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Tears as a Window to Alzheimer's Disease: A Systematic Re-view on Biomarkers for Early Detection

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 December 2024 and was last updated on 9 December 2024.

INTRODUCTION

Review question / Objective This systematic review discusses the main tear findings in AD, as well as the value of tear biomarkers and how they contribute to the early diagnosis of the disease.

Rationale Tear as a biomarker offers advantages including: the close relationship between the eye and the brain described above, that it can be collected using non-invasive and easily accessible techniques, that it can be reproducible and thus allows monitoring of biomarker fluctuations. Furthermore, the technique is cost-effective and minimally stressful for pa-tients, regardless of their cognitive status, and can be collected in a short period of time.
Numerous studies have proposed tears as indicators of normal biological processes as well as pathogenic conditions due to advances in tear collection and analysis tech-niques . Different studies have been carried out to study biomarkers in the tears of AD patients.

Condition being studied Alzheimer's disease (AD) is a heterogeneous, multifactorial, neurodegenerative dis-ease that is the leading cause of dementia worldwide. This age-related neurodegenerative disorder affects more than 50 million people worldwide and accounts for 60-70% of all dementia cases . The number of cases increase in the worldwide is related to the pro-gressive ageing of the population, as well as to the improvement in the diagnosis of this disease and the increased survival of patients . Histopathological it is characterised by the abnormal aggregation of two proteins: extraneuronal amyloid beta (Aβ) in the form of plaques and intraneuronal hyperphosphorylated

Tau protein in the form of neurofibrilla-ry tangles (NTF) , leading to neuronal death, which ultimately results in brain atro-phy. In addition to the accumulation of these proteins, other factors involved in the de-velopment of this disease are genetic, environmental, vascular and metabolic factors.

The search for new biomarkers is necessary because both the study and monitoring of subjects at high risk for the development of AD, as well as the importance of developing reliable and sensitive tools for the early diagnosis of this disease, would make possible both early intervention through drugs that slow down its progression, preserving cogni-tive capacity, as well as the improvement in the understanding of the neurodegenerative process**.**

METHODS

Search strategy We performed a search of the medical literature using the "MESH" terms in PubMed and Scopus up to April 2024. This review adhered to the PRISMA 2020 Statement guide-lines The search terms were: "Alzheimer's disease", "tears", "biomarkers for Alzheimer's dis-ease", "proteins", "micro ARN" and "Extracellular vesicles" as well as their possible combinations.The terms had to be in the title, in the abstract, or in the text of the article. The articles selected were written in English. All of them had to relate to the relationship between tears and AD; we also included articles defining the concept of tears biomarker in Alzheimer's disease or generalizations about tears and AD as the main topic. These articles may be older than those focused on the review topic.

Study selection process flowchart as per PRISMA guidelines

Clear inclusion and exclusion criteria were established to select the studies. The inclusion criteria were: i) Studies investigating Tear biomarkers in Alzheimer's disease, ii) Publications in English, iii) Studies with complete and accessible data.

The exclusion criteria included: i) Duplicate studies, ii) publications without full text access, iii) Studies with insufficient or irrelevant data.

The process of selecting studies was conducted in several stages. Initially, we identi-fied records from various databases, including 1,346 from PubMed and 1,420 from Sco-pus, along with 2,766 from specific registers. Following this, we removed 854 duplicate records and 633 records for other reasons.

Participant or population We included studies with AD, MCI and healthy controls.

Intervention Not applicable.

Comparator Study of the tear film in pathological and healthy subjects. The methods of tear collection, sample analysis, and tear composition will be studied.

Study designs to be included Analytical, descriptive cross-sectional studies.

Eligibility criteria The inclusion criteria were: i) Studies investigating Tear biomarkers in Alzheimer's disease, ii) Publications in English, iii) Studies with complete and accessible data.

The exclusion criteria included: i) Duplicate studies, ii) publications without full text access, iii) Studies with insufficient or irrelevant data.

The process of selecting studies was conducted in several stages. Initially, we identified records from various databases, including 1,346 from PubMed and 1,420 from Scopus, along with 2,766 from specific registers. Following this, we removed 854 duplicate records and 633 records for other reasons . Next, we screened the titles and abstracts of the 1,279 identified records, excluding 836 that did not meet the inclusion criteria. We then sought to retrieve 443 potentially relevant reports for further evaluation.

In the full-text report evaluation phase, we assessed 443 reports to determine their eligibility. We excluded 56 articles that analyzed the tear in other diseases, 175 articles that analyzed other fluids, and 104 articles written in languages other than English.

Ultimately, we included a total of 108 studies in the systematic review.

Information sources PubMed and Scopus.

Main outcome(s) Author Biomarkers
Method of Sample Collection Analytical Method Results
Kalló et al. (2016)[67]
Lysozyme-C, lipocalin-1, lacritin, dermcidin Microcapillary tube Electrophoresis and LC-MS/MS. Mass spectrometry-based approach.
Higher tear flow rate and increased protein concentration in patients with Alzheimer's disease (AD). The combination of Lysozyme-C, Lipocalin-1, Lacritin, and Dermcidin demonstrates a sensitivity of 81% and a specificity of 77% for detecting AD
Gijs et al. (2019)[56]
Aβ42 and t-tau Schirmer strip Immunoassay. A mass spectrometry-based approach. Positive correlation between t-tau and Aβ42 levels with Alzheimer's disease t-tau levels were significantly higher in AD patients compared to those with late

mild cognitive impairment and (mild cognitive impairment
Kenny et al. (2019)[52]
MicroARN-200b-5p, eF4E Schirmer strips Mass spectrometry, SDS-PAGE, Western blot, and qPCR Higher RNA levels in patients with Alzheimer's disease (AD). Elevated levels of microRNA-200b-5p in AD patients. The eF4E biomarker is only present in patients with AD.
Gijs et al. (2020)[57]
Aβ38, Aβ40, Aβ42, t-tau, p-tau Schirmer strip Mass spectrometry Increased levels of Aβ38, Aβ40, Aβ42, t-tau, and p-tau were observed for all conditions except in healthy subjects. According to the severity of the disease t-tau levels significantly increased when comparing samples from patients with neurodegeneration to healthy samples. The presence of Aβ, t-tau, and p-tau was demonstrated for the first time in tear fluid.
Gijs et al. (2021)[50]
Aβ38, Aβ40, Aβ42, t-tau, p-tau Schirmer strip without anesthesia Multiplex immunoassay Aβ40 and t-tau are detected in 94% of tear samples from patients with subjective cognitive decline, mild cognitive impairment, Alzheimer's disease and healthy controls. In the control patients, p-Tau was not detected, which increases the specificity and sensitivity for detecting AD when t-Tau is found in CSF. t-tau levels are elevated in patients with neurodegeneration. t-tau concentrations were up to 10 times higher in tears than in cerebrospinal fluid (CSF).

Quality assessment / Risk of bias analysis Quality Criteria: Aspects such as study design, methodology, internal and external validity, and consistency of results will be evaluated. Evaluation Tools: The Cochrane risk of bias tool for clinical trials and the STROBE checklist for observational studies will be used. Evaluation Process: The evaluation will be conducted independently by two reviewers. In case of discrepancies, they will be resolved by consensus or with the intervention of a third reviewer. Quality Categorization: Studies will be classified as high, medium, or low quality according to the established criteria. Documentation and Reporting: The results of the quality assessment will be documented and reported in detail in the review.

Strategy of data synthesis Method of Synthesis: A narrative synthesis will be used to summarize the findings of the included studies. Additionally, a meta-analysis will be conducted when the data are sufficiently homogeneous. Inclusion and Exclusion Criteria: Studies will be included if they meet the established quality criteria and are relevant to the research question. Studies with a high risk of bias will be excluded.

Subgroup analysis Not applicable.

Sensitivity analysis Purpose of Sensitivity Analysis: The sensitivity analysis will be conducted to evaluate the robustness of the systematic review results. Methods Used: Several sensitivity analyses will be performed, including the exclusion of studies with a high risk of bias, variation in inclusion criteria, and the use of different statistical models (e.g., fixed-effects and random-effects models).

Language restriction Only articles in English.

Country(ies) involved Spain.

Keywords Alzheimer's Disease, Tears, Proteins, microRNA, Extracellular vesicles, biomarker.

Dissemination plans We will present the results of the systematic review at national and international conferences. Additionally, it will be presented as an oral communication at departmental seminars.

Contributions of each author
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