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Biomarkers in Mild Stages of Alzheimer's disease: Utility in clinical practice and their relation with nutritional and lifestyle factors

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ABSTRACT

Background: The use of biomarkers in basic and clinical research as well as in clinical practice has become so common that their presence as primary endpoints in clinical trials is now accepted. A biomarker refers to a broad subcategory of medical signs. The aims of this article are to consider the of use biomarkers in Mild stages of Alzheimer's disease (AD) in research and clinical settings, in addition to defining their utility in clinical practice relating this with nutritional and lifestyle factors as possible treatment.

Methods: We searched MEDLINE, PubMed, and AgeLine databases using different keywords.

Conclusions: A summary of the utility of biomarkers in AD and nutritional and lifestyle factors used as treatment in mild stages are described.

Key words: Biomarkers, Alzheimer's disease, Dementia, Utility, Clinical practice, Nutritional and Lifestyle Factors, Early treatment

BACKGROUND

The use of biomarkers in basic and clinical research, as well as in clinical practice, has become so common that their presence as primary endpoints in clinical trials is now accepted.

Biomarkers are parameters (physiological, biochemical, anatomic) that can be measured *in vivo* and reflect specific features of disease-related pathophysiological processes. They stand for medical signs observed from outside the patient that can be measured accurately and reproducibly. This includes neuropsychiatric tests, neuropsychological batteries, laboratory tests, neuroimaging studies, genetic test, etc. [1].

Alzheimer's disease (AD), accounts for 60% to 70% of cases of dementia [1, 2]. AD is a progressive neurodegenerative disease that is characterized by impairment of cognitive and functional abilities as well as by neuropsychiatric symptoms (NPS). Cognitive impairment can include impairment of memory, visuospatial functions, language, and executive functions [1-3]. Additionally, NPS such as depression, apathy, and agitation appear to be symptoms already common in the early stages of AD and can have an impact on the well-being of both patients and caregivers [4, 5]. Cognitive performance has been consistently associated with functional ability [6].

The cause of Alzheimer's disease is poorly understood [7]. About 70% of the risk is believed to be genetic, with many genes usually being involved. Some of them predispose (APOE in late onset) and some are involucrated (amyloid precursor protein (APP) on chromosome 21, the gene presenilin-1 (PS-1) on chromosome 14 and the presenilin gene 2 (PS-2) in early onset or familiar type) in the development of AD [8], while other genes act as protector factors [9].

Moreover, there are clinical risk factors which include a history of head injuries, depression, or hypertension [7], dyslipemia, cigarrette smoking, sedentarism, obesity, and diabetes. In fact, the data which demonstrated that AD may have vascular modifiable risk factors came from studies on cardiovascular conditions and diabetes [10].

The disease process is associated with the deposit of amyloid plaques and tangles in the brain [8]. A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes [8].

Several biomarkers are used in clinical practice for the detection of mild stages of AD in order to implement different treatments to ameliorate the conversion to dementia. Prevention of vascular risk factors by implementing lifestyle changes in nutrition, promoting aerobic exercise [11, 12], diminishing stress, and treating depression are important for this matter. Moreover, cognitive stimulation and social interaction are also key factors in the treatment of mild stages [13].

Aims: The aims of this article are:

1) To consider the use of biomarkers in mild stages of Alzheimer´s Disease (AD) in research and clinical settings
2) To define their utility in clinical practice
3) To relate this with nutritional and lifestyle factors as possible treatments

Searching strategy: We searched MEDLINE, Pubmed, and AgeLine databases using the keywords "Biomarkers", "Alzheimer´s disease", "Complementary methods", "Neuropsychological test in Alzheimer´s Disease", "Neuroimaging in dementia", "Genetics in Alzheimer´s disease". We focused on research studies and review papers. We selected articles published in Spanish and English language.

We also selected papers published in different international journals that were related to research studies developed by our research group.

Biomarkers used in Research and Clinical Settings: The evaluation of an elderly patient consulting for cognitive impairment and/or neuropsychiatric symptoms (NPS) should begin with a complete history of cognitive and functional status, co-morbidities, family history, prescribed and non-prescribed medications, sleep patterns, and concerns regarding social and environmental changes.

Detailed neuropsychiatric and medical examinations should be conducted to evaluate concomitant or triggering clinical intercurrences.

Neuropsychiatric markers: Validated instruments, both general scales and focused scales, can be used to determine the presence, intensity, or frequency of NPS in patients with mild cognitive impairment (MCI) and dementia. General scales allow a broad spectrum of NPS to be assessed, while focused scales are used to assess one or more behavioral symptoms (for example, scales for depression or agitation) [3].

General scales are used to conduct multidimensional examinations, and include the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), [14] the Neurobehavioral Rating Scale (NRS) [15], the Behavioral Rating Scale for Dementia (BRSD) [16], and the Neuropsychiatric Inventory (NPI) [17].

The NPI is the most widely used scale to measure NPS associated with cognitive disorders. It is a fully structured interview, which obtains data from an informant, usually from the patient's caregiver. Recently, the NPI – Clinician (NPI-C) was developed [18]. The revised NPI-C can be used to assess single or multiple domains [19]. Unlike the NPI, each domain and potentially each sub-question within a domain, can be rated on the NPI-C. Caregivers and patients rate the frequency, severity, and distress of each item. Then, the clinician provides an overall rating based on interviews and additional chart information, which brings additional strength to the measure compared with the original scale.

The NPI-C was field tested in an international validation study and compared with focused scales to determine behavioral symptoms in cognitive disorders convergent validity. It was trimmed to 142 items (61 more than the NPI) and has been translated to several European languages [19].

Focused scales are instruments that are used to conduct uni-dimensional evaluations, including the Hamilton Depression Rating Scale [20], the Cornell Scale for Depression in Dementia [21], the Geriatric Depression Scale [22], or the Cohen–Mansfield Agitation Inventory [23].

Neuropsychological markers: Individuals who will develop AD present with specific cognitive difficulties several years before any clinical sign of pathology is detected [24, 25]. Typically, memory is the most common domain involved among patients in preclinical stage of AD [25]. In fact, amnestic forms of MCI have been considered as the most prominent subgroup with the highest rate of conversion to AD, while the non-amnestic forms are seen as those which most frequently progress to a non-AD dementia [26, 27].

In this regard, studies have identified decline in episodic memory (i.e., the ability to learn and retain new information) as the earliest and most salient manifestation of typical AD [24, 25, 28] and this impairment is generally considered as a core requirement for MCI due to AD [29]. Episodic memory tests, that are useful for identifying those MCI patients who have a high likelihood of progressing to AD dementia, share the same characteristic in that they assess both immediate and delayed recall; thus, it is possible to determine retention over a delay. Many of the tests that have proven to be useful in this way are word-list learning tests with multiple trials [2].

Since recall deficits can be caused by different conditions from AD (e.g., depression, or frontotemporal lobar degeneration), the Research Diagnostic Criteria proposed for the Diagnosis of AD suggested a more specific memory signature as the core clinical symptom of AD, which consists of a recall deficit which does not improve with cueing [26, 27]. Moreover, evidence has proved that clued recall deficits are associated with a progression of atrophy that closely parallels the spatiotemporal distribution of neurofibrillary degeneration in early AD. A recent prospective volumetric brain study has revealed that patients with impaired free recall but normal total recall (high index of cueing) on the Free and Cued Selective Recall Reminding Test (FCSRT) developed subcortical and frontal grey matter loss, while patients with impaired free and total recall (low index of cueing) developed grey matter atrophy within the left anterior and lateral temporal lobe [31].

A recent research has found that deficits in binding test can also be a marker for the early detection of AD [32].

We cannot fail to consider the importance of examining domains in addition to memory, and to also be aware of the possibility that atypical clinical presentations of AD may arise and need to be recognized [2] .

Differential profiles of cognitive impairment are described in Table 1 [33].

Laboratory Tests: Proper evaluation of patients with mild cognitive impairment and dementia should include studies of blood pressure, heart function, blood variables, and inflammatory conditions.

A routine that includes a complete blood count, erythrocyte sedimentation rate, urea, glucose, electrolytes, liver function and cholesterol is also mandatory.

In populations at risk, serum studies should be completed as VDRL and FTA-ABS, and HIV to rule out differential diagnosis. To study possible dislipemias, a lipid panel is necessary. If there are nutritional problems or the patient has neuropathy, myelopathy or anemia, laboratory tests should be completed with the dosage of B12 and folic acid. Other tests that should be included are thyroid function tests.

Table 1. Cognitive impairment differential profiles[1]

	Posterior cortical dementia	**Anterior cortical dementia**	**Dysexecutive subcortical dementia**	**Attentional subcortical dementia**
Disease	Alzheimer´s type dementia	Frontotemporal dementia	Vascular dementia small vessel disease	Depression
Cognition task				
Language	**Semantic anomia**	Evocation anomia	Conserved	Conserved
Speech	Conserved	Conserved	**Dysarthria and hypophonia**	Slowed
Episodic memory	**Amnesia - storage deficit**	Memory loss - retrieval deficit	Memory loss - retrieval deficit	Memory loss - retrieval deficit
Semantic memory	**Early alteration semantic anomia**	Conserved	Conserved	Conserved
Procedural memory	Late alteration	Early alteration	Early alteration	Conserved
Attention	Conserved	Conserved	Conserved	**Altered**
Visuospatial skills	Altered	Conserved - Except planning failures	Conserved - Except planning failures	Conserved
Calculation	Altered	Conserved	Conserved	Conserved
Executive skills	Late alteration	**Early alteration**	**Early alteration**	**Early alteration**
Social skills	Late alteration	**Early alteration**	Conserved	Conserved
Behavior task				
Disinhibition	Late	**Early and remarkable**	Variable	Late
Psychotic traits	Late	Rare and late	Variable	Frequent
Emotion	Apathy and depression	**Severe apathy**	**Apathy**	**Depression**
Motor skills	Conserved	Conserved	**Pyramidal and extrapyramidal signs**	Conserved

[1]Translated with permission from Dillon C, Allegri RF. Vertex 2010 May-Jun;21(91):301-13 [33]

Specific Laboratory Tests for AD: For a long time, diagnosis of Alzheimer's disease has relied largely on documenting mental decline, identifying dementia, and confirming the disease through postmortem anatomopathological findings. However, researchers have worked hard to discover an easier and more accurate way to detect AD before its devastating symptoms begin. Nowadays, it is well established that AD has already caused severe brain damage in individuals who are diagnosed in this documentary way, mainly due to accumulation of neurofibrillary tangles and amyloid plaques [1, 2].

Intracellular neurofibrillary tangles are formed due to hyperphosphorylation and oligomerization of tau, a microtubule-associated protein mainly present in axons. Extracellular amyloid plaques are formed from b-amyloid protein peptides (Ab), which are fragments formed by cleavage of an APP present in cellular membranes. APP can be processed by alfa-and gamma-secretases, generating a non-amyloidogenic product, or by beta- and gamma-secretases, generating Ab peptides, which are amyloidogenic and are prone to form plaques [34].

In the study developed by Braak and Braak, in which they studied eighty three brains of autopsy from non-demented and demented individuals, they found out that distribution pattern and packing density of amyloid deposits turned out to be of limited significance for differentiation of neuropathological stages [35]. Additionally, they observed the intraneuronal accumulation of insoluble abnormal phosphorilated tau proteins. Neurofibrillary tangles and neuropil threads exhibited a characteristic distribution pattern permitting the differentiation of six stages [35].

Animal models have greatly contributed to elucidate different aspects of the disease´s pathogenesis [36]. Data generated using genetically modified mice support the "amyloid cascade theory" explaining that the accumulation of Ab is the initial pathophysiological event in AD, leading to tau aggregation, synaptic loss, and cell death [36]. Mice models overexpressing APP display progressive Ab deposition in diffuse pattern and neuritic plaques, cerebral amyloid angiopathy, astrocytosis, microgliosis, mild hippocampal atrophy, neurotransmission changes, and cognitive and behavioral deficits [37].

Levels of total tau, phosphorylated tau at threonine 181 and ß-amyloid 1-42 (Aß42) determined in cerebrospinal fluid have become well-established AD biomarkers [38], and their profiles have been proposed to predict the course and the outcome of persons with amnestic mild cognitive impairment [39].

Many studies of patients with MCI have demonstrated that abnormal baseline levels of cerebrospinal fluid (CSF) total tau (T-tau), phosphorylated tau at threonine 181 (P-tau), and A42 are associated with subsequent conversion to AD dementia [40-49]. However, these previous studies [40-43; 46-49] have had short clinical follow-up of 1 to 3 years, except for 2 studies [44, 45] with follow-up of 4 to 5 years. Given that AD is a slowly progressive disorder, it probably takes at least 10 years before most patients with prodromal AD develop dementia and can be diagnosed as having clinical AD.

The study by Hansson et al [44], with a median clinical follow-up of 5.2 years, is still the most extensive follow-up of a cohort of patients with MCI at baseline in which the diagnostic accuracy of biomarkers for prodromal AD has been studied [50].

Neuroimaging studies: The development of three-dimensional imaging techniques has substantially improved the chances of neurological diagnosis. While computed tomography (CT) and magnetic resonance image (MRI) are routinely used for the detection of brain morphological lesions; neuroimaging through the Positron radiotracers as single photon emission (SPECT-single photon emission tomography) and positron emission tomography (PET-positron emission tomography) allow us to access the functionality of certain brain areas, by measuring blood flow (SPECT), or metabolism (PET). This is obtained from the morphology to study the function, opening an endless range of possibilities in cognitive impairments and dementia.

Neuroimagining biomarkers are valuable diagnostic and prognostic tools for AD. These biomarkers provide evidence of downstream brain changes that correlate with regional distribution of Alzheimer´s pathology, including regional brain atrophy seen by structural techniques and regional glucose hypometabolism or hypoperfusion detected with functional techniques [2, 30].

Structural imaging techniques: The main structural imaging techniques used are CT and MRI. In AD, the CT may reveal diffuse cerebral atrophy with enlargement of the cortical sulci and increased size of ventricles. However, these are late changes, so CT does not have any role in the early diagnosis of AD [51]. Therefore, the principal utility of the CT is limited to rule out any potentially treatable cause of dementia (e.g. tumour or subdural haematoma) and to evaluate the presence and extent of cerebrovascular disease [52].

Conversely, MRI is currently the imaging modality of choice for assessing subjects with suspected dementia [52]. Indeed, a characteristic pattern of brain atrophy involving the medial temporal lobes, paralimbic and temporoparietal cortices is considered a biomarker of AD-related neurodegeneration [53]. Hipoccampal atrophy is the best established and validated *MRI marker of AD* [54]. Significant atrophy of the hippocampal formation can be demonstrated by MRI even in preclinical stages of AD and it predicts later conversion to AD with about 80% accuracy. Likewise, hippocampal volume is a potential structural marker of disease progression [55]. Regarding their limitations, structural MRI measures are not as specific to AD as amyloid measurements and may include effects of aging and other neurodegenerative diseases and processes. Among its benefits are its ease of use, non-invasiveness, and relatively low cost (compared with PET) [56].

Memory impairment is an early manifestation of Alzheimer's disease (AD). The structures most involved in the pathology, including the early stage are: the hippocampal formation and parahippocampal rotation. A reduction in the volume of these structures has proven to be predictive of AD [57, 58]. The atrophy in this region correlates with neuropsychological performance of AD [59]: performance on verbal tests correlates with the volume of the left medial temporal lobe, in addition to nonverbal tests with the volume of the right medial temporal lobe. Golebiowski et al and Frisoni et al described high sensitivity and specificity of the medial temporal lobe volume in AD [60, 61].

Pantel et al revealed that the corpus callosum atrophy in AD is probably cause a syndrome of cortico-cortical disconnection that contributes to the severity of dementia [62].

In contrast to normal aging, the hippocampus is atrophied in the early stages of AD, making it a perfect candidate to be a diagnostic marker. Maximum neuronal loss in hippocampal formation occurs in the CA1, subiculum region and entorhinal cortex [63]. In patients with more than four years illness course, loss of volume in the anterior cingulate was the most sensitive to discriminate AD patients from normal controls measure. Other structures with significant sensitivity in the later stages of AD include the lower and medial temporal lobe, the basal ganglia and the amygdale [63].

Moreover, parietal atrophy (precuneos) is also an anatomical sign of probable AD.

Functional imaging techniques: Functional neuroimaging studies detect changes in perfusion and metabolism well before brain atrophy can become apparent in structural neuroimaging studies.

SPECT is one of the neurophysiological studies that measures cerebral perfusion while PET with fluorodeoxyglucose measures neuronal metabolism; labeled $Oxigen^{15}$ water measures perfusion and helps doing activation studies.

AD has a characteristic progression. According to the pathological stages of Braak and Braak [35], it begins with the deposition of neuritic plaques in hippocampal CA1, subiculum and entorhinal cortex, and then progresses to the rest of the crust subsequent association (parietal, temporal and posterior cingulate). Thus, the onset of the disease is characterized by loss of episodic memory with difficulty learning new information, which correlates with the first stage of Braak and Braak, then the visual-spatial and semantic aspects disorders and Language processing subsequent association cortex are added. These changes can be detected with functional neuroimaging studies of SPECT and PET. PET has greater spatial resolution and therefore, it is possible to detect the hypometabolism in medial temporal cortex (hippocampal and parahippocampal).

SPECT is a method to determine changes in regional cerebral blood flow at rest, through a radioisotope (Technetium 99) and a vehicle such as HMPAO or ECD. The changes in blood flow are more precocious than the structural changes detected by CT or MRI, so it is useful to see the pattern of changes in the various dementias. AD is recognized by temporal and bilateral posterior parietal hypoperfusion [64].

Dementia associated with psychiatric symptoms add alterations to SPEC; for example, a patient with Alzheimer's disease and apathy will have temporoparietal hypoperfusion added with hipoferfusion in medial prefrontal and anterior cingulate cortex [65].

Regarding the use of the neurophysiological studies investigating early detection and progression of dementia, tracking longitudinal studies found that normal subjects who developed mild cognitive impairment showed temporomedial hypometabolism measured by (fluorodeoxyglucose) FDG PET up to three years before it could be clinically detected [63]. Activation studies with PET and Oxigen15 labeled water, in addition to functional MRI studies demonstrated that, for a given cognitive task, patients with cognitive impairment activated older brain areas compared to controls. This finding is interpreted as a compensatory mechanism where patients should activate more brain areas to achieve the same performance as controls [66]. However, when atrophy progresses and the patient can no longer perform the cognitive task, a lack of activation of involved brain areas is observed [67].

We cannot fail to mention other methods recently developed as tractography or image voltage-diffusion (it allows an MRI study observe the paths of the great white tracts like the corpus callosum, cingulate, the internal capsule and the superior longitudinal fasciculus) where patients with Alzheimer's disease show atrophy tracts of associative linking areas, however not in the internal capsule [68].

Moreover, studies of diffusion-perfusion MRI are used to differentiate the new cerebral infarcts from the old ones. There is also research and development of new radioligands for viewing amlyliod deposits and enzyme activity with PET [69].

PET and SPECT are the main functional neuroimaging techniques used in AD. These techniques detect changes in regional metabolism and regional perfusion in the brain, respectively. PET with 18F-2fluoro-2-deoxy-D-glucose (FDG-PET) in AD shows a pattern of glucose hypometabolism involving temporoparietal, posterior cingulate and precuneus cortices [70-72]. On SPECT examinations, patients with AD show temporal and parietal lobe hypoperfusion [73, 74]. In a recent study comparing the relative diagnostic accuracy of both techniques for the diagnosis of degenerative dementia (AD and dementia with Lewy bodies) [75], FDG-PET was superior to SPECT, with a sensitivity and specificity of 85% and 90% respectively, for FDG-PET and 71% and 70% respectively, for SPECT.

Regarding early diagnosis of AD, in a prospective, community based study [76], the sensitivity and specificity of FDG-PET was 78% and 81% respectively, for the diagnosis of early-stage AD. Furthermore, FDG-PET predicts progression from MCI to dementia with high sensitivity and specificity [77, 78].

As mentioned above for structural imaging techniques, these functional imaging are also neuronal injury markers and not specific for AD [2, 30]. Nonetheless, neuroimaging measures are considered valuable markers to monitor disease progression, to characterize the clinical phenotype in atypical AD [30], and to differentiate AD from other neurodegenerative diseases [51].

Beta amiloid imaging: Molecular neuroimaging techniques have made it possible to visualize human brain amyloid β (Aβ) deposition during life using PET. Currently, several amyloid tracers are in use in AD research, including carbon-11 Pittsburgh compound B (PiB) [79],18Fflutemetamol (18F-PiB derivate) [80], Florbetapir F 18 (18F-AV-45) [81], Florbetaben (BAY 94-9172) [82]. These ligands have shown high specificity correlating with neuritic plaques in post-mortem studies [81, 83] and biopsy studies [84]. Thus, Amyloid PET is considered a specific biomarker of AD [30].

Regarding the value of amyloid PET in the early diagnosis of AD, a recent study that included 426 subjects [85], concluded that in a longitudinal analysis Aβ deposition (but not hypometabolism) was associated with ongoing cognitive decline in normal subjects, suggesting that in normal older individuals, amyloid is closely linked to the earliest indications of clinical decline. Additionally, in patients with MCI amyloid PET might be a valuable tool for predicting progression to dementia [86, 87]. The Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association have reviewed the indications for amyloid PET and have developed the following criteria for its use [88].

Amyloid imaging is appropriate in the situations listed here for individuals with all of the following characteristics:

1. Patients with persistent or progressive unexplained MCI
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

Amyloid imaging is inappropriate in the following situations:

1. Patients with core clinical criteria for probable AD with typical age of onset
2. To determine dementia severity
3. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) ε4
4. Patients with a cognitive complaint that is unconfirmed on clinical examination
5. In lieu of genotyping for suspected autosomal mutation carriers
6. In asymptomatic individuals
7. Nonmedical use (e.g., legal, insurance coverage, or employment screening)
8. Discussion of individual indications

Genetic studies: Other biological markers used are the genetic studies. The early onset of the disease is related to three genes: the APP on chromosome 21, the PS-1 gene on chromosome 14, and the PS-2 16. No chromosome exist in epidemiological studies on the subject but mutations in these genes seem to explain only half of early-onset AD. There are probably more genes involved. New predictive and diagnostic testing these AD early genes could be useful in diagnosis and genetic counseling for the family [88].

The gene for apolipoprotein E (APOE) located on chromosome 19 has three alleles E2, E3 and E4 [88]. The presence of the allele E4 / E4 is associated with an earlier onset of the disease [89, 90]. The partnership between AD and apo E4 has been confirmed in various ethnic groups [91]. However, because the APOE gene is not a deterministic gene but a gene for susceptibility or risk factor, its role in clinical practice is not yet clearly defined. It could be of interest to use as a complement to other tests in the diagnosis of AD, but not advised for determining whether an individual is a carrier presymptomatic AD.

There are sporadic forms and genetic forms of AD, usually early onset. 10-15% of AD cases correspond to familial forms [92-93]. The first-degree relatives of patients with AD have increased 2-4 times the personal risk of developing the disease [92-93]. In a small group of families, there is an autosomal dominant AD transmittance, which manifests in middle age [92-93]. To date, there are three identified genes responsible for early-onset familial forms; on chromosome 21, 14, and 1. For familial forms of AD it has been reported late ligament to chromosome 12 but the gene is not cloned [93].

The APOE confers susceptibility to both sporadic and late EA family. APOE gene on chromosome 19 has three alleles 2, 3, and 4. In the general population, the presence of the APOE genotype 4 is associated with an increased risk of AD. However, the sensitivity (about 50%) and

specificity (about 75%) for the presence of the APOE genotype 4 in the diagnosis of AD, is insufficient to guide diagnosis or quantify accurately the genetic risk [94, 95].

Cathepsin D (CATD) is an intracellular acidic protease that cleaves the amyloid beta precursor protein (APP-B). An allelic variant of that enzyme, CATD * T, is related to the degenerative process of AD through the excision of the B-amyloidogenic APP components. Allele carriers CATD * T have a 3.1 times increase in the risk of developing AD. If a patient has two alleles, the APOE-4 and T * CATD, the risk of AD is increased 19 times [96].

Jonsson et al studied coding variants in APP in a set of whole-genome sequence data from 1,795 Icelanders. They found a coding mutation (A673T) in the APP gene that protects against Alzheimer's disease and cognitive decline in the elderly without Alzheimer's disease [9].

The place of genetic testing and genetic risk assessment remains unclear. Genetic testing in the dementing diseases of the elderly is an underdeveloped field.

Although no effective prevention or treatment measures are available today, it is agreed that early diagnosis (including Genetic Testing - GT) of the disease should be emphasized [97].

However, given the enormous advances in this area, GT for the diagnosis of AD will become available in the near future to millions of individuals who are at risk of developing the disease and an increasing amount of research is being devoted to this topic in the last years.

Atypical presentations of Alzheimer´s Disease: Alzheimer disease (AD) is the most common cause of dementia. The cardinal manifestation of AD is progressive loss of memory. However, there are some non-amnestic presentations of AD, also called atypical AD. Symptoms of AD can sometimes start suddenly. In the presence of atypical symptoms or sudden onset, it may be difficult to distinguish AD from other dementias. Posterior cortical atrophy (PCA) is a neurodegenerative syndrome characterized by striking progressive visual impairment and a pattern of atrophy mainly involving posterior cortices. PCA is the most frequent atypical presentation of Alzheimer disease. Signal characteristic features of the PCA syndrome are: the early onset, focal loss of visual perception and focal posterior brain atrophy [98]. Cases of Primary Progressive Aphasia, like semantic dementia (SD) with the initial complaint of forgetfulness can diagnose as AD [99].

Primary progressive aphasia (PPA) is caused by selective neurodegeneration of the language-dominant cerebral hemisphere; a language deficit initially arises, as the only consequential impairment and remains predominant throughout most of the course of the disease [100].

Agrammatic, logopenic and semantic subtypes, each reflecting a characteristic pattern of language impairment and corresponding anatomical distribution of cortical atrophy, represent the most frequent presentations of PPA. The underlying neuropathology of PPA is, most commonly, frontotemporal lobar degeneration in the agrammatic and semantic forms, and Alzheimer disease (AD) pathology in the logopenic form; the AD pathology often displays atypical and asymmetrical anatomical features consistent with the aphasic phenotype. The PPA syndrome reflects complex interactions between disease-specific neuropathological features and patient-specific vulnerability [101].

A careful clinical history, a detailed mental evaluation, and neuroimaging will overcome this difficulty in diagnosis.

Utility of Biomarkers in Clinical Practice: Biomarkers are useful in clinical practice for:

1) Helping physicians to diagnose patients in early phases.

2) The determination of differential diagnosis.

3) Establishing guidelines for researchers and clinicians to communicate securely and efficiently diagnosing preclinical AD.

4) The establishment of a process that effectively translates this diagnosis in clinical practice and health policy.

5) The adaptation of the laws, regulations and professional practices for the diagnosis of preclinical AD.

Among the causes that lead patients to want these types of studies performed are the following:

1) The ability to better plan their future.

2) The possibility to adopt changes that are focused on improving the quality of life.

3) The practice of cognitive stimulation, physical activity, control of cardiovascular risk factors, eating a proper diet as preventive interventions [102].

Nutritional and Lifestyle factors: The importance of early diagnosis in AD is to try to reduce the conversion to dementia, the clinical stage where the patient starts depending on caregivers and has lost independence, something crucial in a human being's life.

Biomarkers nowadays, help clinicians to make earlier diagnosis and therefore to implement certain therapies to cope with the symptoms.

Over the past decade, there has been increasing focus on the influence of a number of lifestyle factors; including: intellectual engagement, social interaction, nutrition, and physical activity; on the cognitive vitality of older adults. Some studies have examined changes in cognition within the normal range, whereas others have asked whether lifestyle factors reduce the risk or delay the onset of age-associated diseases such as Alzheimer's, Cerebrovascular Disease, or Depression. Physical activity in midlife seems to protect from dementia in old age. Leisure-time physical activity (LTPA) is particularly important due to its broader effects in general and cardiovascular health [103].

Moreover, other lifestyle factors as nutritional components or changes in dietary recipes are also important in mild stages.

More than two decades of research on nutritional risk factors for dementia has yielded promising, but not yet definitive, findings of the foods and nutrients to either include or avoid in one's diet to prevent dementia [104].

Crichton GE, Elias MF and Akerwi A, investigated whether chocolate intake was associated with cognitive function, with adjustment for cardiovascular, lifestyle and dietary factors. Authors concluded that chocolate intake was positively associated with cognitive performance, across a range of cognitive domains in a dementia free community-dwelling population. The associations between more frequent weekly chocolate consumption and cognitive performance remained

significant after adjustment for a number of cardiovascular risk factors, including total and LDL-cholesterol, glucose levels, and hypertension. Associations were not attenuated with the addition of dietary variables (alcohol, meats, vegetables, and dairy foods), suggesting that chocolate may be associated with cognition irrespective of other dietary habits [105].

Other research studies have supported the action of the methylxanthinesin chocolate, caffeine and theobromine, in relation to cognitive function. Coffee is consumed by millions of individuals from all over the world, possibly in part, due to its caffeine content. It is the best known psychoactive stimulant acting to improve short-term alertness and arousal [106, 107]. Longer-term, population based studies have provided evidence that long-term caffeine intake may offer some protection against cognitive decline [108].

Moreover, epidemiological and animal studies have provided research data on which to consider the neuroprotective effects of individual nutrients, including vitamin E, B vitamins, and the n-3 fatty acid docosahexaenoic acid [109]. Positive associations were observed for vegetables (especially green leafy vegetables, which are good sources of folate, vitamin E, and carotenoids), seafood (a source of n-3 fatty acids), and berries (a source of polyphenols) [110].

More limited data are available on the neuroprotective benefits of monounsaturated fat, carotenoids, polyphenols, and vitamin D. Diets high in saturated and trans fats have been shown to increase cognitive decline and the risk of developing dementia, 2 and deleterious effects have been suggested for excessive intake of iron,3 copper (in conjunction with high saturated fat diets), 4 and synthetic folate or folic acid, among individuals with low vitamin B12 status [110-112].

Most of the epidemiological studies of dietary patterns have investigated the Mediterranean diet, and only four [113-116] of the 10 informative studies on this diet have found clear protective effects against cognitive decline or dementia [113-119].

It is evident that nutrients in foods exert differential effects on the brain.

As has been repeatedly demonstrated, isolating these nutrients and foods enables the formation of dietary interventions to optimize neuropsychological health. Adopting dietary patterns to delay or slow the onset of cognitive decline is an appropriate avenue, given the limited treatments available for dementia [120].

There are three medical foods that claim to offer symptomatic benefits: Axona®, Souvenaid® and CerefolinNAC®. Axona supplies ketone bodies as alternative energy source to neurons. Souvenaid provides precursors thought to enhance synaptic function. CerefolinNAC addresses the role of oxidative stress related to memory loss [121].

The characteristic of a medical food is that it is expected to be used under the regular care of a physician, so patients who are interested in using this type of material should discuss it carefully with their own physician and make sure that they, the physician, and the family understand appropriate use, realistic treatment expectations, and potential adverse effects [121].

CONCLUSIONS:

After describing the different biomarkers that can be used for the diagnosis of mild stages of AD and explaining their utility both in research settings and clinical practice, we intended to relate this with the implementation of different nutritional and lifestyle changes. The aim of the

implementation of this type of treatment is try to reduce the vascular risk factors that can influence the conversion to dementia and to improve the patient's quality of life in mild stages of the disease.

However, all the data obtained by the use of new and more specific biomarkers has to be indicated following scientific and clinical criteria. These biomarkers in clinical practice could impact costs and the incidence of incidental findings, which could be a concern. Thus, this matter has to be considered, since presently there is not a disease modification treatment, and lifestyle changes are a global recommendation for the overall population.

Abbreviations: Alzheimer's Disease (AD), neuropsychiatric symptoms (NPS), amyloid precursor protein (APP), gene presenilin-1 (PS-1), presenilin gene 2 (PS-2), mild cognitive impairment (MCI), Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Neurobehavioral Rating Scale (NRS), Behavioral Rating Scale for Dementia (BRSD), Neuropsychiatric Inventory (NPI), Neuropsychiatric Inventory-Clinician (NPI-C), Free and Cued Selective Recall Reminding Test (FCSRT), visual short term memory (VSTM), b-amyloid protein peptides (Ab), ß-amyloid 1-42 (Aß42), cerebro spinal fluid (CSF), total tau (T-tau), phosphorylated tau at threonine 181 (P-tau), computed tomography (CT), magnetic resonace image (MRI), single photon emission tomography (SPECT), positron emission tomography (PET), (fluorodeoxyglucose) FDG, apolipoprotein E (APOE), Cathepsin D (CATD), Genetic Testing (GT), Posterior cortical atrophy (PCA), semantic dementia (SD), Primary progressive aphasia (PPA), Leisure-time physical activity (LTPA)

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