study participants was 3.7 ± 3.3 μU/mL, a value consistent with mean values ranging from 4.6 to 10.5 μU/mL that other authors have found.[8,9] HOMA%B of 36%, which is indicative of poor pancreatic function, was measured in the current study and has been described previously in elderly adults.[10] The HOMA-IR level of 0.49 indicates that there was no insulin resistance in the studied population, but subjects with HOMA-IR values less than 1 had lower insulin and HOMA%B levels than did subjects with HOMA-IR values greater than 1. This finding explains why, when insulin resistance is present, the pancreas responds by increasing insulin production, and the elderly adults without DM in this study had lower insulin levels than those reported in individuals with insulin resistance.

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LATIN AMERICAN EXPERIENCE WITH ALZHEIMER'S DISEASE CEREBROSPINAL FLUID BIOMARKERS

To the Editor: A promising advance to complement clinical diagnosis at an early stage of Alzheimer's disease (AD) has been the measurement of biomarkers in cerebrospinal fluid (CSF).[1] A decrease in CSF amyloid beta 42 ($A\beta_{42}$) is a marker of AD pathology caused by the accumulation of amyloid-β in brain parenchyma,[2] whereas increased total tau (t-tau) and hyperphosphorylated tau (p-tau) reflect neuronal degeneration and tangle pathology.[3] AD is characterized by episodic memory loss, cognitive impairment, behavioral disorders, and finally, dementia.[4] Individuals with mild cognitive impairment (MCI) have memory deficits but, in contrast to those with AD, are functionally intact and at higher risk of converting to AD than those without MCI.[4] It is difficult to predict clinically which individuals with MCI possess AD brain pathology and will therefore progress to clinical AD.

The aim of the present study was to evaluate CSF AD biomarkers in their capacity to discriminate AD from frontotemporal dementia (FTD) and to predict progression from MCI to AD. Data are presented on the first experience to the knowledge of the authors in Latin America of the use of CSF biomarkers in a clinical follow–up study.

Individuals with MCI (n = 10), probable AD (n = 7), and FTD (n = 3) were recruited at the memory disorder clinic of an academic center in Argentina between 2005 and 2007. A trained neurologist performed a clinical evaluation, brain imaging, laboratory tests, and physical examination to exclude individuals with reversible causes of dementia. The Boston Naming Test,[5] Rey Auditory and Visual Design Learning Verbal Test (RAVLT),[6] Signoret's logical memory,[7] Mini-Mental State Examination (MMSE),[8] and Clinical Dementia Rating (CDR)[9] were performed. Mean age was 69 for the groups with AD and MCI, whereas the group with FTD had a mean age of 60. Mean MMSE score was 28 for the group with MCI, 20

Table 1. Results

	Mild Cognitive Impairment			AD, n = 7	Frontotemporal Dementia, n = 3
	Progressed to AD, n = 5	Did Not Progress to AD, n = 5			
Marker	Mean ± SD		*P*-Value	Mean ± SD	
Amyloid-beta 42, pg/mL	355 ± 88	800 ± 345	.02	443.6 ± 65.8	855 ± 270
Total tau, pg/mL	304 ± 242	189.6 ± 113	.21	358.6 ± 218	108.3 ± 45
Hyperphosphorylated tau, pg/mL	66.2 ± 52.1	35.8 ± 18.5	.30	42.8	18.3
Amyloid- beta 42/hyperphosphorylated tau	12.7 ± 12.8	30.6 ± 22.1	.11	11.8 ± 5.7	48.5 ± 6.9
Cerebrospinal fluid biomarkers for AD profile	0.68 ± 0.41	1.9 ± 1.17	.02	0.75 ± 0.32	2.3 ± 0.50

AD = Alzheimer's disease; SD = standard deviation.

points for the group with AD, and 22 for the group with FTD. CDR was 0.5 for the group with MCI and 1 for the other groups. RAVLT mean results were 31 points for the group with MCI, 20 for the group with AD, and 15 for the group with FTD.

$A\beta_{42}$, t-tau, and p-tau were quantified in CSF using an enzyme-linked immunosorbent assay. Ratios of Aβ-42 to p-tau and CSF AD profile (Aβ42/(240 + [1.18 × t-tau]))[10] were calculated. (A CSF ratio <1.3 was considered suggestive of AD pathology.) The Mann-Whitney one-tailed test was used to determine the difference between groups.

Mean clinical follow-up was 4.7 years (range 1–8 years). As expected, functional status and overall cognitive tests deteriorated over time for individuals with AD and FTD. CDR was 2 for the groups with AD and FTD. For the group with MCI, participants were classified based on clinical and cognitive evolution into a group that progressed to AD (n = 5), with a mean MMSE score of 24 and CDR of 1, and a group that did not (n = 5), with MMSE and CDR scores that did not change from baseline.

The mean value of biomarkers and the ratios were not significantly different in the three main groups (AD, MCI, FTD) because of the high dispersion observed in the MCI group. There were significant differences between the groups with AD and FTD in the biomarkers and ratios (Aβ42, $P = .01$; t-tau, $P = .04$; p-tau, $P = .03$).

When the group with MCI was analyzed and divided according to clinical progression to AD over time, the mean value of $A\beta_{42}$ was 355 pg/mL in those with progression, versus 800 pg/mL in those without AD progression, which was significantly different (Table 1). Regarding AD profile, a statistically significant difference was found in this subgroup analysis.

A receiver operating characteristic curve analysis for each biomarker was performed between the groups with and without AD. The cutoff values for each biomarker were Aβ42, 532.5 pg/mL (sensitivity 100%, specificity 87.5%); t-tau 100 pg/mL (sensitivity 84.5%, specificity 87.5%); p-tau, 26.5 (sensitivity 69.2%, specificity 87.5%); Aβ42/p-tau, 20.5 (sensitivity 92.3%, specificity 87.5%); AD CSF profile 1.350 (sensitivity 100%, specificity 100%).

Collectively, these results support the role of CSF biomarkers in the differential diagnosis of dementia and in the prediction of progression from MCI to AD. The conclusions of this study should be taken cautiously because of the small sample size and lack of confirmatory pathological examination, but active patient recruitment is underway to strengthen these observations. Overall, this first AD biomarker study in Latin America supports that combined analysis of all three core AD biomarkers represent a powerful tool in clinical setting.

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ALZHEIMER'S DISEASE CORRELATES WITH GREATER RISK OF HIP FRACTURE IN OLDER PEOPLE: A COHORT IN TAIWAN

To the Editor: Alzheimer's disease and hip fracture are two common disorders in older people, and both result in severe socioeconomic burden. Growing evidence has demonstrated that individuals with Alzheimer's disease have 2.1 to 3.2 times greater risk of hip fracture.[1–3] Little evidence is available about the relationship between Alzheimer's disease and risk of hip fracture in older people in Taiwan, so this cohort study was conducted to explore this question by analyzing the Taiwan National Health Insurance program database. Information about the program can found in previous studies.[4,5] In this cohort study, the diagnosis of Alzheimer's disease and hip fracture was based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes. Nine hundred thirty-six individuals aged 65 and older with newly diagnosed Alzheimer's disease (ICD-9 code 331.0) were chosen as the Alzheimer's disease group (429 men, 507 women, mean age 78.2 ± 6.8, mean follow-up 3.5 ± 2.9 years) and 3,744 without Alzheimer's disease as the control cooperator group (1,716 men, 2,028 women, mean age 77.1 ± 7.1, mean follow-up 4.4 ± 3.2 years) from 2000 to 2010. The index date was defined as the date of diagnosis of Alzheimer's disease. Both groups were matched according to sex, age, and index year. Both groups were followed up to determine the incidence of hip fracture (ICD-9 code 820) until a subject received a diagnosis of hip fracture or until December 31, 2010. Subjects with hip fracture, other dementia (ICD-9 codes 290.0, 290.1, 290.2, 290.3, 290.4, and 294.1), or mental retardation (ICD-9 codes 317–319) diagnosed before index date were excluded.

The Alzheimer's disease group had a significantly higher incidence of hip fracture than the non-Alzheimer's disease group (27.8 vs 11.7 per 1,000 person-years, 95% confidence interval (CI) = 2.02–2.80). The incidence rates, as stratified according to sex, age, and follow-up period, were all significantly higher in the Alzheimer's disease group. Women with Alzheimer's disease had a higher incidence of hip fracture (30.8 per 1,000 person-years) than men (24.0 per 1,000 person-years). Subjects with Alzheimer's disease aged 75 to 84 had the highest incidence of all subgroups (incidence rate 37.8 per 1,000 person-years). The stratified analysis according to follow-up period showed a higher risk of hip fracture within 2 years of Alzheimer's disease diagnosis (incidence rate ratio = 3.30, 95% CI = 2.78–3.92). Overall, 59.3% (54/91) of hip fracture cases in the group with Alzheimer's disease occurred within 2 years after index date, as opposed to 36.8% (70/190) in the group without Alzheimer's disease (Table 1).

Epidemiological studies have reported that Alzheimer's disease correlates with greater risk of hip fracture in western countries.[1–3] The present study found that the incidence rate ratio of hip fracture was 2.38 in individuals with Alzheimer's disease compared with the group without

Table 1. Incidence Density of Hip Fracture in Participants with and without Alzheimer's Disease

	No Alzheimer's Disease				Alzheimer's Disease				
Factor	N	Cases, n	Person-Years	Incidence Rate[a]	N	Cases, n	Person-Years	Incidence Rate[a]	Incidence Rate Ratio (95% Confidence Interval)[b]
All	3,744	190	16,292	11.7	936	91	3,276	27.8	2.38 (2.02–2.80)
Sex									
Male	1,716	69	7,655	9.01	429	35	1,459	24.0	2.66 (2.08–3.42)
Female	2,028	121	8,638	14.0	507	56	1,818	30.8	2.20 (1.77–2.73)
Age									
65–74	1,288	43	6,863	6.27	322	20	1,396	14.3	2.29 (1.72–3.04)
75–84	2,456	147	9,429	15.6	614	71	1,881	37.8	2.42 (1.99–2.94)
Years of follow-up									
≤2	1,097	70	6,382	11.0	362	54	1,491	36.2	3.30 (2.78–3.92)
>2	2,647	120	9,910	12.1	574	37	1,785	20.7	1.71 (1.38–2.13)

[a]Per 1,000 person-years.
[b]Alzheimer's disease versus no Alzheimer's disease.