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Advancements in Alzheimer's disease: early diagnosis, biomarkers, and future perspectives

Avanços na doença de Alzheimer: diagnóstico precoce, biomarcadores e perspectivas futuras

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ABSTRACT

Introduction: Recent advancements in biomarker research and diagnostic frameworks, such as the ATN classification system, have redefined the approach to early diagnosis and treatment. However, challenges remain in differentiating biological from clinical AD and in ensuring equitable access to emerging therapeutic interventions.

Objective: Explore the latest advancements in AD diagnosis and management, focusing on biomarkers, neuroimaging techniques, molecular insights, and future therapeutic approaches.

Method: An integrative review was conducted using PubMed, Scopus, and Embase databases. Inclusion criteria encompassed systematic reviews, meta-analyses, and clinical guidelines discussing AD pathophysiology, diagnostics, and therapeutic developments. Studies with inadequate methodology or duplicate data were excluded.

Result: Advances in molecular diagnostics, including amyloid and tau biomarkers, have significantly enhanced early detection of AD. The ATN framework categorizes the disease's progression, integrating neurodegenerative and inflammatory markers. Novel imaging techniques, such as TRODAT and PET-FDG, offer improved disease monitoring. Immunological therapies, particularly monoclonal antibodies like aducanumab and lecanemab, have shown promise in slowing disease progression, but accessibility and cost remain major barriers.

Conclusion: While substantial progress has been made in AD diagnosis and treatment, critical challenges persist regarding early detection, therapeutic efficacy, and healthcare accessibility. Future research should focus on integrating precision medicine approaches, developing cost-effective interventions, and expanding preventive strategies.

KEYWORDS: Alzheimer's disease. Early diagnosis. Biomarkers. Future perspectives.

RESUMO

Introdução: Avanços recentes na pesquisa de biomarcadores e estruturas diagnósticas, como o sistema de classificação ATN, redefiniram a abordagem do diagnóstico e tratamento precoces. No entanto, permanecem desafios na diferenciação da DA biológica da clínica e na garantia de acesso equitativo a intervenções terapêuticas emergentes.

Objetivo: Explorar os mais recentes avanços no diagnóstico e tratamento da DA, com foco em biomarcadores, técnicas de neuroimagem, insights moleculares e futuras abordagens terapêuticas.

Método: Foi realizada uma revisão integrativa nas bases de dados PubMed, Scopus e Embase. Os critérios de inclusão abrangeram revisões sistemáticas, metanálises e diretrizes clínicas discutindo fisiopatologia, diagnóstico e desenvolvimentos terapêuticos da DA. Foram excluídos estudos com metodologia inadequada ou dados duplicados.

Resultado: Os avanços no diagnóstico molecular, incluindo biomarcadores amilóides e tau, melhoraram significativamente a detecção precoce da DA. A estrutura ATN categoriza a progressão da doença, integrando marcadores neurodegenerativos e inflamatórios. Novas técnicas de imagem, como TRODAT e PET-FDG, oferecem melhor monitoramento da doença. As terapias imunológicas, particularmente anticorpos monoclonais como aducanumabe e lecanemab, mostraram-se promissoras em retardar a progressão da doença, mas a acessibilidade e o custo continuam sendo as principais barreiras.

Conclusão: Embora tenham sido feitos progressos substanciais no diagnóstico e tratamento da DA, persistem desafios críticos em relação à detecção precoce, eficácia terapêutica e acesso aos cuidados de saúde. Pesquisas futuras devem se concentrar na integração de abordagens de medicina de precisão, no desenvolvimento de intervenções econômicas e na expansão de estratégias preventivas.

PALAVRAS-CHAVE: Doença de Alzheimer. Diagnóstico precoce. Biomarcadores. Perspectivas futuras.

Central Message

Recent advancements in Alzheimer's disease (AD) research, particularly in biomarker discovery, diagnostic frameworks like the ATN classification system, and novel therapeutic approaches, have significantly enhanced early diagnosis and monitoring of the disease. However, challenges persist in differentiating biological from clinical AD, and in ensuring equitable access to emerging treatments, such as monoclonal antibodies. Despite substantial progress, critical issues remain regarding early detection, treatment efficacy, and healthcare accessibility.

Perspective

Future research in AD should focus on integrating precision medicine approaches, which tailor treatments to individual patients based on genetic, environmental, and lifestyle factors. Additionally, there is a need to develop cost-effective therapies and expand preventive strategies to ensure broader access to emerging treatments. Addressing these challenges will be essential for improving both the clinical outcomes for patients and the accessibility of care across diverse populations.

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INTRODUCTION

Alzheimer's disease (AD) represents the most prevalent form of dementia, accounting for approximately 60–80% of diagnosed cases worldwide. It is a progressive neurodegenerative disorder characterized by the gradual deterioration of cognitive, behavioral, and motor functions, with profound implications for the individual's functionality and the caregivers' quality of life.[1] It is no longer synonymous with dementia. Biological AD constitutes risk factor for cognitive decline, which may take years to manifest clinically or may never do so. The biological diagnosis of it is of great importance due to advancements in the detection of pathological hallmarks prior to the onset of clinical symptoms, utilizing biomarkers identified in cerebrospinal fluid and neuroimaging modalities. A critical challenge lies in distinguishing between biological and clinical AD and effectively communicating the implications of this paradigm shift to healthcare professionals and the general population. This is essential to mitigate stigma and prevent premature decisions regarding patients' careers or lifestyles. Additionally, the paucity of evidence regarding the efficacy of interventions in the very early stages of the disease further complicates this discussion.[2,3]

This review aims to explore recent diagnostic advancements and to examine future perspectives in the treatment of this condition. The objective is to provide a comprehensive overview to enhance understanding and support the ethical management of this complex disease.

METHOD

This integrative literature review was conducted searching the PubMed, Scopus, and Embase databases. Articles addressing the pathophysiology of AD, diagnostic advancements, biomarkers, current treatments, and future perspectives were included. Inclusion criteria encompassed: studies exploring pathophysiological, diagnostic, or therapeutic aspects, systematic reviews, meta-analyses, and clinical guidelines. Additionally, articles discussing the ethical considerations of early and biological diagnosis of AD were included. Duplicate studies and those with inadequate methodology were excluded. The objective was to compile updated and relevant information, providing a comprehensive overview of the current state of knowledge on AD. So, 26 papers were included in this review.

DISCUSSION

Current understanding of Alzheimer's disease

The pathophysiology of AD is predominantly explained by the amyloid-tau hypothesis, which suggests that the extracellular accumulation of beta-amyloid plaques and the intracellular formation of hyperphosphorylated tau neurofibrillary tangles act as primary triggers for neurodegeneration. These pathological processes lead to a cascade of events, including synaptic dysfunction, neuroglial inflammation, neuronal death, and progressive brain atrophy. The hippocampus and temporoparietal regions are among the earliest affected areas, correlating with the memory deficits and spatial disorientation that characterize the initial stages of the disease.[4,5]

Beyond the amyloid-tau axis, several other factors contribute significantly to the complex pathophysiology of AD. Oxidative stress and mitochondrial dysfunction play a critical role in amplifying cellular damage, while neuroinflammation driven by hyperactive microglia exacerbates neuronal injury and synaptic loss. Additionally, alterations in brain glucose metabolism, often described as "cerebral insulin resistance," further impair neuronal function and energy homeostasis.[4,5]

Genetic predisposition also exerts a profound influence on the risk of developing AD, with the presence of the apolipoprotein E4 (ApoE4) allele being the strongest genetic risk factor identified to date. ApoE4 is associated with increased beta-amyloid deposition and impaired clearance, as well as heightened vulnerability to neuroinflammatory processes and metabolic disturbances.[6]

Together, these interconnected mechanisms underscore the multifactorial nature of AD, reflecting a complex interplay between genetic, molecular, and environmental factors that drive the progression of this debilitating neurodegenerative disorder.

Perspectives on Alzheimer's disease

The understanding and management of AD have evolved significantly, particularly with recent advances in dementia prevention, intervention, and care, as outlined in the 2024 Report of the Lancet Standing Commission. This report highlights the multifaceted nature of AD, encompassing its prevention, early diagnosis, and comprehensive care. Central to these efforts are frameworks such as the ATN classification system, which has refined the understanding of AD pathophysiology and diagnostic criteria, and innovations like the use of transcriptomics for a molecular-level understanding of the disease.[7]

The ATN system and reactive astrocytes

The ATN (Amyloid, Tau, Neurodegeneration) framework categorizes biomarkers for AD into 3 core pathological domains. In this system, "A" represents amyloid beta disease; "T" refers to tau-related abnormalities; and "N" indicates neurodegeneration. This classification has become a cornerstone for stratifying patients in clinical and research settings, enabling targeted interventions.[8]

Reactive astrocytes play a crucial intermediary role within the ATN system. Following the deposition of beta-amyloid plaques, astrocytes are activated and become reactive. These cells, intimately associated with cerebral vasculature, mediate the transition from amyloid pathology (A) to tau hyperphosphorylation (T). Their vascular interactions suggest a role in modulating the blood-brain barrier and influencing

downstream tau-related changes. Understanding the timing and mechanisms of astrocyte reactivity may provide a window for therapeutic intervention before extensive tau pathology develops.[9]

Neurodegeneration and biomarkers

Neurodegeneration, as measured by neuronal atrophy and functional decline, is a critical element of the ATN system. It is closely associated with a reduction in glucose metabolism, which can be visualized using PET-FDG scans. Neuroimaging plays a pivotal role in identifying and monitoring the progression of neurodegenerative changes. Markers such as TRODAT, which measure dopamine transporter activity, are emerging as tools to understand dopaminergic dysfunction and its relation to cognitive decline in AD. While primarily linked to Parkinsonian disorders, TRODAT findings in AD may reveal overlapping pathophysiological mechanisms involving synaptic and neurotransmitter integrity.[9]

Advances in diagnosis and molecular insights

Diagnostic paradigms for AD continue to evolve with consensus guidelines such as the AA2024 and IWG2021 criteria. These frameworks emphasize the integration of biomarkers into clinical diagnosis, moving beyond symptomatic assessment to molecular characterization. Advances in transcriptomic technologies are shedding light on the gene expression profiles associated with Alzheimer's pathology. These insights not only enhance the understanding of disease mechanisms but also pave the way for personalized medicine approaches.[10,11]

The field of AD research and management has undergone substantial evolution, as highlighted by the 2024 report from the Lancet Standing Commission. A critical focus of contemporary research lies in dementia prevention, intervention, and care, with an emphasis on integrating novel diagnostic tools and therapeutic strategies that target early stages of the disease.[7]

One cornerstone of this advancement is the ATN (Amyloid, Tau, Neurodegeneration) framework, which provides a structured approach for classifying AD pathology using biomarkers. The ATN system delineates the pathophysiological progression of AD, where amyloid-beta deposition (A) precedes tau hyperphosphorylation (T) and neurodegeneration (N). Emerging evidence suggests that reactive astrocytes play a pivotal role at the A-to-T transition, mediating vascular and inflammatory responses that contribute to the downstream tau pathology. This astrocytic activity represents a potential therapeutic target, bridging the molecular gap between amyloid and tau cascades.[4-8]

The concept of neurodegeneration in AD is closely associated with neuronal atrophy and loss of function, which can be quantitatively assessed through glucose metabolism via imaging modalities such as PET-FDG. The introduction of TRODAT, a dopamine transporter imaging marker, expands the scope of molecular diagnostics, enabling more refined assessments of neural integrity beyond traditional amyloid and tau markers. These advancements align with international guidelines such as the IWG 2021 and AA 2024 frameworks, which advocate for biomarker-driven definitions of AD to enhance diagnostic precision.[9,11,12]

Transcriptomic analyses are another frontier in AD research, offering insights into gene expression profiles associated with disease progression. These data not only elucidate the molecular underpinnings of AD but also aid in identifying novel therapeutic targets. Meanwhile, the identification of 14 modifiable risk factors underscores the importance of prevention. Lifestyle interventions — ranging from physical activity and dietary modifications to cognitive training — are increasingly recognized as integral components of dementia prevention strategies.[5,6,8]

Immunology and biomarker-based therapies: a paradigm shift

The advent of immunology-based therapies, including monoclonal antibodies such as aducanumab and lecanemab, has marked a paradigm shift in AD management. These therapies aim to mitigate amyloid burden and slow cognitive decline, exemplifying the potential of precision medicine. However, significant barriers persist. High costs and limited accessibility to these advanced treatments disproportionately affect low- and middle-income countries, exacerbating global health inequities.[13]

Biomarker-driven approaches not only facilitate earlier diagnoses but also enable tailored interventions that align with an individual's specific pathological profile. Despite these advances, their widespread implementation is hindered by infrastructural and economic limitations, underscoring the need for scalable solutions to democratize access to these technologies.

Differential diagnosis Alzheimer's disease

AD is the most common form of dementia in the elderly, with its prevalence increasing markedly with age. Aging is the most significant risk factor for the development of AD, although family history and genetic predisposition also contribute. However, autosomal dominant familial forms, typically characterized by an early onset (before the age of 65), account for less than 5% of all cases. Among genetic factors, the presence of the apolipoprotein E4 (ApoE4) allele is highly associated with both sporadic and familial cases of AD.[1,3-6]

From a pathological perspective, AD is characterized macroscopically by cortical atrophy, particularly in associative neocortical areas and mesial temporal regions, such as the hippocampus. Microscopically, intracellular neurofibrillary tangles composed of tau protein and extracellular deposits of beta-amyloid peptide in neuritic plaques are hallmark findings. Neuropathological examination remains the gold standard for the diagnosis of AD, based on the distribution and quantity of these lesions.[4-6]

Clinically, the earliest and most prominent feature is episodic memory impairment. This typically

manifests as difficulty recalling recent events, repetitive questioning, and misplacing personal items. In some cases, AD may initially present as amnestic mild cognitive impairment, where functional independence is preserved, and dementia is not yet established. As the disease progresses, involvement of the frontal, temporal, and parietal associative cortices leads to the emergence of additional cognitive and behavioral symptoms. Although the amnestic presentation is the most common, non-amnestic forms are also recognized, particularly in early-onset AD cases.[8,9]

The most accurate biological markers currently include structural and functional neuroimaging and cerebrospinal fluid biomarkers. Structural imaging, particularly brain MRI, typically reveals atrophy of mesial temporal structures and dilation of the temporal horns of the lateral ventricles. Cerebrospinal fluid analysis shows increased tau and hyperphosphorylated tau proteins with decreased beta-amyloid levels. Functional neuroimaging, such as positron emission tomography (PET) with fluorodeoxyglucose, demonstrates characteristic posterior temporoparietal hypometabolism.[8-11]

Vascular dementia

Vascular disease is now recognized as one of the most identifiable and modifiable risk factors for dementia, alongside aging. The most widely accepted criteria for diagnosing vascular dementia are those established by the National Institute of Neurological Disorders and Stroke – *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN). These criteria require the presence of dementia associated with cerebrovascular disease, which is defined by neurological examination findings or imaging evidence, along with a clear relationship between the two. Such a relationship may include the onset of dementia within 3 months of a recognized stroke, an abrupt cognitive decline, or a stepwise progression of cognitive deficits.[13]

Several features strengthen the diagnosis, such as early gait disturbances (e.g., petit-pas or apraxic gait), reports of imbalance, pseudobulbar palsy, early urinary urgency, and personality or mood changes. Conversely, the presence of early and progressive amnestic deficits, the absence of vascular lesions on imaging, or the lack of focal neurological signs makes the diagnosis less likely. The pathophysiology of cognitive impairment in vascular dementia — now frequently referred to as vascular cognitive impairment — involves small vessel disease leading to cerebral white matter changes (leukoaraiosis), strategic or extensive small infarcts, and diffuse subcortical lesions. These changes disrupt neural networks, resulting in variable symptoms depending on the vascular territory affected and the extent of the damage.[14]

The progression rate of vascular dementia is variable and may be slower than that observed in AD. However, the mortality rate tends to be higher in vascular dementia. With advancements in stroke management and better control of vascular risk factors, this trend may change in the coming years. Continued research is needed to clarify the interplay between vascular pathology and neurodegenerative processes and to optimize therapeutic strategies for this complex condition.[13,14]

Frontotemporal dementia

Frontotemporal lobar degeneration (FTLD) encompasses a heterogeneous group of neuropathological diagnoses and distinct clinical syndromes. It is the second most common cause of degenerative dementia in individuals under 65 years of age, with AD being the first. FTLD presents with different predominant syndromes: when behavioral changes dominate, it is classified as the behavioral variant of FTLD (bvFTLD). Conversely, when language impairments predominate, the condition is termed primary progressive aphasias, which include semantic dementia and non-fluent/agrammatic progressive aphasia.[15]

In the behavioral variant, symptoms stem from damage to the prefrontal lobe, including reduced empathy, inappropriate affect, irritability, and loss of self-awareness. Apathy, linked to anterior cingulate gyrus involvement, is a hallmark feature. Other symptoms include altered food preferences, hypersexuality, and utilization behavior, which are associated with orbitofrontal damage. Patients with right temporal lobe involvement may exhibit antisocial behaviors, hyperreligiosity, and compulsive tendencies. Cognitive assessments typically reveal executive dysfunction, with relatively preserved memory and visuospatial abilities. Parkinsonism is observed in approximately 20% of cases.[16-18]

Semantic dementia manifests as a fluent language disorder characterized by the progressive loss of word knowledge and comprehension, often accompanied by semantic paraphasias. Pathologically, it is associated with asymmetric anterior temporal atrophy, predominantly linked to TDP-43 proteinopathy. Non-fluent/agrammatic progressive aphasia, on the other hand, features agrammatism, speech apraxia, and phonemic paraphasias, with a marked reduction in word production and articulation difficulties.[16-18]

Diagnosing FTLD relies on neuroimaging techniques such as brain MRI and FDG-PET, which can reveal patterns of atrophy and hypometabolism characteristic of the condition. In pre-senile cases, cerebrospinal fluid analysis is also recommended to support the diagnosis. Ongoing research into biomarkers and genetic contributions continues to refine diagnostic accuracy and inform treatment strategies for this complex group of dementias.[16-18]

Dementia with Lewy bodies (DLB)

DLB is recognized as the second most common cause of neurodegenerative dementia, surpassed only by AD. It is characterized by progressive dementia accompanied by parkinsonism — typically symmetrical with minimal tremor —recurrent visual hallucinations, and cognitive fluctuations.[15]

Cognitive fluctuation is among the most prevalent symptoms, affecting up to 90% of patients. It manifests as variations in attention, consciousness, and daytime somnolence. Visual hallucinations often emerge in the early stages of DLB, contrasting with AD, where they typically appear later. Parkinsonism in DLB demonstrates a limited response to levodopa, aiding in the differential diagnosis. Cognitive assessments in DLB often reveal impairments in attention, visuospatial skills, and constructional praxis, while episodic memory is relatively preserved in the early stages. Functional neuroimaging techniques, such as SPECT and PET, can assist in diagnosis by showing reduced perfusion or metabolism in the posterior parietal and occipital regions.[19,20]

Assessment tests

The diagnostic workup for dementia requires a comprehensive approach involving cognitive testing, laboratory analyses, and imaging studies to exclude reversible causes and confirm the underlying pathology.[15]

Cognitive testing plays a pivotal role in assessing the extent and nature of cognitive impairment. Standardized tools such as the Montreal Cognitive Assessment, the Mini-Mental State Examination, verbal fluency tests, and the clock-drawing test are employed to evaluate memory, executive function, language skills, and visuospatial abilities. These assessments provide critical insights into the pattern of cognitive deficits, which may guide differential diagnosis.[21-23]

Laboratory investigations are essential to exclude metabolic or infectious causes of cognitive decline. Routine tests include measurements of vitamin B12 levels and thyroid-stimulating hormone to identify deficiencies or thyroid dysfunction, renal function tests to detect underlying nephropathy, assessment of electrolytes for imbalances, and inflammatory markers to rule out systemic or central nervous system infections.[21-23]

Neuroimaging is a cornerstone in the evaluation of dementia, offering structural and functional insights. Magnetic resonance imaging is utilized to detect hippocampal atrophy, a hallmark of AD and other neurodegenerative conditions. Advanced functional imaging techniques, such as amyloid positron emission tomography (PET) and fluorodeoxyglucose PET (FDG-PET), are valuable for detecting amyloid plaques and evaluating cerebral metabolic activity, respectively. These modalities help distinguish between different types of dementia and provide prognostic information.[23]

This integrative diagnostic approach is critical for accurately characterizing the type and stage of dementia, guiding treatment decisions, and facilitating individualized patient care.

Emerging perspectives

In recent years, monoclonal antibodies such as aducanumab and lecanemab have demonstrated promising efficacy in slowing cognitive decline by reducing cerebral beta-amyloid burden. These developments represent a paradigm shift in the treatment landscape of neurodegenerative diseases, particularly AD. Additionally, ongoing research into tau protein modulators offers a complementary avenue for addressing neurofibrillary pathology. Non-pharmacological approaches, including deep brain stimulation, have also gained significant attention, with preliminary findings suggesting potential benefits in modulating neural networks and improving cognitive function.[12]

Other notable advancements include the early identification of individuals at high risk for dementia through genetic testing and biomarker profiling. Advances in precision medicine have enabled the stratification of patients based on their genetic and biochemical profiles, paving the way for targeted interventions. Furthermore, lifestyle-based interventions aimed at enhancing cognitive reserve have emerged as a vital component of preventive strategies. These interventions encompass tailored physical activity programs, cognitive training, and nutritional optimization, underscoring the importance of a holistic approach to mitigating the impact of neurodegenerative diseases.[3,8,15]

Collectively, these advancements reflect a multi-faceted approach to dementia research and care, integrating pharmacological innovations, technological breakthroughs, and preventive strategies to address the complex challenges posed by these disorders.

Modifiable risk factors and prevention strategies

The identification of 14 modifiable risk factors for dementia, including hypertension, diabetes, obesity, physical inactivity, and social isolation, has shifted the focus toward prevention. Targeted interventions addressing these factors could potentially delay or prevent up to 40% of dementia cases worldwide. Lifestyle modifications, such as cognitive engagement, physical activity, and vascular health optimization, are now integral to comprehensive dementia prevention strategies.[4,6]

The integration of innovative diagnostic tools, such as TRODAT imaging and transcriptomics, alongside the ATN framework, represents a paradigm shift in the approach to AD. These advances are complemented by a growing emphasis on prevention through the modification of risk factors. As highlighted by the 2024 Lancet Report, the future of AD management will likely depend on a combination of early detection, molecularly targeted therapies, and broad-based preventive measures. Together, these strategies aim to reduce the burden of AD and improve the quality of life for affected individuals and their families.[7]

Future directions and challenges

The future of AD research must prioritize several key areas to drive meaningful progress. First, therapeutic interventions should aim to intervene earlier in the amyloid-tau cascade, particularly at the A-to-T

transition, to alter the disease's trajectory before irreversible damage occurs. Second, preventive strategies targeting at-risk populations are crucial, with an emphasis on lifestyle modifications such as physical activity and dietary interventions to reduce the incidence and delay disease progression.[3]

Furthermore, the integration of Artificial Intelligence into AD research has the potential to revolutionize diagnostic capabilities, enabling more accurate risk prediction, early detection, and real-time monitoring of disease progression, thereby improving patient outcomes.

The field stands at a critical crossroads, with significant advances in biomarkers, immunological therapies, and transcriptomic research paving the way for personalized treatment approaches. However, overcoming economic and infrastructural barriers to access remains essential, particularly in low- and middle-income countries, to ensure that these innovations benefit all patients. As the scientific community continues to decode the complexities of AD, a balanced focus on early intervention, prevention, and scalable solutions will be paramount in translating these breakthroughs into tangible global health improvements.[3]

Limitations

As a narrative review, the ability to quantitatively assess the effectiveness of the new therapies and interventions discussed is constrained. The qualitative analysis limits the objectivity of the findings, making it difficult to draw direct comparisons across different approaches and to establish firm conclusions regarding their relative efficacy.

The article did not include grey literature, such as unpublished theses, dissertations, and reports, which may result in a somewhat limited perspective on the current state of AD. The omission of such sources could potentially overlook important studies and findings not published in peer-reviewed journals.

The review did not incorporate comprehensive longitudinal data regarding the progression of the disease, which would provide a more robust understanding of how novel therapies influence the natural course of AD over time. Long-term follow-up studies are essential for evaluating the sustained impact of interventions.

The analysis of biomarkers and emerging immunological therapies is constrained by the availability and accessibility of these advanced diagnostic tools. This limitation may not reflect the real-world application in settings with limited resources, where these technologies might not be readily available.

The lack of data from diverse and representative populations may hinder the generalizability of the findings. Given the disparities in healthcare access and technological availability, especially in low- and middle-income countries, the conclusions may not be applicable across different demographic groups or geographic settings.

CONCLUSION

AD remains one of the most formidable challenges in modern medicine due to its high prevalence and profound impact on quality of life. Advances in understanding its pathophysiology and the development of novel biomarkers have been instrumental in enabling early diagnosis and refining therapeutic strategies. However, significant hurdles persist, including the high costs of new treatments, inequitable access, and limitations in therapeutic efficacy. The ultimate goal in the field is to develop effective treatments that not only address symptoms but also prevent the onset of dementia. Nevertheless, diagnosing AD based solely on clinical and biological constructs without a comprehensive understanding of when the symptoms will manifest is both premature and problematic. It is recommended that amyloid-positive individuals or those with biomarker evidence of AD but who remain cognitively normal should not be labeled as having AD. Instead, these individuals should be considered at risk for AD, with the expansion of presymptomatic AD as a more accurate diagnostic construct. This approach emphasizes biomarkers as indicators of proximity to symptom onset, rather than definitive diagnoses. Future research directions should focus on two critical areas: longitudinal observational studies that simultaneously evaluate lifestyle risk factors and biomarkers to determine their independent contributions to cognitive impairment and dementia over extended follow-up periods. Interventional clinical trials testing the efficacy of therapies targeting Alzheimer's pathology and other risk reduction strategies, aiming to decrease the incidence of cognitive impairment while carefully assessing the therapeutic risk-benefit profiles, are needed. Moreover, early diagnosis based on biomarkers could improve prognostic accuracy and inform variations in mortality risk. However, the translation of these advancements into clinical practice requires robust investments in both basic and translational research, alongside effective public health policies to ensure accessibility and equity. These efforts are essential for transforming the landscape of AD care in the coming decades.

Author´s contribution

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