42 / α-synuclein	ELISA	n=70 (24 early AD; 24	≥65	NIA-AA	Elevated p-tau in AD; elevated Aβ in AD and PD; reduced α-

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	PD stages I–II; 22 CTL)	synuclein in PD and AD

16S rRNA: 16S ribosomal RNA; AChE: Acetylcholinesterase; AOPP: Advanced Oxidation Protein Products; AUC: Area under the curve; Aβ: Amyloid-beta; MCI: Mild Cognitive Impairment; COX-2: Cyclooxygenase-2; CRP: C-reactive protein; CTL: Controls; AD: Alzheimer's disease; FTD: Frontotemporal dementia; PD: Parkinson's disease; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EE-EV: Endosome-derived extracellular vesicles; EG-ISFET: Extended-gate gold ion-sensitive field-effect transistor; ELISA: Enzyme-Linked Immunosorbent Assay; ESI-IT-MS: Electrospray ionization coupled to ion-trap mass spectrometry; FUPLC-MS / UPLC-MS: Fast ultra-performance liquid chromatography coupled to mass spectrometry; GFAP: Glial Fibrillary Acidic Protein; ^{1}H NMR / NMR: Hydrogen nuclear magnetic resonance spectroscopy; IHC: Immunohistochemistry; IL-1β / IL-6: Interleukin-1 beta / Interleukin-6; IMR: Immunomagnetic reduction assay; LC-MS: Liquid chromatography coupled to mass spectrometry; LC-MS/MS: Liquid chromatography coupled to tandem mass spectrometry; LF: Lactoferrin; Lumipulse: Automated chemiluminescence immunoassay system; MDA: Malondialdehyde; miRNA: MicroRNA; MMSE: Mini-Mental State Examination; NIA-AA: National Institute on Aging and Alzheimer's Association; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NO: Nitric oxide; NR: Not reported / Not referenced; PCA: Principal Component Analysis; p-tau / p-tau181: Phosphorylated tau protein / Phosphorylated tau protein at threonine residue 181; qRT-PCR: Reverse transcriptase real-time polymerase chain reaction; RP-HPLC: Reversed-phase high-performance liquid chromatography; sens.: Sensitivity; spec.: Specificity; t-tau: Total tau protein; TNF / TNFα: Tumour necrosis factor / Tumour necrosis factor alpha; vs.: Versus; Western Blot: Protein immunotransfer method.

Source: Developed by the authors (2026).

Alzheimer's disease: pathophysiology and epidemiology

AD is a progressive and irreversible neurodegenerative condition characterized by the abnormal accumulation of proteins within cerebral tissue, notably extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein, which result in synaptic dysfunction, neuronal loss, and progressive cognitive decline (Jack Jr. *et al.*, 2024). Clinically, it manifests as episodic memory impairment, deficits in language, spatial orientation, judgment, and executive functions, with an escalating impact on the individual's functional capacity and autonomy (Alzheimer's Association, 2025).

The pathophysiology of AD precedes the onset of clinical symptoms by decades; therefore, the disease is conceptualized as a continuum spanning stages 0 through 6, with stage 6 representing the most severe impairment. The A/T/N framework, proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) and updated in 2024, classifies disease biomarkers into three categories: amyloid (A), tau (T), and neurodegeneration (N) markers (Jack Jr. *et al.*, 2024). This understanding has broadened the diagnostic concept of AD beyond clinical manifestations alone, incorporating measurable biological markers even during the pre-symptomatic phase.

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AD represents the most prevalent form of dementia, accounting for 60% to 80% of cases, with an estimated 55 million people affected worldwide in 2024 and projections exceeding 150 million by 2050 (Alzheimer's Disease International, 2025). Accelerated population aging renders this growth even more pronounced in low- and middle-income countries, where socioeconomic conditions, reduced access to formal education, and a higher prevalence of modifiable risk factors, such as hypertension, diabetes mellitus, obesity, and physical inactivity, amplify population vulnerability (Livingston *et al.*, 2024).

In Brazil, it is estimated that approximately 2.71 million people live with some form of dementia, with AD similarly accounting for the largest share of cases. Regional disparities are significant, with dementia prevalence being highest in the Northern and Northeastern regions (Suemoto *et al.*, 2023). Paradoxically, these are the regions with the lowest density of specialized neurological services and restricted access to reference diagnostic methods, creating a cycle of epidemiological invisibility wherein cases exist but remain formally undiagnosed (Paschalidis *et al.*, 2023).

Diagnosis of AD: reference methods, limitations, and accessibility

Definitive diagnosis of AD relies on post-mortem histopathological confirmation; however, clinical diagnosis during life can be supported by validated biomarkers obtained through three primary modalities: cerebrospinal fluid (CSF) analysis, molecular neuroimaging via positron emission tomography (PET), and, more recently, plasma biomarkers (Janelidze *et al.*, 2020).

In CSF, established markers include decreased Aβ42 and elevated total tau and p-tau181, demonstrating high sensitivity and specificity for symptomatic AD (Jack Jr. *et al.*, 2024). Amyloid PET and tau PET allow for the direct visualization of cerebral protein loads, offering high accuracy for diagnosis and staging; however, they entail substantial costs and restricted availability even in high-income countries.

All these methods present structural limitations that render them unfeasible for population-based screening in resource-limited settings. Lumbar puncture for CSF collection is invasive, associated with discomfort and the risk of post-procedure headache, and requires specialized hospital infrastructure. PET imaging bears an exorbitant cost within the Brazilian context, lacking coverage by the Unified Health System (SUS) for dementia indications. Plasma biomarkers, although promising, still lack widespread

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standardization for primary care use and depend on sophisticated analytical platforms (Suemoto *et al.*, 2023).

The Brazilian Academy of Neurology recognizes diagnostic stratification by level of complexity: at the primary care level, available tools include cognitive screening tests, basic laboratory examinations, and computed tomography; at the secondary level, access to magnetic resonance imaging and CSF analysis; and exclusively in tertiary centers, advanced neuroimaging and specialized biomarkers (Studart-Neto *et al.*, 2024).

Saliva as a diagnostic fluid: composition, advantages, and biological fundamentals

Saliva is a complex biological fluid produced by the major salivary glands, parotid, submandibular, and sublingual, and by minor salivary glands distributed throughout the oral mucosa. Its composition comprises water (99%), electrolytes, enzymes, glycoproteins, immunoglobulins, hormones, lipids, DNA, RNA, microbiota, and numerous proteins with immunological, digestive, and protective functions (Yoshizawa *et al.*, 2013).

The presence of systemic proteins and metabolites in saliva stems from multiple transfer mechanisms: passive transudation of blood plasma via diffusion across glandular epithelial cells, active transport mediated by membrane proteins, ultrafiltration, and active secretion by acinar cells (Carpenter, 2013). This bidirectional communication between the vascular compartment and salivary fluid underlies the hypothesis that systemic alterations, including neurodegenerative processes, may be reflected in salivary composition.

In the specific context of AD, two biological hypotheses support the presence of relevant markers in saliva. The first is the systemic transfer hypothesis: proteins such as Aβ42 and tau, present in altered concentrations in the plasma of AD patients, would cross the glandular barrier and become detectable in saliva (Liang; Lu, 2019). The second is the local production hypothesis: neurons and glial cells of the autonomic nervous system innervating the salivary glands could directly secrete AD-associated proteins, rendering saliva not merely a mirror of systemic status, but a site of local biomarker production (Bermejo-Pareja *et al.*, 2010, 2020).

From an operational standpoint, salivary collection presents unequivocal advantages for large-scale clinical application. It is non-invasive, painless, cost-effective, and exhibits high cultural acceptability, including among older adults. It can be self-collected, repeated over time for longitudinal monitoring, and performed in any healthcare

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setting without the need for specialized laboratory or hospital infrastructure (Ng *et al.*, 2025).

Classical protein biomarkers: salivary Aβ42 and Tau Protein

Research within this axis investigates whether the core proteins of disease pathology, Aβ42 and tau protein, in their total (t-tau) and phosphorylated (p-tau) forms, are detectable and clinically relevant in saliva.

Aβ42 is the amyloid peptide with the highest aggregation propensity and the primary component of the senile plaques characteristic of AD. In CSF, its reduction indicates sequestration of the peptide into cerebral plaques. In saliva, pioneering studies by Bermejo-Pareja *et al.* (2010) identified the presence of Aβ42 and Aβ40, with altered levels in AD patients compared to controls. A recent meta-analysis of 30 studies demonstrated that salivary Aβ42 levels were significantly elevated in AD patients, with a pooled area under the curve (AUC) of 0.803, indicating moderate to good diagnostic accuracy (Nijakowski *et al.*, 2024). The direction of the effect (increase in saliva *versus* reduction in CSF) remains a subject of debate and may reflect differences in production and clearance mechanisms between the two compartments.

Tau protein, in its hyperphosphorylated form (p-tau), is the primary component of neurofibrillary tangles in AD. Shi *et al.* (2011) demonstrated for the first time the presence of immunoreactive tau in human saliva and its association with AD. Subsequent studies investigated both total tau and phosphorylated forms, particularly p-tau181. However, results are more inconsistent than those for Aβ42: while some studies report elevated salivary tau in AD, others fail to confirm correlation with CSF and plasma markers, which currently limits its isolated diagnostic value (Marksteiner; Defrancesco; Humpel, 2022).

Indirect and inflammatory biomarkers

The second axis encompasses salivary compounds that indirectly reflect AD pathological processes, neuroinflammation, cholinergic dysfunction, and immune response, without being primary components of neuropathological lesions.

Lactoferrin is an abundant salivary glycoprotein with antimicrobial and immunomodulatory functions. Its investigation as an AD biomarker gained prominence following a study (Carro *et al.*, 2017) that demonstrated significantly reduced levels of salivary lactoferrin in patients with AD and amnestic mild cognitive impairment compared

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to healthy controls, with diagnostic performance superior to that of other salivary biomarkers tested in the same study. Its measurement via conventional ELISA and affordable cost render lactoferrin one of the salivary biomarkers with the greatest potential for immediate application in low-technological-complexity settings.

Cholinergic system dysfunction is one of the central neurochemical alterations in AD, and acetylcholinesterase (AChE), the enzyme responsible for acetylcholine degradation, has been investigated in saliva as an indirect marker of this dysfunction. Studies demonstrate alterations in salivary AChE activity in AD patients, although the specificity of this marker is limited by its expression across multiple tissues (Liang; Lu, 2019). Inflammatory markers such as IL-1β, IL-6, and TNF-α have also been investigated, exhibiting a profile suggestive of elevation in AD, yet remaining similarly non-specific (Wolgin *et al.*, 2022).

Multi-omics approaches: metabolomics, proteomics, and the oral microbiome

The third axis represents the most advanced frontier of the field. Salivary metabolomics (Huan *et al.*, 2018) has identified differentially expressed metabolites in AD, including amino acids, lipids, and energy metabolism products, suggesting that systemic metabolic alterations are reflected in salivary composition.

The multi-omics study integrating proteomics, metabolomics, and the salivary microbiome, conducted by François *et al.* (2024) in an Australian cohort, identified diagnostic signatures in each omic layer and correlated them with plasma p-tau181. The oral microbiome, via the oral-gut-brain axis hypothesis, emerges as a promising area: dysbiosis associated with periodontitis may contribute to systemic neuroinflammation and, potentially, to the exacerbation of AD (Dominy *et al.*, 2019).

Pre-analytical standardization challenges

The fourth axis is recurrently identified in the literature as the primary obstacle to the consolidation of salivary biomarkers. Variables with documented impact include: type of saliva collected, time of collection, fasting state, medication use, oral health status, salivary flow, collection technique, storage temperature and duration, and analytical method employed (Ng *et al.*, 2025).

In response to this gap, the Salivary Biomarkers for Dementia Research Working Group published international pre-analytical standardization guidelines in 2025,

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establishing specific recommendations for each step of the process, which are deemed necessary conditions for future studies to yield comparable and clinically interpretable results.

Implications for primary care and health equity in Brazil

Brazil faces a documented epidemiological paradox: the regions with the highest prevalence of dementia are precisely those with the least access to specialized diagnosis. The prevalence of AD is highest in the Northern and Northeastern regions, whereas specialized diagnostic infrastructure is concentrated in the Southeastern and Southern regions. Data on hospitalizations for AD within the SUS reveal that the North accounted for less than 2% of recorded cases between 2013 and 2022, not due to the absence of the disease, but rather owing to underdiagnosis (Araújo *et al.*, 2023).

The Family Health Strategy (FHS) constitutes the primary gateway of the Unified Health System (SUS) and the structure with the greatest territorial capillarity in Brazil, with estimated coverage exceeding 60% of the national population (Ministry of Health, 2026). Oral Health Teams (OHTs) integrated into the FHS total more than 34,000 teams distributed nationwide, with priority expansion in the Northern and Northeastern regions, precisely where the diagnostic deficit for dementias is most pronounced (Ministry of Health, 2024).

The dental surgeon occupies a singular strategic position in this scenario: they are healthcare professionals who routinely collect, handle, and analyze saliva in clinical practice; who already regularly care for the elderly population in primary care; and who operate in regions of greatest social vulnerability and restricted access to specialized services. The interface between oral health and cognitive health is biologically substantiated, given that conditions such as periodontitis, reduced salivary flow, and alterations in oral microbiota composition have been associated with an increased risk of AD (Dominy *et al.*, 2019; Hajishengallis; Chavakis, 2021; Qian *et al.*, 2024).

The integration of cognitive screening protocols based on salivary biomarkers into dental practice within primary care represents, therefore, not merely a technical possibility, but a health equity strategy capable of bringing early diagnosis of AD to populations that would otherwise remain beyond the reach of conventional methods. For this to materialize, validation studies conducted in low-complexity settings with diverse Brazilian populations and protocols adapted to primary care conditions are required.

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The contradictions identified in the literature do not invalidate the field; rather, they highlight that the diagnostic potential of saliva cannot be evaluated without rigorous control of pre-analytical variables. The limitations of this review include: methodological heterogeneity among studies; predominance of European and Asian studies; absence of primary Brazilian studies on the topic; variability in diagnostic criteria and detection methods; and conclusions restricted to the qualitative and interpretative dimension.

FINAL CONSIDERATIONS

The present review demonstrated that salivary biomarkers, especially Aβ42 and lactoferrin, and prospectively multi-omics markers, exhibit sufficient biological and diagnostic evidence to sustain them as a legitimate object of investigation in the field of early AD diagnosis.

Within the Brazilian context, salivary biomarkers represent a strategy with a clear health equity dimension. The Northern and Northeastern regions, where underdiagnosis is most pronounced, are the regions with the greatest capillarity of Oral Health Teams within the FHS. The dentist emerges as a strategic agent for the integration of saliva-based cognitive screening protocols.

For this perspective to materialize, validation studies in Brazilian populations are required, featuring protocols adapted to primary care, cost-effectiveness evaluations, and the development of referral pathways across different levels of care.

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