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Alzheimer's Disease and Vascular Dementia: Diabetes-Related Cognitive Impairment Evaluation of Diagnostic Tools and Research Progress

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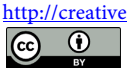

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Abstract

Type 2 diabetes mellitus (T2DM) is closely related to cognitive dysfunction and an increased risk of dementia. Type 2 diabetes-related cognitive dysfunction (TDACD) is an important complication of the central nervous system of diabetes, and its diagnosis mode is highly dependent on neuropsychological scales. With the development of imaging and molecular detection technologies, marker systems represented by MRI, PET, and humoral biomarkers provide an objective basis for accurate diagnosis. This article aims to systematically review the diagnostic and differential diagnosis-related markers related to T2DM-related cognitive dysfunction or dementia, including neuropsychological scales, neuroimaging markers, and humoral biomarkers, and analyze their characteristics (such as sensitivity, specificity, predictive value, etc.), and provide ideas for accurate diagnosis of TDACD patients.

Keywords

Diabetes-Related Cognitive Impairment, Alzheimer's Disease, Vascular Cognitive Impairment, Scales, Biomarkers, Precision Diagnosis, Individualized Treatment

1. Introduction

Diabetes is a risk factor for cognitive decline. Compared with non-diabetic patients, diabetic patients have a 73% higher risk of all types of dementia, a 56% higher risk of Alzheimer's disease (AD), and a 127% higher risk of vascular dementia (VaD) [1]. Type 2 diabetes-related cognitive impairment (TDACD) is

characterized by cognitive decline, abnormal executive function, and limited information processing ability and speed. Based on severity, it can be divided into three stages: cognitive decline, mild cognitive impairment (MCI), and dementia [2]. The first two stages often present with progressive decline in memory or other cognitive functions, but do not affect daily living ability and do not meet the criteria for a dementia diagnosis. It is the intermediate stage between normal cognition and dementia. Dementia can be classified by common pathological types into vascular dementia (VaD), Alzheimer's disease (AD), and mixed dementia (combining VaD and AD characteristics).

With the progress of the times, changes in human living structures, and intensifying population aging, the incidence of diabetes is on the rise. It is estimated that by 2050, the number of patients worldwide will increase to 853 million, of which 90% are type 2 diabetes mellitus (T2DM) [3]. T2DM is a systemic metabolic disease that progresses chronically due to insulin resistance and hyperglycemia, and long-term hyperglycemia can lead to chronic damage to the central nervous system through multiple mechanisms such as oxidative stress, neuroinflammation, and impaired insulin signaling in the brain, leading to the occurrence and development of TDACD. Studies have shown that patients with T2DM are more likely to develop cognitive dysfunction than normal people, and more than 46% of patients with mild cognitive impairment develop clinical dementia within 3 years [4]. Diabetes is an independent risk factor for multiple dementias. Therefore, early identification and diagnosis of TDACD are of great importance.

Common pathogenesis of dementia includes Alzheimer's disease (AD) and vascular dementia (VaD). Clarifying their pathogenesis is of great significance for diagnosis and treatment. AD is the most common cause of dementia, and its mechanisms include abnormal deposition of amyloid peptides (such as Aβ), over-phosphorylation of tau protein and aggregation to form neurofibrillary tangles, and Aβ promotes the spread of tau within synapses [5], further leading to synaptic dysfunction, neuroinflammation, and neuronal death [6]. In addition, Aβ plaques and tau tangles can also activate astrocytes and release a large number of inflammatory factors, which in turn exacerbate tau phosphorylation and cause neuronal death, forming a vicious cycle that ultimately leads to cognitive collapse. VaD is the second most common cause of dementia after AD, with a variety of pathogenesis, the most common cause being cerebral small vessel disease (SVD) [7], including cognitive decline due to ischemia (e.g., lacunar infarction), hemorrhagic (cerebral microhemorrhage), vascular atherosclerosis, and white matter damage [8]. Among patients with cognitive impairment, there is a high possibility of multiple pathological changes simultaneously. Mixed dementia (AD + VaD) often presents neuroimaging features of various types of dementia, such as hippocampal atrophy and cerebral infarction. Vascular risk factors can not only be the main cause of VaD, but also lead to AD.

2. The Evolution of Diagnostic Tools: Systematic Comparison and Critical Analysis

2.1. Psychometric Scales: The Cornerstones and Limitations of Cognitive Screening

The Mini-Mental State Examination Scale (MMSE) has been widely used since its publication in 1975 as a practical tool for assessing cognitive impairment [9], providing a holistic assessment of cognitive function in clinical practice and scientific research. A prospective study [10] indicated that, when using only baseline MMSE measurements, the sensitivity to distinguish between dementia and healthy older adults was 80% (95% confidence interval [CI] = 75% - 84%) and specificity was 89% (95% CI = 88% - 90%). In Alex J. Mitchell's meta-analysis [11], the sensitivity of MMSE was 76.1% (95% CI = 75.3%, 77.0%) and the specificity was 88.6% (95% CI = 87.5%, 89.6%) in 2981 cases of dementia. As a single screening tool, there is a lack of substantial evidence to support the use of MMSE in predicting the conversion to all types of dementia in the MCI population [12].

The Montreal Cognitive Assessment Scale (MoCA), as the first "short screening tool" for normal scores on the MMSE but with MCI, contains more cognitive-related subtests [13], showing higher sensitivity in detecting MCI. In more than 30 language versions of MoCA at home and abroad [14], the Chinese version of the basic MoCA (MoCA-BC) has been shown to be a reliable and sensitive tool for screening for MCI and AD at different levels of education. Comparative studies and epidemiological studies have found that MoCA may be better than MMSE in different populations, especially in the early stages of cognitive decline [15]. Additionally, after adjusting for education level, MoCA's ability to distinguish between cognitively normal and cognitively impaired elderly (MOCA AUC = 0.943 vs MMSE AUC = 0.826), sensitivity (90.2% vs. 78.4%), and specificity (87.2% vs. 76.9%) were all superior to MMSE [16]. In the longitudinal study, healthy elderly people were used as the control group; the sensitivity difference between MOCA and MMSE in detecting MCI patients was more significant (MoCA 95.3%; MMSE 53.8%) [17]. Regarding the "ceiling effect", an early cross-sectional study [18] showed that in healthy controls and MCI, 71.4% of individuals had MMSE scores concentrated between 28 and 30, whereas only 18.1% had MoCA scores in this range, suggesting that the ceiling effect of MoCA is less pronounced. Cross-sectional studies also confirm this conclusion [19]. Overall, MoCA outperforms MMSE in terms of sensitivity, specificity, and discriminative ability for identifying MCI, and it exhibits a smaller ceiling effect.

Of course, there are many other neuropsychological scales used to diagnose cognitive impairment and dementia. The Rapid Mild Cognitive Impairment Screening (QMCI), which takes about five minutes to operate, has high sensitivity, specificity, and structural validity in detecting cognitive impairment [20]. The "Test Your Memory" test (TYM), a rapid screening method used to distinguish between normal and mild cognitive decline, is performed by the patient himself, takes about 5 minutes [21]. Memory Change Test (M@T), Addenbrooke Cognitive Assessment-

Revised (ACE-R), Alzheimer's Disease Registry Federation Neuropsychological Assessment Kit (CERAD), etc., test only the more susceptible areas to distinguish between MCI, dementia, and healthy cognitive aging [22] [23]. In addition, there are some psychological tests, such as psychological test batteries (CAMCOG, ADAS-Cog, etc.) and clinical dementia rating scales [17], which require more time and professional training due to their complexity of operation, and have low clinical utilization [24].

2.2. Neuroimaging Biomarkers: Uncover Brain Structure and Function

Neuroimaging holds irreplaceable significance and value in disease diagnosis. It not only directly shows structural changes in the brain (such as brain atrophy and white matter hyperintensity), but also reveals abnormalities in brain perfusion, functional connectivity, and brain region metabolism through fMRI and PET, providing objective evidence for differentiating the etiology and staging of TDACD. CT or MRI, fMRI, PET, and other diagnostic tools are commonly used and recommended by multiple diagnostic and research guidelines for the assessment and diagnosis of dementia patients [25]. Using imaging to visualize intracerebral lesions not only facilitates early disease detection but also enables differentiation of cognitive impairment based on different types of lesions in specific brain regions, providing a basis for precise treatment.

2.2.1. Structural Magnetic Resonance Imaging (MRI)

1. White matter hyperintensities (WMH)

There is an association between white matter hyperintensities (WMH) and β-amyloid (Aβ) pathology. Some studies have found that posterior white matter hyperintensities (WMH) may be associated with Alzheimer's Disease (AD) pathology, such as the presence of WMH around the posterior ventricles in AD patients [26]. Longitudinal studies [27] show that people with autosomal dominant AD have already had an increase in WMH volume before cognitive decline, suggesting that WMH may not only be a vascular complication but also a core feature of the AD pathological process. This perspective is further refined in the impact studies of AD and VaD: WMH in AD patients is often focal punctate or early fusion (Fazekas grade 1 - 2), and often coexists with hippocampal and temporal lobe atrophy; In VaD patients, WMH shows a broad convergence (Fazekas grade 3) distribution with increasing load [28]. This difference in imaging distribution patterns suggests that the progression trajectories of WMH may be completely different between the two types of diseases. A DIASPORA study found that in early-onset (<65-year-old) cognitive impairment patients, adjusting neurodegenerative markers (P-tau217, NfL) still significantly predicted functional decline [29]. WMH is one of the imaging markers of VaD, with its load correlated with the degree of cognitive impairment [30], playing an important role in VaD diagnosis. A multi-cohort study including 148 VaD patients found that the WMH loading rate (62%) in VaD patients was significantly higher than in AD (27%) and Lewy body dementia (43%),

indicating that WMH is an effective imaging marker distinguishing VaD from other types of dementia [31]. Second, WMH can lead to different cognitive impairment manifestations in different brain regions, such as frontal WMH associated with executive impairment, bilateral parietal temporal lobe WMH associated with memory impairment, and WMH in the upper deep white matter associated with decreased motor speed [32], so it seems to be able to assess the type of cognitive impairment.

2. Enlargement of the perivascular space (EPVS)

Amyloid-β (Aβ)-laden interstitial fluid is transported through the perivascular space (PVS), and when its drainage is restricted, abnormal enlargement of PVS can be shown on MRI, which is a marker of decreased Aβ clearance [33]. Enlarged perivascular space (EPVS) was previously considered a normal manifestation of aging, but there is now growing evidence that this view seems inaccurate. EPVS is associated with small vessel disease, and studies have highlighted the importance of EPVS as an imaging landmark of SVD on MRI and have received widespread attention. Wardlaw's review [34] proposed that EPVS is one of the histological features of SVD and speculated that it may be an early imaging marker of small vessel disease and blood-brain barrier alteration. EPVS is also thought to be associated with cognitive decline, especially in memory, information processing speed, and executive ability [7]. A systematic review by Smeijer *et al.* suggests that multiple studies have reported associations between basal ganglia EPVS and vascular dementia (VaD) [35]. However, the heterogeneity of EPVS distribution in neurodegenerative diseases remains to be clarified. Fu Qingyang and colleagues shifted their research focus to the clinical spectrum of AD, finding that EPVS scores in semi-oval centers increase with the severity of cognitive impairment [36]. These results suggest that EPVS can serve as a potential marker for vascular lesions, serving as a strong differentiating marker for small vessel disease under various pathologies, and is also meaningful for monitoring the progression of neurodegenerative diseases.

3. Brain atrophy

Structural brain atrophy on MRI is often used as an alternative imaging marker for neurodegenerative changes. A longitudinal study based on the ADNI cohort found that in elderly people with a lower burden of cerebrovascular disease, T2DM was associated with reduced baseline cortical thickness and led to cognitive decline through this neurodegenerative change [37]. Brain atrophy contributes significantly to the development of cognitive impairment. Smaller brain volume (global indicators of brain atrophy) and cortical gray matter volume (indicators of cortical atrophy) and enlarged ventricles (indicators of subcortical brain atrophy) are associated with poorer executive function in patients and are exacerbated with cerebral infarction or severe WMH [38]. Cerebral atrophy can assess cerebral vascular damage to some extent and is considered an important predictor of regional cognitive impairment and one of the characteristic alterations of AD (hippocampal atrophy). The hippocampus is involved in delayed memory and memory reten-

tion. The reduction in overall gray matter and hippocampal volume is closely related to T2DM, and the hippocampus and parahippocampal gyrus are also among the first areas of atrophy in MCI or AD, which are the best markers for identifying patients with AD in the early stages of MRI [39]. MRI in AD patients shows extensive brain atrophy, and studies have found that hippocampal or entorhinal cortex atrophy is more significant [40]. A study on elderly patients with dementia after stroke found that atrophy of subcortical gray matter structures such as the thalamus and basal ganglia contributes to dementia [41]. MRI imaging provides direction for diagnosis in different regions, and the results can be considered in conjunction with the patient's age and other clinical examinations.

2.2.2. Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is a novel magnetic resonance imaging technique that captures changes in tissue microstructure that cannot be directly displayed by WMH by measuring the diffusion of water molecules in the white matter of the brain [42]. As early as 2007, Huang *et al.* found in their research that DTI exhibits high sensitivity in detecting white matter microstructural damage that appears normal on conventional MRI [43]. In addition, changes in longitudinal parameters of DTI can objectively reflect the dynamic changes of neurodegenerative processes, providing a basis for individualized treatment [44]. Several main parameters in DTI and their pathological significance (see **Table 1**): Anisotropy score (FA) represents the integrity of nerve fibers and is used as an indicator to reflect white matter tract damage [45]; mean diffusion rate (MD) represents the degree of obstruction of free water diffusion and is associated with neurodegeneration [46]; Axial diffusivity (AD) and radial diffusion rate (RD) measure the diffusion of water molecules along and perpendicular to the long axis of nerve fibers, respectively, and are closely related to axonal and myelin integrity, respectively [47]. Decreased FA and elevated MD, AD, and RD are sensitive indicators of white matter damage, axonal injury, and demyelination, and are associated with declines in cognitive abilities such as memory, executive function, and information processing speed [48] [49]. DTI indicators outperform WMH volume, lumen volume, brain volume, and other indicators in terms of interpretation processing speed [50].

Table 1. Diffusion tensor imaging (DTI) parameters and their pathological significance.

Parameters	Change direction	Pathological significance
FA	↓ Lower	The integrity of the white matter fiber bundles is destroyed, and the axon arrangement is disordered
MD/RD/AD	↑ Elevated	Myelin damage, axon loss, and destruction of tissue microstructures

Note: FA: Anisotropic Score; MD: Average Diffusion Rate; RD: Radial Diffusion Rate; AD: Axial Diffusion Rate.

2.2.3. Functional Magnetic Resonance Imaging (fMRI)

1. Resting state functional magnetic resonance imaging (rs-fMRI)

Resting-state functional magnetic resonance imaging (rs-fMRI) indirectly infers whether neuronal activity in brain regions is synchronized by measuring changes in blood oxygen level-dependent (BOLD) signals during resting state. Functional connectivity within specific brain networks is studied in the resting state by measuring the correlation between BOLD time series activated in different brain regions. rs-fMRI provides a new perspective on differentiating different types of dementia by revealing abnormal patterns in functional connectivity. Different types of dementia affect different brain functional networks. In patients with AD, the default mode network (DMN) connectivity in regions such as the posterior cingulate gyrus is significantly reduced, and the functional connectivity (FC) between brain regions is widely disrupted [51]. Among them, the decline in FC in the middle occipital gyrus and middle temporal gyrus regions may be the mechanism leading to Aβ deposition and executive dysfunction [52]. In addition, patients with MCI in cerebral small vessel disease also had weakened FC of the DMN and executive control network (ECN) [53]. rs-fMRI has great potential to identify cognitive impairment. Another fMRI study [54] pointed out that in AD-risk populations, ultra-early cerebrospinal fluid Aβ deposition is closely associated with decreased connectivity in the temporal occipital lobe (DMN), and changes in this functional connectivity are associated with executive function impairment.

2. Task-state functional magnetic resonance imaging (task-fMRI)

Task-state functional magnetic resonance imaging (task-fMRI) localizes functional brain regions by detecting changes in BOLD signals in brain task-activated regions. For example, under the Stroop task, patients with subcortical vascular dementia (SIVD, the most common type of VaD) have all-round functional impairment and low activation of the prefrontal and posterior parietal lobes, where the posterior parietal activation volume is correlated with executive, attention, delayed recall, etc., which are areas of SIVD prominent impairment [55]. Visual-spatial task fMRI studies found that the degree of fMRI activation in the left supraparietal lobule of AD patients was positively correlated with clock test performance, suggesting that neuropathological changes in the parietal lobe region may be involved in the occurrence of visuospatial processing disorders [56]. When performing the Stroop test, there were differences in the BOLD signal activation patterns in specific brain regions between the patient group and the normal control group: AD or SIVD patients produced similar cortical activation in the prefrontal cortex, anterior cingulate gyrus, etc., but their activation levels were significantly lower than those of normal controls [57]. Both AD and MCI patients were activated in the bilateral dorsolateral prefrontal lobe and ventromedial prefrontal lobe, and the activation volume of AD patients was significantly smaller than that of normal controls, while MCI patients were the opposite [58].

BOLD signals can simultaneously reflect neural activity and vascular responses. Decreased cerebrovascular reactivity (CVR) weakens BOLD signaling changes, leading to underestimation of neural activity. Therefore, whether rs-fMRI or task-

fMRI, CVR must be included in the analysis when interpreting results; otherwise, BOLD results may be misinterpreted [59]. In addition, CVR also plays a role in the differential diagnosis of AD and VaD. CVR responds to vascular perfusion reserve by dilation of blood vessels after carbon dioxide inhalation, which is used to indicate the ability of cerebral blood vessels to stimulate the expansion of vasoactivity, which is impaired in SVD [60]. Research [61] found that CVR is significantly correlated with cognitive performance and independent of AD pathology. This suggests that whole-brain CVR may be a useful biomarker for assessing vascular disease-related cognitive impairment in older adults. Multicenter studies [62] have shown that whole-brain CVR is positively proportional to MoCA scores, supporting its utility as a sensitive biomarker for SVD and VCID. The instrumental validity of CVR and its reliability in testing have also been validated in other studies [63]. Cross-sectional studies [61] found that after adjusting for AD pathological markers such as cerebrospinal fluid Aβ42 and tau, whole-brain CVR remained significantly correlated with cognitive performance, suggesting that whole brain CVR may be a useful biomarker for assessing vascular disease-related cognitive impairment in the elderly.

2.2.4. Positron Emission Tomography (PET)

PET scans are currently the most commonly used brain metabolic imaging system, often used in conjunction with an artificial glucose analogue (FDG) to measure brain energy metabolism and identify regional patterns in neurodegenerative lesions [64]. 18F-FDG-PET has become a reliable method for diagnosing and differentiating dementia. Patients with AD usually show low metabolism in the posterior cingulate gyrus and parietal temporal cortex, as well as in the frontal lobe (advanced) [65]. Patients with VaD exhibit reduced glucose metabolism in the frontal lobe, thalamus, and caudate nucleus, and this abnormal metabolic pattern aligns with their clinical manifestations of executive dysfunction [66]. The development of amyloid β (Aβ) and tau-specific tracers has made AD-specific markers measurable *in vivo* and has potential applications in the diagnosis and prognosis of AD [67]. PET ligands targeting amyloid and tau proteins can improve the differential diagnosis between AD and non-AD dementia, and even recognize diseases during the prodromal stage [68]. Another study found that AD-related tau pathology is most prominent in neocortical regions such as the temporoparietal lobe and posterior cingulate gyrus, and this widespread elevation of neocortical tau is only seen in individuals with high Aβ load [69]. Aβ-PET in AD patients shows diffuse distribution characteristics in multiple regions [70]. Aβ and tau are typical pathological features of AD patients and are generally negative in VaD patients.

The previous paper has reflected the different dimensions of neurodegenerative degeneration and vascular injury at the structural (MRI), microstructure (DTI), functional (fMRI), and molecular (PET) levels. However, in the differential diagnosis of AD and VaD, the sensitivity and specificity of each indicator differ, and cross-influence is common. To intuitively compare the differentiated performances of these parameters between the two diseases, the main results are sum-

marized here (see Table 2).

Table 2. Characteristic differences between key parameters of MRI, DTI, rs-fMRI, and PET in VaD and AD.

Technology	Parameters	AD type manifestations	VaD
MRI	WMH	Mild, punctate, posterior (parietal occipital) predominantly	Heavy, Integration, widely distributed
MRI	EPVS	The center of the semi-oval is dominant, and the degree is mild	The basal ganglia area is significantly increased
MRI	Brain atrophy	The hippocampus/entorhinal cortex was dominated by atrophy, and the medial temporal lobe was prominent	Subcortical/basal ganglia/thalamic atrophy is the main focus
DTI	FA	Lowering (temporal lobe/posterior white matter)	Lowering (extensive white matter)
DTI	MD/AD/RD	Elevation (temporal lobe/posterior white matter)	Elevated (extensive white matter)
fMRI	DMN connection	Significantly reduced (early features)	Reduced (execution network is more pronounced)
fMRI	CVR	Normal or mildly reduced	Significantly reduced, suggesting impaired vascular reserve function
18F-FDG PET	Brain glucose metabolism	Reduced temporoparietal/posterior cingulate return metabolism	Decreased basal ganglia/thalamus/frontal lobe metabolism
Aβ PET	β-Amyloid deposition	Positive (diffuse deposition)	Negative or occasionally positive
Tau PET	Nerve fiber tangle distribution	Positive (medial temporal lobe/predominantly temporal lobe)	Negative or atypical distribution

Note: WMH: white matter hyperintensity; EPVS: enlarged perivascular space; FA: Anisotropic Score; MD: Average Diffusion Rate; RD: Radial Diffusion Rate; AD: Axial Diffusion Rate; DMN: default mode network; CVR: cerebrovascular reactivity.

2.2.5. Summary: Advantages and Limitations of Various Imaging Methods

The target pathology, advantages and limitations of each technique are summarized below, and the results are shown in Table 3 due to space constraints:

Table 3. Comparison of imaging techniques.

Technology	Target pathology	Advantages	Limitations
CT	Space-occupying lesions (tumors/hematomas), severe cerebral atrophy, cerebral hemorrhage	Fast scanning, bleeding sensitivity, metal compatibility, high penetration, and low cost	Early hippocampal atrophy is insensitive and has ionizing radiation
Structural MRI	Hippocampal atrophy, brain volume, cortical thickness, white matter hyperintensity	Excellent soft tissue contrast, no ionizing radiation, accurate quantification	Slow scanning, claustrophobia, metal implant limitations
DTI	White matter fiber bundle integrity, axon injury, demyelination	The only living viable showed white matter fiber orientation and sensitivity to early ischemia	Data analysis is complex, lacks uniform standards, and is susceptible to edema

Continued

fMRI	Neuronal activity (BOLD signal), default network connection abnormal	Non-invasive, high spatial resolution, can be used for functional area positioning	Low temporal resolution, Head movements are sensitive
18F-FDG PET	Glucose metabolism (decreased temporoparietal/posterior cingulate gyrus)	Abnormalities detected earlier than MRI	There is radiation, it is affected by blood sugar, and the cost is high
Aβ PET	β-Amyloid deposition	Diagnosis of AD and clinical trial screening	The cognitively normal elderly can be positive and the cost is extremely high
Tau PET	Distribution and density of nerve fiber tangles	Associated with cognitive decline and tracking disease progression	Tracers may bind non-specifically and have the lowest Popularity

2.2.6. Humoral Biomarkers: A Convenient and Dynamic "Window"

There is growing evidence of the potential value of humoral biomarkers in the diagnosis and differential diagnosis of dementia. Cerebrospinal fluid markers are regarded as the "gold standard" for AD diagnosis due to their direct response to pathological changes in the brain, and are given the same weight as pathological diagnosis in the 2024 Alzheimer's Association (AA) revision [71]. Cerebrospinal fluid (CSF) biomarker detection can reflect the aggregation of Aβ and tau in the brain [72], and because CSF is distributed around the central nervous system, Aβ and tau in CSF can suggest corresponding neuropathological changes in the brain. CSF Aβ reflects amyloid burden in the brain [73]; total tau (T-tau) can reflect synaptic degeneration or neuronal degeneration [74]; Phosphorylated tau (P-tau) is considered a pathological marker of nerve fiber tangles [75]. Milà-Alomà *et al.* conducted CSF biomarker modeling in cognitively unimpaired preclinical individuals and found that the earliest detectable change in the AD continuum was a decrease in the CSF Aβ42/40 ratio, followed by rapid increases in CSF p-tau, t-tau, and synaptic protein neurogranin [76]. The typical manifestations of cerebrospinal fluid markers in AD patients are decreased Aβ42 and elevated t-tau, but the overall level of these markers is affected by hyperglycemia and hyperinsulinemia [77], so comprehensive consideration is required when interpreting markers.

For example, blood glucose control levels, kidney function, age, vascular factors, use of Hypoglycemic drugs and cardiovascular drugs, and education level are all important confounding factors. Indicators such as HbA1c, fasting or postprandial blood glucose can reflect disease status, but they are directly influenced by treatment plans and patient compliance, interfering with the evaluation of independent effects of other biomarkers. In addition, as many circulating biomarkers are metabolized by the kidneys, their nonspecific accumulation in the bloodstream during renal dysfunction does not reflect the true pathophysiological process. Vascular lesions themselves can also trigger inflammatory responses and endothelial damage, thereby confusing the causal relationship between spe-

cific biomarkers and diabetic complications. The use of hypoglycemic drugs and cardiovascular drugs directly regulates indicators such as blood glucose, blood lipids, and blood pressure, which may obscure or amplify the true correlation between biomarkers and clinical manifestations. Metabolic characteristics of diabetes patients at different age groups affect biomarker levels; Education level can influence outcome analysis by affecting health literacy, treatment adherence, and lifestyle.

A meta-analysis evaluating the conversion of MCI to AD [78] showed that although Aβ1-42, T-tau, and P-tau in CSF can also predict AD-type dementia transformation in MCI subjects, the accuracy is relatively low (odds ratio (OR) 7.5 - 8.1), but the combination of Aβ1-42 and tau in CSF has good predictive accuracy for AD (OR 18.1, 95% CI 9.6 - 32.4). Based on autopsy pathology, Grothe *et al.* confirmed that T-tau/Aβ1-42 and p-tau181/Aβ1-42 have good accuracy in distinguishing between AD and non-AD dementia (AUC 0.94 - 0.97) [79]. Dakterzada *et al.* used clinical diagnosis as a reference to compare AD and non-AD patients, finding that the CSF Aβ42/Aβ40 ratio AUC = 0.879 (95% CI 0.766 - 0.992) [80]. p-tau181/Aβ42 in CSF is recommended for the diagnosis of AD in the revised criteria for AD diagnosis and staging [81].

The novel CSF biomarkers have extremely high accuracy in distinguishing AD patients from non-AD patients. A study using neuropathological examination as a reference standard comparing AD and non-AD subjects found that CSF p-tau235 had extremely high accuracy in distinguishing between the two, with an AUC of 0.99 (95% CI 0.97 - 1.00) [82]. Additionally, Lipid carrier protein 2 (LCN2) (secretory glycoprotein) plays an important role in differentiating AD from VaD as another novel cerebrospinal fluid marker. It is thought to potentially mediate vascular injury or inflammatory responses [83]. Research indicates that, using clinical consensus diagnosis as the gold standard for distinguishing VaD from AD, CSF LCN2 levels are significantly elevated in the VaD group. The Area Under the Curve (AUC) for distinguishing the two is 0.9 (95% CI 0.82 - 0.98), with a sensitivity of 82% and a specificity of 87%. [84].

The use of cerebrospinal fluid markers is limited by the invasiveness of obtaining CSF. Blood-based biomarkers are ideal for screening, diagnosis, and tracking of disease progression in the population. Aβ plaques and neurofibrillary tangles are characteristic pathological markers of AD that can be detected decades before symptoms appear [85], and biomarkers reflecting this underlying pathology provide an important opportunity for early identification of MCI patients who are most likely to develop AD.

There is a correlation between plasma P-tau181 levels and CSF P-tau181 levels, suggesting that plasma P-tau181 can serve as a non-invasive marker for responding to central nervous system tau pathology [86]. Longitudinal cohort studies [86] using clinical consensus diagnosis as the reference standard found that plasma P-tau181 distinguishes between AD and non-AD neurodegenerative diseases, with an AUC of 0.93 (95% CI 0.88 - 0.98), and this result was also validated in the pa-

thology subgroup of autopsy (AUC = 0.91). A multicenter study found that p-tau181 is the best single natural plasma marker to distinguish AD from other types of dementia, but cutoff values need to be adjusted for different situations to achieve maximum diagnostic efficacy [87].

Plasma p-tau217 is a high-value marker. Based on a review of 13 studies, Suresh *et al.* found that p-tau217 exhibited high accuracy (AUC > 0.90) in all comparisons [88]. Cohort studies [89] showed that the p-tau217/Aβ42 ratio performed excellently in distinguishing between AD and non-AD pathologies, with AUC = 0.963-0.966 for identifying Aβ-PET positive and AUC = 0.947 - 0.974 for tau-PET-positive detection.

Using CSF marker detection as the reference standard, the AUC for predicting amyloid-positive plasma p-tau231 in elderly people without dementia was 0.87 [90]. In the development of AD pathology, cerebrospinal fluid P-tau231 levels are the first to be elevated, which can be used as an ideal indicator for detecting early Aβ pathology [91].

The plasma Aβ42/Aβ40 ratio can also reflect cerebral amyloidosis, offering potential application value in distinguishing AD from other types of dementia [87]. In the revised criteria for AD diagnosis and staging, it is recommended to diagnose AD together with other indicators [81]. A multicenter study [92] showed that when distinguishing PET-positive and PET-negative cases, the AUC of Aβ42/Aβ40 was 0.87, p-tau181/np-tau181 was 0.74, and p-tau217/np-tau217 was 0.92, but the combined PPC model could increase AUC to 0.95.

In T2DM patients, glial fibrillary acid protein (GFAP) predicted incident dementia (diagnosed over 15 years) with an AUC of 0.71 (95% CI: 0.67 - 0.76) [93]. GFAP, as a marker of astrocyte activation and neuroinflammation, is elevated in the plasma of patients with early AD and individuals at high risk of AD [94] and is associated with the transformation of MCI patients to AD pathology and AD dementia [95]. In AD, astrocytes exhibit reactive hyperplasia with GFAP upregulation, and its concentrations are associated with Aβ plaque density and white matter damage, as well as cognitive decline [96]. Cohort studies showed that plasma GFAP was significantly correlated with imaging indicators of vascular brain injury and had potential in distinguishing vascular cognitive status, but the study also found that elevation does not simply reflect vascular injury [97]. Another study on middle-aged people found that placental growth factor (PLGF) indirectly affects GFAP via WMH, which in turn positively affects P-tau181 and neurofilament protein light chain (NfL), suggesting that blood-brain barrier dysfunction may be involved in AD-related pathological cascades during adolescence [98].

Imaging excels at locating brain structural injury, while humoral biomarkers are sensitive to capturing early molecular events. To intuitively compare the specific changes of these humoral markers between the AD and VaD groups, all core indicators and their clinical significance are summarized here (see **Table 4**).

Table 4. Characteristic differences in humoral biomarkers in VaD and AD.

specimen	Markers	AD	VaD/Hybrid change	Clinical significance
Plasma	Aβ42/40 ratio	significantly reduced	Normal or mildly reduced	Distinguish between AD and non-AD
Plasma	P-tau181/217/231 p-tau217/Aβ42 ratio	significantly elevated	Normal or mildly elevated	AD-specific markers
Plasma	T-tau	Elevated	Normal or mildly elevated	Nerve axon injury
Plasma	GFAP	Elevated	Significantly elevated (vascular injury response)	Astrocyte activation /blood-brain barrier disruption
Plasma	LCN2	Normal or mildly elevated	Significantly elevated (blood-brain barrier disruption)	Inflammation of Vascular inflammation/blood-brain barrier dysfunction
CSF	Aβ42/40 ratio	significantly reduced	Normal or mildly reduced	AD core markers
CSF	P-tau231/P-tau 235 T-tau/Aβ1-42 ratio p-tau181/Aβ1-42 ratio	significantly elevated	Normal	AD specificity was the highest, distinguishing AD from VaD
CSF	T-tau	Elevated	Elevated (non-specific)	Degree of neuronal damage

Note: Aβ: β-amyloid; P-tau: phosphorylated tau protein; T-tau: total tau protein; GFAP: glial fibrillary acidic protein; LCN2: lipid carrier protein 2; CSF: cerebrospinal fluid.

3. Discussion

In summary, cognitive scales, neuroimaging, and humoral biomarkers provide a basis for the identification and etiology of TDACD from different dimensions, but various screening and diagnostic methods have their advantages and limitations. Through scale scores [99] [100], patients are screened and stratified at risk, and follow-up treatment plans are specified accordingly, which greatly improves the detection rate of TDACD, improves prognosis, and avoids waste of resources. Although we have used MOCAs with higher sensitivity and less ceiling effect for screening, there is still a risk of false negatives due to the influence of age, education, and cultural background, and it is difficult to capture patterns of cognitive decline [101].

At the imaging level, **Table 3** systematically sorts out the typical differences between various imaging and PET markers in AD and VaD, and clearly shows the essential differences between the damage patterns of the two pathological types: AD is mainly characterized by posterior cortex, neuronal degeneration, and protein deposition, while VaD is dominated by vascular reserve decline and extensive white matter and microstructural damage. Specifically, the core imaging of AD is highly consistent with the temporal lobe and posterior cortical lesions, including hippocampal atrophy, decreased FA and MD in the temporal or posterior white matter, decreased DMN connectivity, decreased FDG metabolism, and positive Aβ or tau. VaD patients mainly have basal ganglia and extensive white matter in-

volvement, such as increased EPVS and decreased metabolism in the basal ganglia, extensive and convergent WMH, decreased FA and MD in the extensive white matter region, and decreased CVR. This suggests that in TDACD, imaging findings can reflect the driving mechanisms of two common pathologies, protein deposition drives neurodegeneration (AD) and hemodynamic disorders drive ischemic injury (VaD). In addition, the two pathologies can coexist, namely mixed dementia, and the core lesions of the two can be directly observed on imaging, and the treatment direction can be determined according to the dominant pathology. Different imaging methods have their own specific target pathologies and adaptations (see Table 4), and according to the patient's dominant pathology, individualized selection of examination methods can achieve twice the result with half the effort.

Humoral markers can also reveal different pathological driving mechanisms between AD and VaD—significantly reduced Aβ42/40 ratio, significantly increased P-tau181/217/231/235 (Aβ protein deposition and tau hyperphosphorylation in AD patients), and significantly elevated GFAP and LCN2 (vascular injury and blood-brain barrier disruption in VaD patients). In addition, humoral markers further strengthen the molecular differentiation between AD and VaD. For example, in TDACD, if plasma or cerebrospinal fluid Aβ42/40 is decreased and P-tau is elevated, AD or mixed type should be highly suspected first. If GFAP and LCN2 are elevated and Aβ or tau is normal, simple VaD is more supportive. If there are abnormalities in Aβ or tau and GFAP or LCN2, the possibility of mixed type is considered. Although the acquisition of humoral markers greatly limits their clinical application due to their invasiveness, especially the detection of cerebrospinal fluid markers. However, it is undeniable that both plasma and cerebrospinal fluid markers (Aβ, tau, GFAP, LCN2, etc.) can improve the specificity of diagnosis.

Cognitive impairment associated with diabetes mellitus is a mixed effect of metabolic disorders, AD pathology, or VaD pathology, and cognitive decline in this context may be more severe than that of non-diabetic patients during the same period. Relevant studies have shown that MOCA [100] and cerebral blood flow [102] have higher diagnostic accuracy at optimal cutoff values, while cerebrospinal fluid or blood markers require establishing diagnostic thresholds for diabetes and its context. Although many studies have used ultrasensitive detection methods to improve the accuracy of humoral marker detection and established cut-off values for some markers, these data vary across different research platforms, so standardization issues remain an obstacle to the widespread application of humoral markers [103].

4. Summary and Outlook

In summary, we should be clear that no single diagnostic technique can provide all answers. Fortunately, the advantages and disadvantages of existing diagnostic technologies and the diagnostic focus are largely complementary. Diagnostic methods such as structural MRI, DTI, fMRI, PET, and humoral markers can achieve a complete diagnostic chain from lesion to etiology, from structural and functional

localization to molecular etiology. Specifically, structural imaging (structural MRI, DTI) visually shows intracranial structural abnormalities; functional imaging (MRI, FDG-PET) can directly assess the metabolism or activity level of brain regions; molecular localization imaging (Aβ-PET/Tau-PET/humoral markers) provides molecular etiology. Therefore, the combined application of various "multimodal" methods is an essential path to improving the accuracy and specificity of dementia diagnosis. Several techniques are applied simultaneously or sequentially over the same time period in the same subject; these direct comparisons greatly contribute to our understanding of dementia, dismantling TDACD into quantifiable pathological spectrums that provide a basis for diagnosis and individualized intervention.

In the future, specific markers of glucose metabolism and energy metabolism may be developed, or combined with machine learning to construct individualized encephalopathy continuous spectrums to improve prediction accuracy, and subtypes can be grouped according to treatment methods, such as targeted therapy, metabolic intervention, or vascular risk enhancement. In addition, given the significant increase in the risk of dementia associated with diabetes and the sharing of multiple pathogenesis, reference intervals for humoral markers after correcting the course of diabetes, glycated hemoglobin, and renal function can be established in the future. Changes in plasma markers, such as the rate of change in Aβ or tau, and the trend of GFAP or LCN2, are monitored longitudinally during the course of the disease to predict the transformation of MCI patients to dementia. Patients are classified and stratified according to multimodal diagnostic methods, and individualized treatment plans are given to verify the efficacy of different treatment strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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