

# Leading role of $^{18}\text{F}$ -FDG-PET imaging in early diagnosis of Alzheimer's disease: an overview

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**Abstract:** Early detection of Alzheimer's disease (AD) is important to reveal preclinical pathological alterations, to monitor disease progression, and to evaluate response to therapy. The study of cerebral glucose metabolism through  $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography (FDG-PET) plays a leading role in early detection of AD because the decrease of cerebral glucose metabolism largely precedes the onset of AD symptoms. This technique demonstrated high sensitivity in early diagnosis of AD, allowing a qualitative and quantitative estimate of cerebral glucose metabolism. Furthermore FDG-PET imaging may help to discriminate the subjects of a high-risk population (like patients with mild cognitive impairment) who more probably will develop AD: an early stage of AD generally shows hypometabolism of medial temporal lobes and parietotemporal posterior cortices; other cerebral cortices are later involved. The combination of FDG-PET with other biomarkers, such as genotype, cerebrospinal fluid markers, and amyloid plaque imaging, may increase the preclinical diagnostic accuracy and offer promising approaches to assess individual prognosis in AD patients.

**Keywords:** positron emission tomography, dementia, neuroimaging, Alzheimer's disease,  $^{18}\text{F}$ -FDG

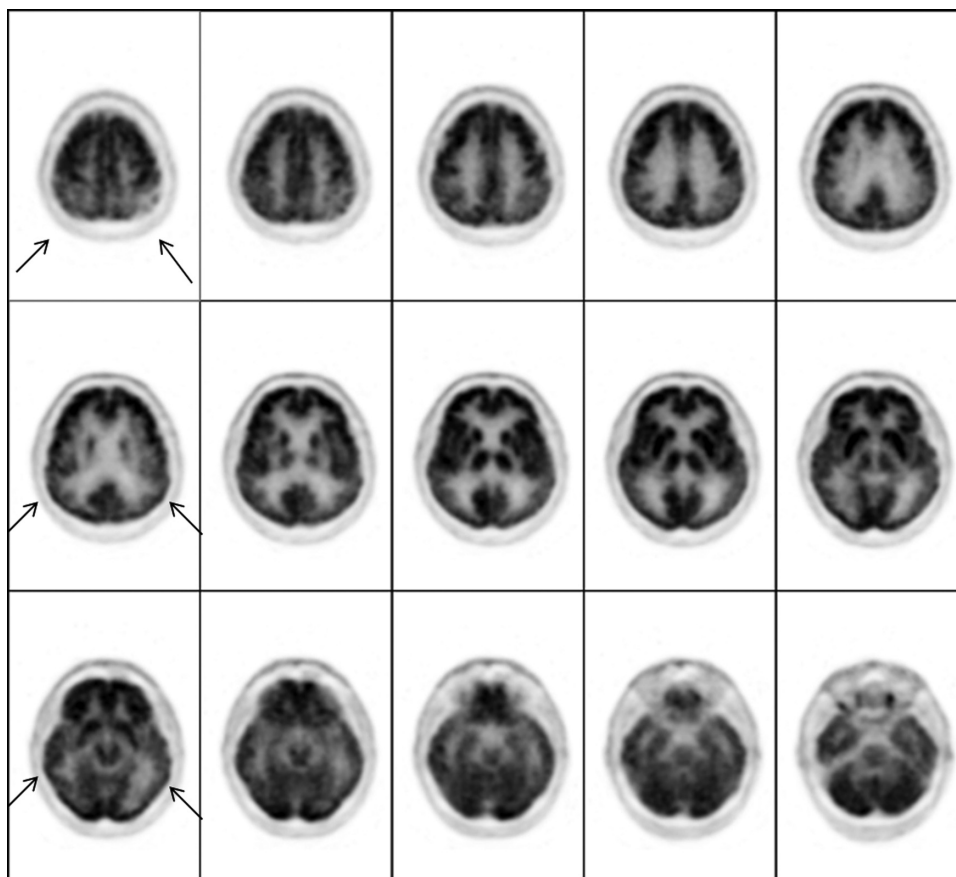
## Introduction

Alzheimer's disease (AD) is a common disorder of older age and represents a serious medical and socioeconomic problem. The interest of the scientific community for AD is now increasingly focused on the possibility of early diagnosis in order to begin treatment before the onset of irreversible neuronal damage. In fact, the pathological changes underlying AD as intracellular neurofibrillary tangles and amyloid- $\beta$ -plaques appear years before the onset of symptoms. The early detection of AD is therefore particularly important to reveal preclinical pathological alterations, to monitor disease progression, and to evaluate the response to therapy. Clinical measures of cognitive dysfunction currently used to define the presence of dementia are not able to early diagnose AD, especially in the mild stages.<sup>1,2</sup>

This diagnostic challenge can be overcome through the use of complementary tools such as sensitive biomarkers, including brain imaging markers. Several functional neuroimaging modalities have shown promising results as tools for early diagnosis of AD, such as positron emission tomography (PET) using a tracer of cerebral glucose metabolism or beta-amyloid ligands.<sup>1,2</sup>

The study of cerebral glucose metabolism through  $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography (FDG-PET) plays a leading role in early detection of AD (Figures 1–3), because the decrease of cerebral glucose metabolism largely precedes the

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**Figure 1** A 56-year-old male patient with mild cognitive impairment; a FDG-PET ( $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography) scan showed bilateral mild hypometabolic areas in the parietal and temporal cortices (arrows).

onset of symptoms; thus FDG-PET has become an excellent tool for early detection and estimation of increased risk of future dementia.<sup>1,2</sup>

Glucose metabolism provides approximately 95% of the ATP (adenosine triphosphate) required for brain function. Under physiological conditions, as well as in several diseases affecting the brain, glucose metabolism is tightly connected to neuronal activity. Therefore, changes in neuronal activity induced by disease are reflected in an alteration in glucose metabolism. FDG is suitable for imaging regional cerebral glucose consumption with PET since it accumulates in brain tissue depending on facilitated transport of glucose and hexokinase-mediated phosphorylation.<sup>3</sup>

Pre-administration procedures are as follows: (1) patients should fast for at least 4 hours, and blood glucose levels should be checked; (2) patients should be positioned comfortably in a quiet room several minutes before FDG administration and during the uptake phase of FDG (at least 20 minutes); and (3) they should be instructed not to speak, read, or be otherwise active. The recommended FDG activity to be administered is 150–250 MBq for adult patients.<sup>3</sup>

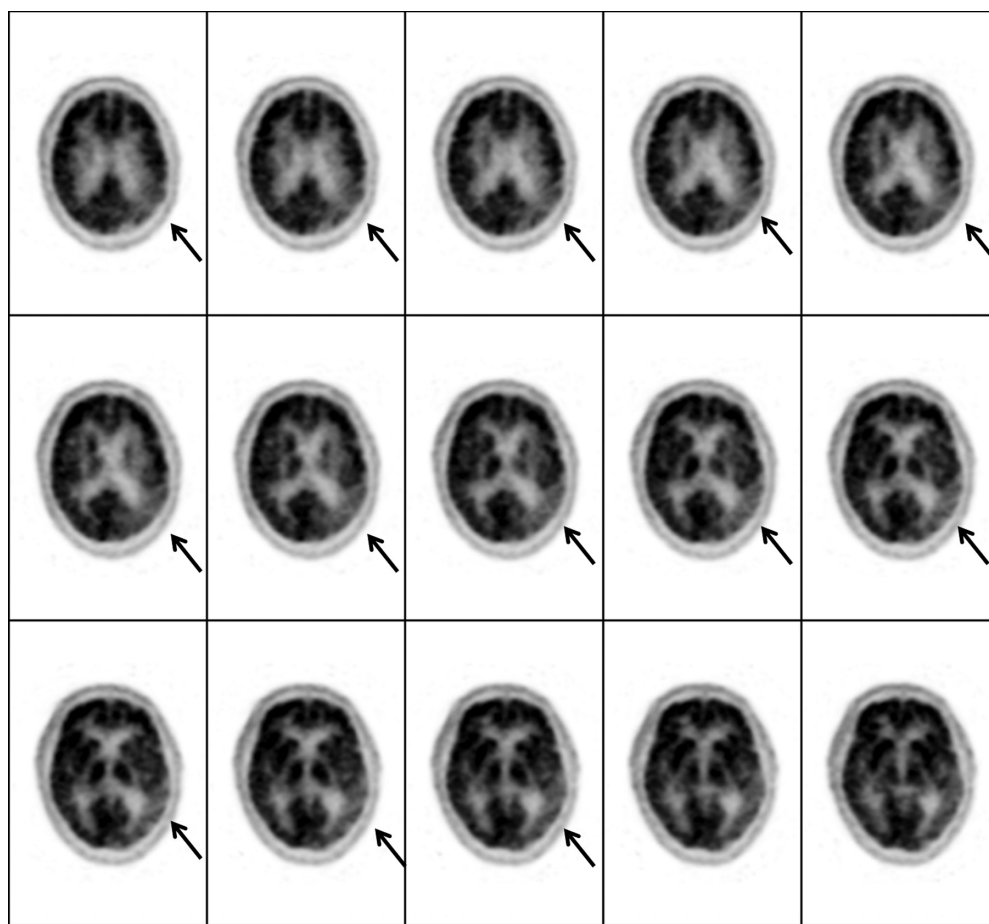
PET acquisition should not start earlier than 30 minutes after FDG injection. The duration of emission image acquisition should be related to the minimum required number of detected events. For PET/computed tomography (CT) systems, the CT scan can be used for attenuation correction. For FDG-PET interpretation, qualitative (visual analysis), semiquantitative, or quantitative estimates can be performed.<sup>3</sup>

The aim of this overview is to describe the recent developments of FDG-PET imaging in early diagnosis of AD.

## Brief history and recent developments of FDG-PET in AD

Nearly 30 years have passed since the publication of the first scientific paper on the applications of FDG-PET in dementia,<sup>4</sup> and during this time this technique has been widely used. For the period from 1980 to 2010, nearly 300 papers have been published in Pubmed/Medline with the keywords “FDG” and “Alzheimer.”

In 2001, Silverman et al demonstrated that the regional brain metabolism studied with FDG-PET was a sensitive indicator of AD and neurodegenerative diseases in patients



**Figure 2** A 73-year-old male patient with cognitive impairment; a FDG-PET ( $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography) scan showed hypometabolic areas in the left parietal and temporal cortices (arrows), suggesting Alzheimer's disease.

presenting cognitive symptoms of dementia; FDG-PET showed a sensitivity of 94% and a specificity of 73% in patients with AD. A negative FDG-PET scan indicated that a pathologic progression of cognitive impairment was unlikely to occur during a 3-year follow-up.<sup>5</sup>

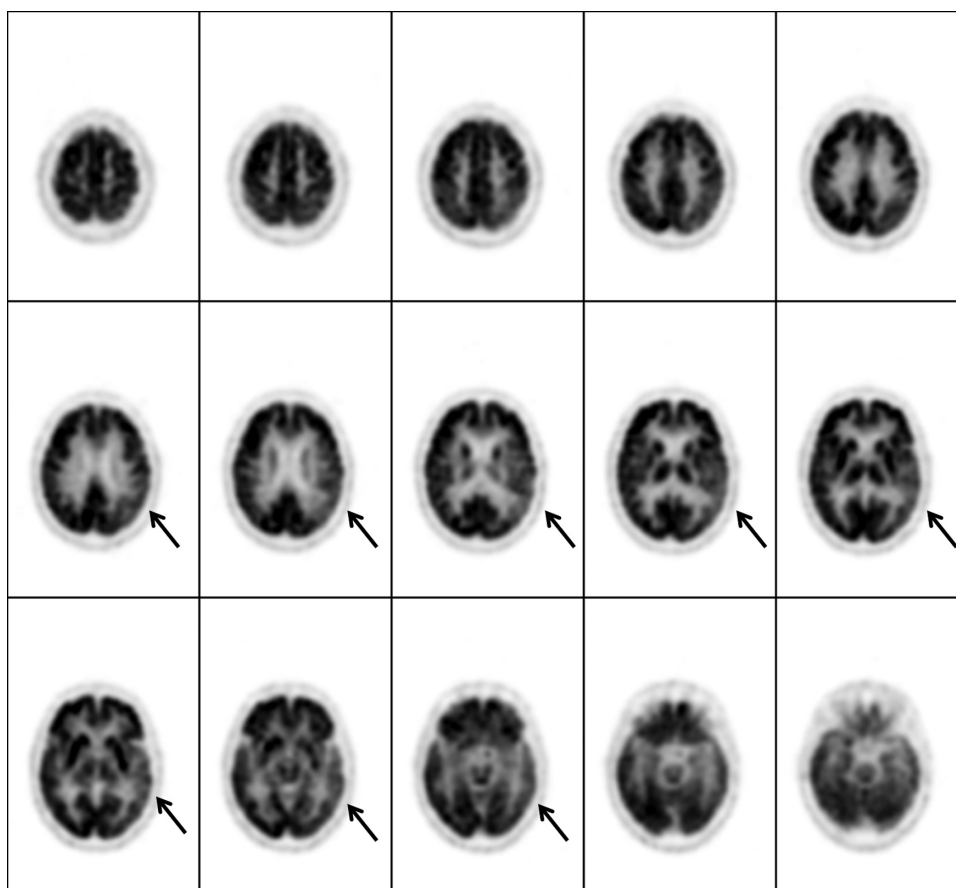
In most of the small single-center studies, AD is associated with characteristic and progressive reduction in FDG cerebral uptake. The Alzheimer's Disease Neuroimaging Initiative (ADNI) project, born in 2003 and involving many investigators, has clearly demonstrated the feasibility and utility of multicentre PET studies in the study of dementia.<sup>6</sup>

In 2005, an interesting review underlined that glucose metabolism reductions revealed by FDG-PET in the medial temporal, parietotemporal, and posterior cingulate cortices are the hallmarks of AD. FDG-PET showed a 90% overall sensitivity in identifying AD, although specificity in differentiating AD from other dementias was lower.<sup>7</sup>

In 2008, a multicenter study examined FDG-PET as a tool for differential diagnosis of AD, frontotemporal

dementia (FTD), and dementia with Lewy bodies (DLB). The authors examined FDG-PET scans of 548 subjects, including 110 healthy individuals (normal control [NC]), 114 mild cognitive impairment (MCI), 199 AD, 98 FTD, and 27 DLB patients, collected from seven participating centers. Standardized disease-specific PET patterns were developed and correctly classified 95% AD, 92% DLB, 94% FTD, and 94% NC. AD PET pattern was observed in 79% of MCI patients with deficits in multiple cognitive domains and in 31% of amnesic MCI. FDG-PET variability in MCI with nonmemory deficits ranged from absent hypometabolism to FTD and DLB PET patterns. On the basis of these findings, the authors demonstrated that FDG-PET may provide an objective and sensitive support to the clinical diagnosis in early dementia.<sup>8</sup>

In 2009, an interesting study was designed to evaluate the diagnostic accuracy of FDG-PET in the differential diagnosis of early-onset AD and other dementias in a community-dwelling population that may be representative of patients in the general population. A prospective sample



**Figure 3** A 74-year-old female patient with cognitive impairment; a FDG-PET ( $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography) scan showed hypometabolic areas in the left parietal and temporal cortices (arrows), suggesting Alzheimer's disease.

of 102 individuals presenting consecutively to a primary care center for suspected early-onset dementia was evaluated using standard clinical criteria for the diagnosis of dementia. Functional neuroimaging data was obtained and nuclear medicine physicians were blind to the clinical diagnosis generated FDG-PET diagnoses. Final clinical diagnoses based on all available data were then established and compared with PET diagnoses. Forty-nine patients received a final clinical diagnosis of early-stage AD; there were also 29 non-AD dementia patients, 11 depressed patients, and a miscellaneous group of 13 patients. Among patients with AD, the sensitivity and specificity of FDG-PET was 78% and 81% respectively. The specificity of FDG-PET in the differential diagnosis of other dementias, including FTD, was greater than 95%, suggesting that this technique might help in the diagnosis of FTD and other forms of early-onset dementia.<sup>9</sup>

In 2009, Langbaum et al, within the large ADNI project, compared baseline FDG uptake measurements from 74 probable AD patients and 142 amnesic MCI patients with those from 82 normal controls, using statistic parametric mapping. In comparison with normal controls, the probable

AD and amnesic MCI groups had significantly lower FDG uptake bilaterally in the posterior cingulate, precuneus, parietotemporal, and frontal cortices. These findings from a large multisite study support those of previous single-site studies, showing a characteristic pattern of baseline FDG uptake reductions in AD and amnesic MCI patients, as well as preferential anterior FDG uptake reductions after the onset of AD dementia.<sup>10</sup>

In the same year, Haense et al investigated the performance of FDG-PET using an automated procedure for discrimination between AD and controls; FDG-PET data were obtained from the ADNI database (102 controls and 89 AD patients) and the Network for Standardisation of Dementia Diagnosis (NEST-DD) database (36 controls and 237 AD patients). AD patients had higher AD scores compared with controls ( $P < 0.01$ ), which were significantly related to dementia severity ( $P < 0.01$ ). Early-onset AD patients had significantly higher AD scores than late-onset AD patients ( $P < 0.01$ ). This automated procedure yielded a FDG-PET sensitivity and specificity of 83% and 78% in ADNI and 78% and 94% in NEST-DD, respectively; differences between databases

were mainly due to different age distributions. On the basis of these findings, the authors demonstrated that the automated FDG-PET analysis procedure provides a good power of discrimination, mainly for early-onset AD.<sup>11</sup>

In 2010, Chen et al, within the ADNI project, described 12-month declines of FDG uptake in 69 probable AD patients, 154 amnesic MCI patients, and 79 cognitively NCs from the ADNI using statistical parametric mapping. These authors introduced the use of an empirically pre-defined statistical region-of-interest (sROI) to characterize declines of FDG uptake. The AD and MCI groups each had significant 12-month declines of FDG uptake bilaterally in posterior cingulate, medial and lateral parietal, medial and lateral temporal, frontal, and occipital cortices, which were significantly greater than those in the NC group and correlated with measures of clinical decline.<sup>12</sup>

Considering that most FDG-PET studies in dementia have used clinical diagnosis as gold standard and that clinical diagnosis is approximately 80% sensitive or accurate, a recent study reviewed the evidence-based data on the diagnostic accuracy of brain FDG-PET in dementia when cerebral autopsy is used as gold standard. The authors found that sensitivity and specificity of FDG-PET for AD are good, but more studies using histopathological diagnosis at autopsy as gold standard are needed in order to evaluate the contribution of FDG-PET to pre-mortem diagnosis of dementia.<sup>13</sup>

## FDG-PET in patients at high risk to develop AD

Brain FDG uptake decline has been observed before the onset of AD symptoms, highlighting the importance of FDG-PET as a valuable tool for early detection and estimation of increased risk for future dementia. Thus, the interest of the scientific community has focused on high-risk populations who are more likely to develop AD as compared with low-risk populations. People at risk of developing dementia include: pre-symptomatic subjects carrying mutations responsible for early-onset familial AD; patients with mild cognitive impairment (MCI), often a prodrome to late-onset sporadic AD; nondemented carriers of the apolipoprotein E epsilon 4 allele (ApoE-E4), a strong genetic risk factor for late-onset AD; cognitively normal subjects with a family history of AD; patients with subjective memory complaints; and the normal elderly. Overall, the high-risk groups show brain FDG uptake reductions years before the clinical decline.<sup>1,2,14</sup>

Reiman et al found that cognitively normal, late-middle-aged carriers of the apolipoprotein E epsilon 4 (ApoE-E4)

allele, a common susceptibility gene for late-onset AD, have abnormally low FDG uptake in the same brain regions as patients with probable AD.<sup>15</sup> The same authors also found that the young ApoE-E4 carriers had abnormally low rates of glucose metabolism bilaterally in the posterior cingulate, parietal, temporal, and prefrontal cortices. The authors demonstrated that carriers of a common Alzheimer's susceptibility gene have functional brain abnormalities in young adulthood, several decades before the possible onset of dementia.<sup>16</sup>

A more recent study examined whether cerebral FDG uptake is altered in cognitively normal ApoE-E4 carriers with subjective memory complaints (SMCs). As compared with ApoE-E4-negative subjects, ApoE-E4-positive subjects showed decreased cerebral FDG uptake in AD-related brain regions; as compared with SMC-negative subjects, SMC-positive subjects showed reduced FDG uptake in parietotemporal and parahippocampal gyrus. These findings demonstrate that normal ApoE-E4 carriers with SMC show altered AD-related FDG-PET measures.<sup>17</sup>

In 2006, Mosconi et al evaluated and compared brain atrophy with hypometabolism as preclinical markers of AD by studying presymptomatic individuals from families with known early-onset autosomal dominant AD (FAD) carrying mutations in the Presenilin 1 gene. The authors found that presymptomatic FAD individuals show widespread FDG uptake reduction consistent with the typical AD PET pattern in the relative absence of structural brain atrophy, suggesting that FDG-PET measures may serve as biomarkers for the preclinical diagnosis of AD.<sup>18</sup>

In 2007, Mosconi et al examined whether cognitively normal subjects with a parental family history of AD show cerebral FDG uptake reductions consistent with AD as compared with those without a family history and whether there are parent gender effects. Those authors found that, as compared with both normal subjects without a family history of AD and normal subjects with a paternal family history of AD, the normal subjects with a maternal family history of AD showed FDG uptake reductions in the same regions as clinically affected AD patients, involving the posterior cingulate cortex/precuneus, parietotemporal, and frontal cortices, and medial temporal lobes ( $P < 0.05$ ). This study showed a relationship between reduced FDG uptake in AD-vulnerable brain regions and a maternal family history of AD in cognitively normal individuals.<sup>19</sup>

A high percentage of patients with MCI develop AD within 1 year. In 2003, a longitudinal study was performed

to identify characteristic patterns of cerebral metabolism at baseline in patients converting from MCI to AD, and to evaluate the changes in these patterns over time. After 1 year, 36% of MCI patients had developed probable AD, whereas 55% of MCI patients were still classified as having stable MCI. Compared with the healthy control group, a reduced FDG uptake in AD-typical regions, including the parietotemporal and posterior cingulate cortices, was detected at baseline in patients with MCI converting to AD. After one year, MCI patients converting to AD demonstrated an additional bilateral reduction of FDG uptake in prefrontal areas, along with a further progression of the abnormalities in the parietal and posterior cingulate cortices. No such changes were observed in the stable MCI group. The authors concluded that in patients with MCI, characteristic cerebral metabolic differences can be delineated at the time of initial presentation, which helps to define prognostic subgroups.<sup>20</sup>

In 2005, Anchisi et al suggested that FDG-PET findings combined with memory scores may be useful in predicting short-term conversion to AD in amnesic MCI patients.<sup>21</sup> A recent study of Pagani et al confirmed that the combination of memory and brain metabolic assessment could identify subgroups of memory decliners and nondecliners before a long follow-up time is available and supply prognostic information in amnesic MCI patients.<sup>22</sup>

Recently, Clerici et al assessed whether FDG-PET differentiates amnesic MCI from nonamnesic MCI with executive dysfunction. At baseline amnesic MCI and nonamnesic MCI exhibited a similar pattern of hypometabolism, mostly in the posterior cingulate gyrus, as compared with normal controls. In the comparison between the MCI subtypes, the amnesic MCI subjects showed reduced metabolism in the medial temporal lobes, hippocampus, fusiform gyrus, and amygdala. At follow-up, 75% of amnesic MCI developed AD, while nonamnesic MCI had a heterogeneous course, including subjects who developed Lewy body dementia. The authors demonstrated that patterns of altered brain metabolism in amnesic MCI and nonamnesic MCI subjects compared with NCs are similar and do not provide evidence for making clinical distinctions between them. However, the comparison between the two MCI subtypes showed medial temporal lobe hypometabolism in amnesic MCI subjects, possibly reflecting the fact that most patients could present prodromal AD.<sup>23</sup>

A more recent study by Landau et al, within the ADNI project, evaluated the prognostic ability of neuroimaging

and cognitive measurements in patients with amnesic MCI. Subjects with MCI who had abnormal results on both FDG-PET and episodic memory scores were 11.7 times more likely to convert to AD than subjects who had normal results on both measures ( $P \leq 0.02$ ). The authors demonstrated that baseline FDG-PET and episodic memory scores predict conversion to AD.<sup>24</sup>

In 2001, de Leon et al examined the hypothesis that FDG-PET may predict cognitive decline during normal aging. In a 3-year longitudinal study of 48 normal elderly individuals, 25% of subjects demonstrated cognitive decline. At baseline, metabolic reductions in the entorhinal cortex accurately predicted the conversion from normal to MCI. Among those who had declined, the baseline FDG uptake reduction in the entorhinal cortex predicted longitudinal memory and temporal neocortex metabolic reductions. At follow-up, those who had declined showed memory impairment and hypometabolism in the temporal lobe neocortex and hippocampus. In summary, these data suggest that brain FDG uptake reduction can be detected in old age and predicts future cognitive decline.<sup>25</sup>

More recently, Mosconi et al demonstrated that progressive brain FDG uptake reductions occur years before clinical AD symptoms in patients with pathologically verified AD; furthermore, the FDG-PET pre-mortem profiles were consistent with the post-mortem diagnoses.<sup>26</sup>

## FDG-PET and other biomarkers in AD and MCI

FDG-PET can be used in combination with other biomarkers of AD for a higher diagnostic accuracy in AD and MCI.<sup>1</sup>

Recently, Walhovd et al combined MRI, FDG-PET, and cerebrospinal fluid (CSF) biomarkers in the diagnostic classification and 2-year prognosis of MCI and AD. These authors found that: (1) all biomarkers were sensitive to the diagnostic group; (2) MRI morphometry and CSF biomarkers together improved diagnostic classification (controls versus AD) – MRI morphometry and FDG-PET were largely overlapping; and (3) baseline MRI and FDG-PET measures were more predictive of clinical change in MCI than CSF measures.<sup>27</sup>

Petrie et al studied the relationship between CSF alterations and brain FDG uptake in early AD. These authors found that higher CSF AD biomarker concentrations were associated with more severe hypometabolism in several brain regions in early AD; these findings suggest that early CSF abnormalities may be associated with subtle synaptic changes

in brain regions vulnerable to AD. A longitudinal assessment of CSF and FDG-PET biomarkers is needed to determine whether these changes predict the cognitive impairment and the incipient AD.<sup>28</sup>

Landau et al, within the ADNI, studied the prognostic ability of genetic, CSF, neuroimaging, and cognitive measurements obtained in MCI patients to predict the conversion to AD. The authors found that baseline FDG-PET and episodic memory scores predict conversion to AD, whereas CSF measures and, marginally, FDG-PET predict longitudinal cognitive decline.<sup>24</sup>

Jagust et al, within the ADNI, studied the relationship between AD and MCI biomarkers (such as FDG-PET, beta-amyloid ligand PET, and CSF measures) and disease severity. The authors found that different biomarkers for AD provide complementary information. Beta-amyloid ligand PET and CSF biomarkers are in agreement but are not related to cognitive impairment. FDG-PET is modestly related to other biomarkers but is better related to cognitive impairment.<sup>29</sup>

Other recent studies compared the diagnostic value of FDG-PET and beta-amyloid ligand PET in the evaluation of patients with AD and MCI compared with normal elderly (NC). Li et al found that the pattern of regional involvement for FDG-PET and beta-amyloid ligand PET differs in patients with AD, but both techniques show high diagnostic accuracy and 94% case-by-case agreement. In the classification of NC and MCI, FDG-PET is superior to beta-amyloid ligand PET. Furthermore, the combination of these techniques improves the diagnostic accuracy for MCI.<sup>30</sup>

Lowe et al found a significant discrimination ( $P < 0.05$ ) between controls and AD, nonamnestic MCI and amnestic MCI, nonamnestic MCI and AD, and amnestic MCI and AD by beta-amyloid ligand PET. FDG-PET showed a similar group separation, but only beta-amyloid ligand PET showed a significant separation of nonamnestic MCI and amnestic MCI subjects. In conclusion, beta-amyloid ligand PET and FDG-PET have similar diagnostic accuracy in early cognitive impairment. However, beta-amyloid ligand PET better discriminates between nonamnestic MCI and amnestic MCI subjects compared with FDG-PET, suggesting that early amyloid deposition precedes cerebral metabolic disruption.<sup>31</sup>

Forsberg et al reported strong correlations between beta-amyloid ligand PET, FDG PET uptake reductions, levels of CSF biomarkers, and episodic memory scores in patients with MCI and AD. Analysis of the MCI group alone revealed significant correlations between beta-amyloid ligand

PET and CSF biomarkers and between CSF biomarkers and episodic memory scores, respectively. A strong correlation was observed in the AD group between FDG uptake reductions and episodic memory scores as well as a significant correlation between beta-amyloid ligand PET and FDG uptake reductions in some cortical regions. Regional differences over time were evident during disease progression. This study confirmed that amyloid imaging is useful for early diagnosis and evaluation of new therapeutic interventions in AD.<sup>32</sup>

Devanand et al recently evaluated FDG-PET and beta-amyloid ligand PET in patients with mild AD, MCI, and healthy controls and demonstrated that beta-amyloid ligand PET and FDG-PET provided complementary information; the authors suggested that the combination of these techniques helped to distinguish the diagnostic groups.<sup>33</sup>

With respect to the comparison of morphological and functional data, a recent meta-analysis evaluated and compared the ability of FDG-PET, single-photon emission tomography (SPECT), and structural MRI to predict conversion to AD in patients with MCI; this analysis showed that FDG-PET performs slightly better than SPECT and structural MRI in the prediction of MCI conversion to AD; similar performance was found between SPECT and MRI.<sup>34</sup>

Another recent study was performed to reveal the morphological and functional substrates of memory impairment and conversion to AD from the stage of amnestic MCI. The authors found that the discordant topography between brain atrophy (studied by MRI) and hypometabolism (studied by FDG-PET) reported in AD is already present at the amnestic MCI stage. Posterior cingulate-precuneus hypometabolism seemed to be an early sign of memory deficit, whereas hypometabolism in the temporal cortex marked the conversion to AD.<sup>35</sup>

Conversely, a more recent study of Karow et al showed no increased sensitivity of FDG-PET compared with MRI in preclinical and mild AD, suggesting that MRI findings may be a more practical clinical method for early detection of AD.<sup>36</sup>

## Conclusion

The study of cerebral glucose metabolism through FDG-PET plays a leading role in early detection of AD because the decrease of cerebral glucose metabolism largely precedes the onset of AD symptoms.

This technique demonstrated high sensitivity in early diagnosis of AD; furthermore, FDG-PET imaging may help

to identify the subjects of a high-risk population who will more probably develop AD; early stage of AD generally shows hypometabolism of medial temporal lobes and parietotemporal posterior cortices; other cerebral cortices are later involved.

The combination of FDG-PET with other biomarkers, such as genotype, cerebrospinal fluid markers, and amyloid plaque imaging, may increase the preclinical diagnostic accuracy and offer promising approaches to assess individual prognosis in AD patients.

## Disclosure

The authors report no conflicts of interest in this work.

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