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Brain-Derived Neurotrophic Factor Plasma Levels: Relationship With Dementia and Diabetes in the Elderly Population

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The mechanisms linking diabetes and cognitive impairment/dementia, two common conditions of elderly people, are not completely known. Brain-derived neurotrophic factor (BDNF) has antidiabetic properties, and reduced circulating BDNF was associated with dementia. We investigated the relationship between plasma BDNF levels, dementia, and diabetes in a sample of 164 community-dwelling elderly individuals, including 50 participants with vascular dementia, 44 with late onset Alzheimer's disease, 23 with cerebrovascular disease not dementia, and 47 controls (C). Presence/absence of diabetes was registered; new diagnoses of diabetes were made by the American Diabetes Association criteria. BDNF plasma levels were measured by ELISA. Both diagnosis of dementia and diabetes were associated with lower BDNF plasma values compared with the respective controls; moreover, dementia and diabetes correlated with BDNF plasma levels, independent of possible confounders. A progressive reductions of BDNF plasma levels from C (383.9±204.6 pg/mL), to cerebrovascular disease not dementia (377.1 ± 130.2), to vascular dementia (313.3 ± 114.8), to late onset Alzheimer's disease (264.7 ± 147.7) was observed, (late onset Alzheimer's disease vs C, *p*: .03; late onset Alzheimer's disease vs cerebrovascular disease not dementia, *p*: .002). Demented patients affected by diabetes had the lowest BDNF mean levels (264.9 pg/mL) among individuals enrolled in this sample, suggesting the existence of a "synergistic" effect of dementia and diabetes on BDNF levels.

Key Words: BDNF—Dementia—Diabetes—Alzheimer's disease—Elderly individuals.

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LIFE expectancy has increased all over the world in the last century (1) leading to an increase in the prevalence of several chronic diseases. Among these, dementia is one of the most common because its overall incidence is about 2%–4% per year in those older than 75 years, raising to 18% in those older than 90 years (2,3). Research is focused on understanding the mechanisms underlying the pathogenesis of dementia in order to counteract the possible transition from mild cognitive impairment to dementia (4). A particular interest has been addressed to modifiable conditions associated with the pathogenesis of dementia. In humans, both type 1 and type 2 diabetes (T2DM) were associated with impaired cognitive functions including learning memory, attention, and processing speed (5,6). Population-based studies have shown that hyperglycemia and T2DM are associated with an increase in the incidence of cognitive impairment/dementia (7,8), whereas others suggest that both hyperinsulinemia and T2DM give a twofold increase in risk of Alzheimer's disease (AD) (9,10). A longer duration of T2DM has been associated with a major risk of cognitive decline (11); moreover, a recent cohort study showed that higher glucose levels may be a risk factor for dementia, even among nondiabetic individuals (12). These findings are in line with the observation that T2DM is associated with structural brain abnormalities, the hippocampus being the most involved area (13). Several mechanisms have been proposed to explain the association between diabetes and dementia. It was first hypothesized that hypoglycemic state might be responsible of dementia (14). Also, cerebrovascular diseases and related risk factors among diabetic patients might be relevant, given the role they play both in vascular dementia (VaD) and late onset Alzheimer's disease (LOAD) (15–17). Indeed, the combination of T2DM and hypertension gives a higher risk for dementia compared with the sum of the single risk factors (18,19). However, several nonvascular mechanisms have been also considered (20), including formation of advanced glycosylation end products (21), brain inflammation (22), alterations of hypothalamus–pituitary adrenal axis with cortisol increase (23), polyol pathway or protein kinase C activation (24), glucose shunting to the exosamine pathway, oxidative stress (25), and disturbed neuronal insulin signaling promoting cerebral amyloidosis (26,27). Interestingly, a high density of insulin receptors

was found in brains from LOAD patients, as possible compensatory mechanism for reduced insulin functionality) (28); moreover, hyperinsulinemia was demonstrated to reduce degradation and clearance of cerebral Aβ (29).

Brain-derived neurotropic factor (BDNF) is a growth factor member of the neurotropin family; its mature isoform binds specifically to the tropomiosine receptor kinase B (Trk B), a tyrosine kinase receptor, whereas the precursor pro-BDNF binds the pan-neurotropin receptor p75NTR, both mediating different neurotropic signaling (30,31). During development and following insults, BDNF plays a critical role in cell differentiation, migration, neuronal survival, dendritic arborization, synaptogenesis, and synaptic plasticity (20). BDNF is also important for learning and memory processes by inducing long-term potentiation in hippocampus with structural changes in synapses (32,33). Decreased BDNF concentrations have been found in brains from mild cognitive impairment or LOAD patients. A positive correlation between brain BDNF concentration and cognitive performance was described (34,35), whereas decreased BDNF production has been proposed as one possible pathogenetic factor for LOAD and major depression (36). Two recent studies investigated serum BDNF levels in patients with different neurodegenerative diseases. Whoolley and colleagues (37) found no differences between LOAD, frontotemporal dementia, mild cognitive impairment, and controls, whereas Ventriglia and colleagues (38) reported lower BDNF values in patients with LOAD, VaD, frontotemporal dementia, and Lewy body dementia. Interestingly, plasma BDNF levels are decreased in T2DM and have been inversely correlated with plasma glucose and insulin resistance assessed by homeostatic model assessment. Moreover, plasma BDNF output from human brain is abrogated by hyperglycemia, but is not regulated by hyperinsulinemia (39). In diabetic mice models, BDNF infusion reduces food intake, lowers blood glucose levels, and reduces insulin resistance enhancing insulin peripheral action (40). Moreover, BDNF seems to protect pancreas islets (41), increases insulin, and decreases glucagon pancreatic content (42). Zhen and colleagues (43) found both lower serum BDNF concentrations and cognitive functions in diabetic patients versus controls; furthermore, a positive relationship between serum BDNF and delayed memory emerged in diabetic patients, suggesting a role of BDNF in cognitive deficit associated with T2DM.

Although T2DM and dementia have been consistently associated in the elderly (7–10), it is not clear whether their correlation with plasma BDNF might be independent or, alternatively, T2DM might mediate the relationship between low BDNF levels and dementia. In order to investigate the possible interplay between BDNF, dementia, and T2DM, we evaluated plasma BDNF levels, according to the presence/absence of T2DM, in a sample of elderly individuals including cognitively normal participants, individuals with cerebrovascular disease but not dementia, and patients affected by LOAD or VaD.

Patients and Methods

Participants

During the period 2008–2010, 164 consecutive participants (62.1% women; mean age: 75 ± 10 years) referring to the Day Service for the study of cognitive decline (Institute of Internal Medicine, Gerontology, and Clinical Nutrition; Geriatrics Unit, S. Anna University-Hospital, Ferrara, Italy) were enrolled. Personal data and medical history were collected by using a structured interview to patients and caregivers. All participants (and/or their caregiver if demented) were informed about the research project during the first visit and gave their written consent in order to participate to the study. The study was approved by the local ethic committee (S. Anna University Hospital, Ferrara, Italy) and was conducted in accordance with the Helsinki Declaration as revised in 1989. The participants were divided into four groups based on cognitive status:

1. Forty-four patients with LOAD (mean age 78 ± 8 years; 33 women) by the NINCDS–ADRDA criteria (44). Only patients with "probable" LOAD were included; patients with "possible" LOAD or with LOAD associated with significant cerebrovascular disease on CT scan were excluded in order to increase specificity. The Global Deterioration scale ranged from stage 3 to stage 5.
2. Fifty patients with VaD (mean age: 79 ± 7 years; 24 women) by the NINDS-AIREN criteria (45). Only patients with "probable" VaD were enrolled. The Global Deterioration scale ranged from stage 4 to stage 6.
3. Twenty-three patients with cerebrovascular disease documented by CT scan and previously affected by transient ischemic attack and/or ischemic stroke, but without evidence of dementia (cerebrovascular disease not dementia [CDND]; mean age 72 ± 11 years; 11 women).
4. Forty-seven normal individuals without evidence of cognitive impairment (controls: C; mean age 69 ± 10 years, 34 women). All these participants were free-living, healthy (no important comorbidity was found), and independent on basic activities of daily living (BADLs; median Barthel Index score: 98/100). The median Mini-Mental State Examination (MMSE) score was 29/30.

Exclusion criteria were participants affected by other types of degenerative dementias (not LOAD), secondary nonvascular dementias, severe liver or kidney disease, severe congestive heart failure (New York Heart Association class III–IV), severe chronic obstructive pulmonary disease, cancer, and evidence of acute illnesses at the time of clinical observation. Clinical chemistry analyses were performed in order to exclude secondary cognitive impairment. No cerebrospinal fluid biomarkers were available for all the patients (LOAD and VaD) enrolled into this study. All patients underwent a general and neurological examination. The diagnosis of dementia was made by trained geriatricians. For neuropsychological assessment, all patients were given a battery of

tests evaluating: verbal memory (Rey's 15-word test), working memory (digit span forward–backward), prose memory (Babcock test), space/time orientation (items from MMSE), attention (Tolouse–Pieron test), constructional and visuospatial functions (clock-drawing test), abstract reasoning (Raven progressive matrices, similarities test), language and comprehension (Token test), verbal fluency (letters and categories), executive functions (Trial-making test A and B), and routine clinical tests for the evaluation of agnosia, apraxia, and afasia. Depressive symptoms were evaluated by the Geriatric Depression scale (GDS). Functional dependence was evaluated by Barthel's Index for BADL, and Lawton–Brody modified index for instrumental activities of daily living.

Participants were further classified according to presence/absence of T2DM. All participants with known history of diabetes or current hypoglycaemic therapy were defined as diabetic patients. Criteria of the American Diabetes Association were used for new diagnosis: fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (46). The glycated hemoglobin (HbA1C) ≥ 6.5% was not used as diabetes diagnostic criteria because it was not available in all participants. Diabetic participants were 37 (mean age 76 ± 9 years), 122 had no diabetes (mean age 74 ± 10), and 5 individuals were not classified with certainty.

The criteria for the diagnosis of hypertension were (a) history of known hypertension or antihypertensive therapy at visit time and (b) blood pressure > 140/90 mmHg in three or more measurements. Eighty patients were affected by hypertension. No patients were taking a statin at the time of enrolment into the study.

Brain CT Scan

All patients (LOAD, VaD, CDND) underwent a brain CT. The instrument used was a third generation SIEMENS SOMATON HQ. The slice thickness was 10 mm. Radiograms were evaluated by two trained radiologists not informed about the patient. The CT scan information supported the diagnosis and excluded other brain pathologies.

Sample Processing and Analytical Methods

Blood samples were drawn from a forearm vein in the morning after overnight fasting. All samples were kept chilled in an ice bath until centrifugation at 3000 rpm for 15 min at 4°C. The separated plasma was stored at −80°C until time of assay. All samples were run in duplicate for the same assay. Glucose concentrations were measured with the glucose oxidase technique using an auto analyzer (ILAB600, Instrumentation Laboratories S.p.A., Milano, Italy). The minimum detectable concentrations was 0.11 mmol/L (2 mg/mL). Intra- and interassay variation coefficients are 3.0% and 3.5%, respectively. Serum total cholesterol and triglycerides levels were assayed by the Trinder method. Serum HDL-C levels were measured after precipitation of the Apo B-containing lipoproteins by adding phosphotungstic acid and magnesium ions to the sample (47). LDL cholesterol (LDL-C) levels were calculated by the Friedewald's formula (LDL-C = total cholesterol − triglycerides/5 − HDL-C) (48).

Immunoassay Systems (Promega) specific for BDNF were performed according to the manufacturer's instructions. The minimum detectable concentrations is 15.6 pg/mL. Intra- and interassay variation coefficients are 3.0% and 5.0%, respectively.

Statistical Analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range), whereas categorical variables were expressed as the number/percentage. Mean values were compared by ANOVA with Fisher's least significant difference (LSD) post hoc test for multiple comparison, whereas medians were compared by nonparametric tests (Kruskal–Wallis). Correlations between continuous variables were tested by Pearson's correlation or Spearman's test when necessary. Prevalence was compared by the χ^2 test.

Multivariate linear regression analysis was used to test the independent association between BDNF serum levels and other variables of interest; diagnosis of dementia or diabetes were entered as dichotomous variables (absent: 0; present: 1). All statistical tests were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL).

Results

In Table 1 are reported the principal characteristics of the four groups of individuals enrolled into the study. Individuals with dementia were older compared with those without dementia. The prevalence of female gender was higher in LOAD and controls compared with CDND and VaD. A trend toward higher GDS score was observed in demented compared with nondemented individuals (not significant). The prevalence of diabetes was higher in participants with cerebrovascular disease (both VaD and CDND) and in LOAD compared with controls, whereas no differences emerged as regards blood glucose levels. The prevalence of hypertension was also significantly higher in participants with cerebrovascular disease (VaD and CDND) compared with the other two groups.

Plasma BDNF levels were significantly lower in diabetic patients (276.4 ± 129.2 pg/mL) compared with nondiabetic patients (341.7 ± 157.6; ANOVA, LSD post hoc test: *p*: .02), as well as in demented (LOAD + VaD: 290.5 ± 132.7) compared with nondemented participants (CDND + C: 381.7 ± 182.6 pg/mL; ANOVA, LSD post hoc test *p*: .001).

As shown in Figure 1, the mean levels of BDNF progressively decreased from C (383.9 ± 204.6 pg/mL), to CDND (377.1 ± 130.2 pg/mL), to VaD (313.3 ± 114.8 pg/mL), to LOAD (264.7 ± 147.7 pg/mL). LOAD displayed significantly lower BDNF compared with C and CDND (ANOVA,

Table 1. Principal Characteristics of Elderly Patients With Cerebrovascular Disease Not Dementia (CDND), Vascular Dementia (VaD), Late Onset Alzheimer's Disease (LOAD), and Controls (means ± standard deviation or median–interquartile range)

	Dementia (n = 94)		No Dementia (n = 70)		
	VaD (n = 50)	LOAD (n = 44)	CDND (n = 23)	Controls (n = 47)	All (n = 164)
Age (y)	79 ± 7	79 ± 8	72 ± 11**.§	67 ± 10***.§§	75 ± 10
Female gender (n/%)^	24/48.0	33/75.0	11/47.8	34/72.3	102/62.2
BADLs (/100)	6/100 (1–16)	17/100 (11–19)	75/100***.§§ (48–100)	100/100***.§§ (96–100)	18/100 (6–96)
MMSE score (/30)	17.5 (11.5–20)	17 (12.5–19)	30***.§§ (27–30)	30***.§§ (30–30)	23 (20–28)
GDS score (/15)+	7 (3.5–13.5)	9 (4–11.5)	5 (4–9)	5 (1.5–6.5)	6 (4–11)
Diabetes (n/%)^^^	17/34.0	10/22.7	8/34.8	2/4.3	37/22.6
Glucose (mg/dL)	102 (97–109)	94 (89–120)	98 (88–118)	100 (93–120)	98 (90–119)
Hypertension (n/%)^^	33/66.0	16/36.4	13/56.5	18/38.3	80/48.8
SBP (mmHg)	141 ± 18	136 ± 21	143 ± 17	130 ± 16#	137 ± 18
DBP (mmHg)	81 ± 7	79 ± 10	81 ± 7	81 ± 8	81 ± 8
Total cholesterol (mg/dL)	199 ± 53	221 ± 53	209 ± 55	221 ± 32	213 ± 49
LDL cholesterol (mg/dL)	117 ± 36	138 ± 42	134 ± 45	145 ± 31*	134 ± 38
HDL cholesterol (mg/dL)	44 ± 15	53 ± 13	43 ± 12	54 ± 13*	50 ± 14
Triglycerides (mg/dL)	119 (117–172)	103 (88–120)	124 (109–220)	106 (76–108)	108 (99–172)
Hematocrit (%)	40 ± 8	39 ± 5	38 ± 4	40 ± 4	39 ± 7
White blood cells (/mm^3)	6817 ± 2188	6689 ± 2234	6633 ± 1438	6048 ± 1627	6635 ± 2023

Notes: BADLs = basis aactivities of daily living; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression scale; SBP = systolic blood pressure; DBP = diastolic blood pressure.

*vs VaD $p < .05$; **vs VaD $p < .01$; ***vs VaD $p < .001$.

§vs LOAD $p < .05$; §§vs LOAD $p < .001$.

#vs CDND $p < .05$.

^Chi square test $p < .01$; ^^Chi square test $p = .05$; ^^^Chi square test $p < .005$.

+.06 Kruskal–Wallis.

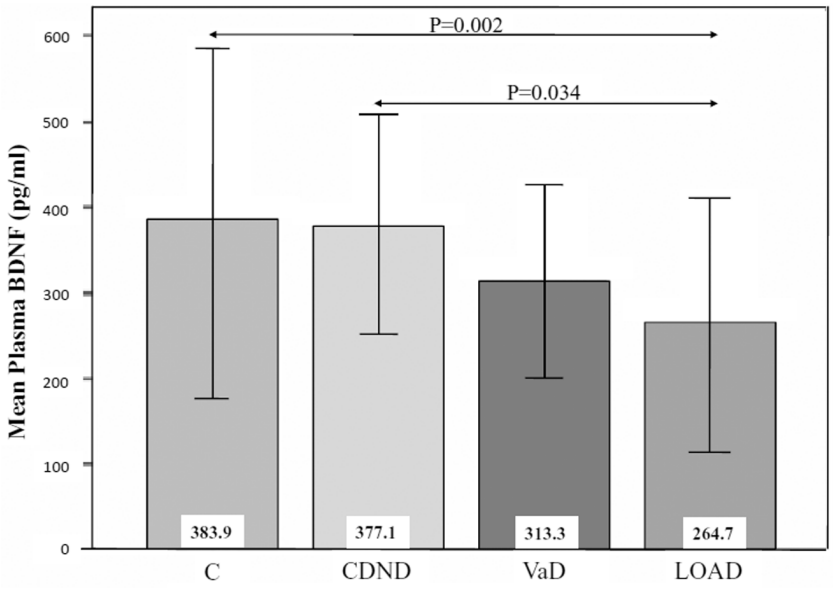

Figure 1. Brain-derived neurotrophic factor plasma levels in healthy controls, participants with cerebrovascular disease not dementia, vascular dementia, and late onset Alzheimer's disease (ANOVA, least significant difference post hoc test).

LSD post hoc test: p: .002 and p: .03, respectively). A similar pattern was observed when the sample was divided according to the presence/absence of T2DM. Among nondiabetic patients, LOAD had lower BDNF compared with C and CDND (ANOVA, LSD post hoc test: p: .05 and p: .03) (C: 380.1 ± 188.6 pg/mL; CDND: 421.7 ± 120.3 pg/mL; VaD: 311.5 ± 123.5 pg/mL; LOAD: 290.5 ± 138.5 pg/mL). Among diabetic patients, LOAD had lower BDNF compared with controls and VaD (ANOVA, LSD post hoc test p: .04 and p: .032, respectively; C: 364.2 ± 105.4; CDND: 293.3 ± 109.7; VaD: 316.7 ± 98.9; LOAD: 176.8 ± 150.8 pg/mL).

Finally, the sample was divided into four groups according to the absence/presence of diabetes and dementia (Figure 2): group 1: no diabetes nor dementia (n: 60); group

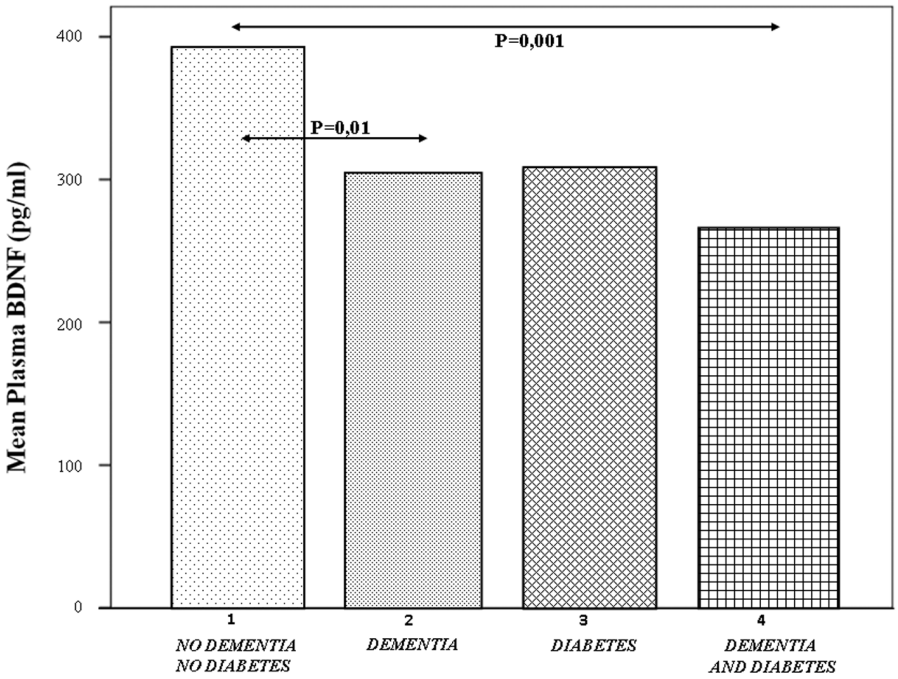

Figure 2. Brain-derived neurotrophic factor plasma levels in 164 older individuals according to absence/presence of diabetes mellitus and dementia (ANOVA, least significant difference post hoc test).

2: only dementia (*n*: 94); group 3: only diabetes (*n*: 10); and group 4: both diabetes and dementia (*n*: 27). Compared with group 1 (391 ± 171 pg/mL), plasma BDNF was significantly lower in group 4 (264.9 ± 136 pg/mL) and group 2 (301 ± 130.7 pg/mL; ANOVA, LSD post hoc test *p*: .001 and *p*: .001, respectively), whereas the difference was not significant for group 3 (307 ± 107 pg/mL), probably due to the small number of individuals with diabetes only. No significant differences in BDNF levels emerged between men and women, nor between nonhypertensive and hypertensive individuals (data not shown).

We also evaluated the principal correlate of plasma BDNF levels. At univariate analysis, BDNF was negatively correlated with age and systolic blood pressure, and positively correlated with MMSE, GDS, total cholesterol, and LDL-C levels (Table 2). By means of multivariate linear regression analysis, we found that dementia (β coefficient: −241.8; *p*: .006) and diabetes (β coefficient:-100.1: p:0.05) significantly predicted BDNF levels, independent of possible confounders including age, MMSE, GDS, total cholesterol, and systolic blood pressure (R^2 for adjusted model: .41; *p*: .001; Table 3).

Table 2. Correlations Between Brain-Derived Neurotrophic Factor Plasma Levels and Other Variables in 164 Older Individuals

	Correlation Coefficient	*p*
Age (y)	−0.22	.004
MMSE score (/30)	0.33	.001
GDS score (/15)	0.31	.008
Glucose (mg/dL)	−0.07	.38
SBP (mmHg)	−0.19	.02
DBP (mmHg)	−0.09	.25
Total cholesterol (mg/dL)	0.23	.004
HDL cholesterol (mg/dL)	0.04	.61
LDL cholesterol (mg/dL)	0.19	.04
Triglycerides (mg/dL)	0.09	.22

Discussion

We found that in a sample of elderly individuals, both dementia and diabetes were independently associated with lower BDNF plasma levels. Moreover, the effect of dementia and diabetes on BDNF was "addictive" because BDNF levels were significantly lower in patients affected by dementia and diabetes, compared with both diabetic controls and nondiabetic, demented individuals.

BDNF and Diabetes

Besides our study, a negative correlation between BDNF levels and diabetes has been consistently reported, but the direction of the association is unclear. The cerebral output of BDNF is inhibited by hyperglycemia, and this might explain the association between low BDNF levels and insulin resistance (25). On the other hand, BDNF decrease might contribute to the pathogenesis of diabetes because it has been shown, in animal and in vitro studies, that BDNF might have

Table 3. Multivariate Linear Regression Analysis for Brain-Derived Neurotrophic Factor Plasma Levels in 164 Older Individuals (R^2 for the adjusted model: 0.41; p: .001)

Model	Unstandardized Coefficients		p
	Beta	Standard Error	
Constant	549.2	261.1	**.04**
Age	−3.06	2.94	.30
Dementia	−241.8	81.8	**.007**
Diabetes	−100.1	50.7	**.03**
MMSE score	9.3	7.7	.23
GDS score	12.4	3.9	**.003**
Total cholesterol (mg/dL)	0.7	0.3	.07
SBP (mmHg)	−0.6	1.4	.65

Notes: Dementia and diabetes were entered as categorical variables (absent: 0; present: 1). Values in bold underline the variables whose p value reached statistical significance.

antidiabetic effects (41,42). A recent study suggests that, in animal models, the brain intraventricular administration of BDNF attenuates diabetic hyperglycemia via an insulin-independent mechanism involving inhibition of glucagon secretion and decrease in hepatic glucose production (49). In this light, a sort of "positive feedback relationship" might be hypothesized between BDNF and diabetes. As regards the prevalence of T2DM in our sample (22.6%), it is in line with the results of a Greek study estimating a prevalence of diabetes among elderly individuals about 22% (50), but it is much higher than that calculated by a British study (7%) among people older than 75 years (51). The finding of a higher prevalence of T2DM in demented patients (28%) compared with controls (4.3%) indirectly support the concept that diabetes might increase the risk of developing dementia through multiple mechanisms (7,8,11).

BDNF and Dementia

On the whole, demented patients had lower BDNF levels compared with nondemented patients; moreover, the reduction of BDNF levels showed a sort of "progressive pattern" decreasing from controls, to CDND, to VaD, to LOAD patients. A complicated relationship has been reported in Literature between BDNF levels and dementia. O'Bryant and colleagues found that among ApoE4 negative AD patients, increased BDNF levels were associated with poorer performances at visual–verbal memory tests, and hypothesized an upregulation of BDNF as possible compensatory mechanism (52). Leyhe and colleagues found reduced BDNF levels in AD patients compared with controls and demonstrated a significant increase in BDNF concentration after treatment with Donepezil (53). Interestingly, Laske and colleagues (54) found that BDNF was increased in early AD compared with both late AD patients and controls, leading to the hypothesis of an initial increase of plasma BDNF (possible compensatory mechanism), followed by a later BDNF decrease with lack of trophic support. This hypothesis is in line with in vitro studies in which BDNF protects neuronal cultures against cytotoxic effects of beta-amyloid (55), whereas sublethal doses of beta-amyloid downregulate BDNF expression in cortical neurons (56) but upregulate BDNF production in astrocytes (57). In this light, our results are in good agreement with literature results; indeed, by comparing MMSE scores of LOAD patients from our and Laske's work (39), it is evident that our patients might be considered in an "advanced" stage of dementia. The lack of significant difference in serum BDNF between LOAD and VaD in our sample is in line with work of Ventriglia and colleagues (38) and supports the concept that low BDNF levels might be a nonspecific marker of neurodegeneration. BDNF is interested early in the development of dementia, as supported by the results from the Framingham study; each standard deviation increment in serum BDNF was associated with a 33% lower risk of developing dementia and LOAD on 10-year follow-up (58). However, the role of BDNF in the pathogenesis of LOAD is not clear yet. In one hand, low BDNF might be a consequence of amyloid deposition because it was demonstrated in AD mice that Aβ oligomer deposition compromises BDNF retro-trafficking by reducing the endosomial vesicles velocity (59). An early involvement of BDNF/pro-BDNF has been also demonstrated, caused by Aβ action on cyclic-AMP response element binding protein phosphorilation, with consequent reduction in BDNF gene expression (60). Allen and colleagues (61) postulated that Aβ deposition should be the "*primummovens*," whereas consequent BDNF reduction should initiate a cascade of events exacerbating the pathology and leading to dementia. In the other hand, it was reported that BDNF is an inductor of SORLA (sorting protein-related receptor containing LDLR class A repeats) transcription (62), a molecule regulating amyloid precursor protein intracellular trafficking and processing into Aβ, which reduces amyloid plaque formation when overexpressed (63,64).This observation suggests that BDNF reduction might be the first step of the process, inducing the accumulation of Aβ.

BDNF, Hypertension, and Cholesterol Levels

In this study, a negative correlation between systolic blood pressure and BDNF levels and a positive correlation between LDL-C and BDNF levels were found at univariate analysis; however, at multivariate analysis, neither systolic blood pressure nor LDL-C predicted BDNF levels, suggesting that other factors included into the model (eg, diabetes, age) might mediate these correlations.

The relationship between serum BDNF, blood pressure, and other metabolic parameters was evaluated by Golden and colleagues (65); a positive correlation of BDNF levels with diastolic blood pressure was found in men and women, whereas a positive correlation with total cholesterol/LDL-C emerged only in women. Because plasma BDNF decreases with age (66), whereas the prevalence of hypertension and

metabolic syndrome increases, these authors concluded that BDNF might contribute to lipids and blood pressure regulation and that their finding might represent a compensatory response to disrupted lipid metabolism and increase in blood pressure. A more recent study (67) analyzed BDNF levels in heart and aorta of hypertensive versus normotensive rats, finding a reduced local expression in the former; moreover, administration of exogenous BDNF induced aortic dilation, confirming the role of BDNF in the regulation of endothelial function.

BDNF and Depressive Symptoms

A significant relationship between GDS score and BDNF plasma levels emerged from our study. In particular, GDS positively correlated with BDNF levels, suggesting that BDNF levels were higher in patients complaining more depressive symptoms. This positive correlation emerged in the whole sample but was confirmed both in demented and nondemented individuals (data not shown). Some studies have reported reduced BDNF levels in patients with major depression (68,69), and it has been suggested that the reduction of BDNF might contribute to AD and major depression pathogenesis (24). Only a few studies have investigated the relationship between depressive symptoms and BDNF in AD patients. Consistent with our results, Hall and colleagues found significantly higher BDNF levels in depressed compared with nondepressed AD patients (70); these authors hypothesized that the increase in BDNF might reflect a chronic inflammatory process related to the pathophysiology of depression (45). Other studies showed different results: Laske and colleagues found a negative correlation between BDNF plasma concentrations and depressive symptoms measured by GDS (71), whereas Lee and colleagues found no differences between depressed and nondepressed AD patients (72). However, in the first study, the number of AD patients assessed was small, whereas in the second, the GDS cutoff for severe depression was high (score ≥ 20/30) so that many of the patients considered "not severely depressed" (and thus excluded) would have met the criteria for depression in our study.

Finally, we have to acknowledge some important limitations of the study. First, the size of the whole sample, and consequently of the four subgroups, was not really large, thus limiting the statistical power of the study. Second, the cross-sectional design does not allow to advance any cause-effect relationships. Consequently, we do not know whether reduced BDNF levels might be the "*primummovens*," inducing both diabetes and dementia or its decrease might result from the presence of diabetes and/or dementia. However, although further longitudinal studies on this topic are needed, our results clearly confirm the existence of an independent relationship between plasma BDNF, diabetes, and dementia among elderly people. Third, we were not aware about the possible antidepressant treatment of our patients, and antidepressant therapies are known to increase serum BDNF in the general population (73,74) and in VaD (75). At last, another limitation of the study regards the physical activity level. In animals, physical activity increases BDNF concentration in the hippocampus (76); moreover, a positive correlation between physical activity and serum BDNF was reported in AD (77). The increase of serum BDNF during physical exercise seems to be due to enhanced brain release because the brain contributes to 70%–80% of circulating BDNF (78). The degree of physical activity was not estimated in our study; nevertheless, indirect information came from the evaluation of BADLs, which express the functional autonomy of the individual. It is evident that patients with low BADLs score perform very limited physical activity. There was a significant difference in BADLs between demented and not demented individuals (see Table 1), the demented participants having the lower scores. Thus, our results might depend, at least in part, from the effect of different degree of physical activity. However, dementia definition requires a loss of function from the previous normal state; of consequence, very often patients with dementia display lower BADLs score compared with healthy elderly participants.

Conclusion

In conclusion, we found that among elderly individuals, both diagnoses of dementia and diabetes mellitus were associated with lower levels of plasma BDNF and correlated independently with BDNF plasma levels. Demented patients also affected by diabetes had the lowest BDNF levels in the sample, suggesting the existence of a "synergistic" effect of dementia and diabetes on BDNF levels.

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