PRIME

Prevention and Remediation of Insulin Multimorbidity in Europe

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D1.3.– Report on the effect of insulin signalling markers on cognitive impairment and AD biomarkers

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Abbreviations

AD	Alzheimer's Disease
DM	Diabetes Mellitus
NC	Normal Cognition
MCI	Mild Cognitive Impairment
CSF	Cerebrospinal fluid
OR	Odds Ratio
MMSE	Mini-Mental State Examination
PET	Positron Emission Tomography
p-tau	Phosphorilated tau
t-tau	Total tau

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1. Executive Summary

As part of PRIME task 4 of WP1, our goal was to explore the relationship between insulin-related markers and Alzheimer's Disease (AD). Diabetes mellitus (DM) and its related markers, such as blood glucose levels, are often associated with cognitive decline and dementia. However, it remains unclear whether DM and related markers are associated with AD biomarkers in the brain or AD-related cognitive decline.

Therefore, our aim was to explore the association of DM with the AD biomarkers amyloid, phosphorylated tau (p-tau) and total tau (t-tau), and whether DM and AD markers interact in their effect on cognitive decline. Data from nine memory clinic and aging cohorts of persons with normal cognition (NC), Mild Cognitive Impairment (MCI), and dementia were harmonised and combined to explore this research question.

Our results indicate that DM diagnosis is unrelated to AD biomarkers. Abnormal blood glucose levels were related to a lower frequency of abnormal t-tau in the total and MCI group, and a lower frequency of amyloid in the total group after adjustment for comorbidities. Moreover, AD biomarker-related cognitive decline was not influenced by presence of DM or abnormal blood glucose levels, except for an increased cognitive decline in patients with both DM and abnormal t-tau levels. After stratification, we found that the presence of AD biomarkers was mainly related to cognitive decline in non-demented persons, while DM was associated with cognitive decline in dementia patients. Together, our findings demonstrate that AD and DM are largely unrelated processes that are independently associated with cognitive decline at different clinical stages.

2. Deliverable report

Diabetes mellitus (DM) and its related markers, such as blood glucose levels, are often associated with cognitive decline and dementia. However, it remains unclear whether DM and related markers are associated with AD biomarkers in the brain or AD-related cognitive decline. Our aim, as part of WP1 Task 4, was to explore the relationship of DM and blood glucose levels with AD biomarkers and its associated cognitive decline.

To this end, we collected and harmonised the existing data of nine memory clinic and aging cohorts. We included participants (N = 3.121) with available data on DM diagnosis or blood glucose measures, any AD biomarker measure, and demographics. Blood glucose measures included HbA1c, fasted and non-fasted blood glucose levels. AD biomarkers included CSF protein measures of amyloid-beta42, p-tau and t-tau, and amyloid PET visual read. Abnormality of blood glucose was based on the ADA guidelines for diabetes, whereas the abnormality of AD biomarkers was based on data-driven or predefined local cut-offs. We used logistic regression to investigate baseline associations between DM or blood glucose levels and AD biomarkers. Mixed models with random slopes and intercepts were used to examine the effects of AD biomarkers in combination with DM or blood glucose levels on global cognitive decline. These longitudinal analyses were performed in a subgroup of the total sample that performed a Mini-Menta State Examination (MMSE) measure at baseline and at least one follow-up visit (N = 2.093). Follow-up visits ranged from 0.5 to 8 years, with a mean follow-up time of 1.83 years. All analyses were adjusted for demographics (i.e. age, gender, education years).

The total number of cases per cohort and per diagnosis group is provided in Table 1. The available measures per cohort are summarised in Table 2. The prevalence of DM increased with diagnosis, with a prevalence of 6.4% in the normal cognition group, 11.6% in the MCI group, and 19.4% in the dementia group.

Table 1. Cohort overview

Cohort	Total number	NC (%)	MCI (%)	Dementia (%)
BBACL	156	69 (44%)	61 (39%)	26 (17%)
Clemens	135	1 (1%)	100 (74%)	34 (25%)
CBAS	227	45 (20%)	144 (63%)	38 (17%)
EMIF PreclinAD	126	126 (100%)	0 (0%)	0 (0%)
EMIF 90+	98	70 (71%)	7 (7%)	21 (21%)
EPAD	1769	1280 (72%)	477 (27%)	12 (1%)
GAP	192	192 (100%)	0 (0%)	0 (0%)
IRS	57	57 (100%)	0 (0%)	0 (0%)
MBD	361	85 (24%)	187 (52%)	89 (25%)
Total	*3.121*	*1.925 (62%)*	*976 (31%)*	*220 (7%)*

Table 2. AD biomarker and diabetes measures per cohort

Cohort	CSF biomarkers	Amyloid PET	Diabetes diagnosis	Blood glucose	Main glucose measure
BBACL	x	-	x	x	Non-fasted blood glucose
Clemens	x	-	x	x	HbA1c
CBAS	x	x	x	x	HbA1c
EMIF PreclinAD	x	-	x	x	HbA1c
EMIF 90+	-	x	x	x	HbA1c
EPAD	x	-	x	-	-
GAP	x	-	x	x	HbA1c
IRS	x	-	x	x	HbA1c
MBD	x	-	x	-	-

The association of DM diagnosis and blood glucose levels with AD biomarkers

DM diagnosis and AD biomarkers

Logistic regression analyses indicate that in the total group as well as in separate diagnostic groups, no association was found between DM diagnosis and AD biomarkers. Adjustment for presence of relevant comorbidities (hypertension, hypercholesterolemia and obesity) did not change our findings. In addition, results were similar for persons with and without diabetic medication in the total group and diagnostic subgroups.

Blood glucose levels and AD biomarkers

In the total group, we found an association between abnormal blood glucose levels and t-tau, with lower odds of t-tau abnormality in persons with abnormal blood glucose levels (OR = 0.42, *p* = 0.02). This effect was driven by individuals with MCI (OR 0.29, *p* = 0.02). In the total group only, a trend was found for an association between abnormal blood glucose levels and less amyloid abnormality (OR = 0.56, *p* = 0.06). After adjustment for obesity, hypertension, hypercholesterolemia, this association became significant (OR = 0.43, *p* = 0.04). Results for p-tau and t-tau remained similar after comorbidity adjustment.

The association of DM diagnosis and blood glucose levels with AD biomarkers in their effect on cognitive decline

DM diagnosis, AD biomarkers and cognitive decline

In the total group, at baseline, the presence of DM diagnosis ($p < 0.05$) or any abnormal AD biomarker (amyloid, p-tau and t-tau all $p < 0.001$) was related to worse global cognition measured by the Mini-Mental State Examination (MMSE). When stratifying for diagnosis, a baseline association with cognitive performance was only shown for amyloid and p-tau.

In the total group, mixed model slope analyses showed that having both DM and abnormal t-tau levels was associated with an accelerated decline in global cognition, compared to having either DM diagnosis or abnormal t-tau separately ($p = 0.01$). However, these findings were not confirmed in the separate diagnostic groups and also became non-significant in the total group when adjusting for hypertension, obesity and hypercholesterolemia. The associations of amyloid or p-tau with global cognitive decline were not influenced by the presence of DM. However, we found significant independent effects of DM diagnosis ($p < 0.01$) and AD biomarkers amyloid and p-tau (both $p < 0.001$) on global cognitive decline for the total group. When stratifying for each diagnostic group, we found that abnormal AD biomarkers but not DM diagnosis were associated with cognitive decline in the NC and MCI groups, while only DM diagnosis was associated with cognitive decline in the dementia group. Use of diabetic medication did not influence these results.

Blood glucose levels, AD biomarkers and cognitive decline

In the total group, baseline analyses showed that amyloid ($p < 0.01$) and t-tau ($p < 0.05$) were related to lower global cognitive scores, while no association was found for p-tau and abnormal blood glucose with cognition. When stratifying for diagnosis, these baseline associations were not shown.

Furthermore, no interaction of blood glucose levels with any of the AD biomarkers was found in the effect on global cognitive decline in the total group. Abnormal AD biomarkers were independently related to cognitive decline (all $p < 0.05$), but abnormal blood glucose was not significantly related to cognitive decline. When stratifying for diagnostic group, the effect of AD biomarkers on cognitive decline was most pronounced in the NC group, and in none of the groups an effect of abnormal blood glucose on cognitive decline was shown. Adjusting for hypertension, obesity and hypercholesterolemia again did not change the results.

3. Conclusion

Our results indicate that DM diagnosis is unrelated to AD biomarkers, and that abnormal blood glucose levels were shown to be related to less t-tau abnormality. Overall, AD biomarker related cognitive decline was not influenced by the presence of DM or abnormal blood glucose levels. Still, an accelerated cognitive decline was shown in persons with both DM and t-tau. As t-tau is a non-specific AD biomarker, its interaction with DM on cognitive decline may reflect non-AD processes. Additionally, presence of AD biomarkers was mainly related to cognitive decline in non-demented persons, while DM was associated with cognitive decline in demented persons. Together, these findings demonstrate that AD and DM are largely independent processes that are associated with cognitive decline at different clinical stages.

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