

Decadimento cognitivo e diabete mellito

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Guidelines Abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update

*American Geriatrics Society Expert Panel on the Care of Older Adults with
Diabetes Mellitus*

Cognitive Impairment

Clinicians should assess older adults with DM for cognitive impairment using a standardized screening instrument during the initial evaluation period and with any significant decline in clinical status. **Increased difficulty with self-care should be considered a change in clinical status.** (III A)
Systematic review and meta-analyses of up to 15 studies found that **dementia was more likely in persons with DM** and suggested that **DM was associated with faster cognitive decline in older adults.**

10. Older Adults

Diabetes Care 2015;38(Suppl. 1):S67–S69 | DOI: 10.2337/dc15-S013

**American
Diabetes
Association
(ADA)**

Standard of
medical care in
Diabetes 2015

Recommendations

- Older adults who are functional and cognitively intact and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults. **E**
- Glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. **E**
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials. **E**
- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment. **E**
- Older adults (≥ 65 years of age) with diabetes should be considered a high-priority population for depression screening and treatment. **B**

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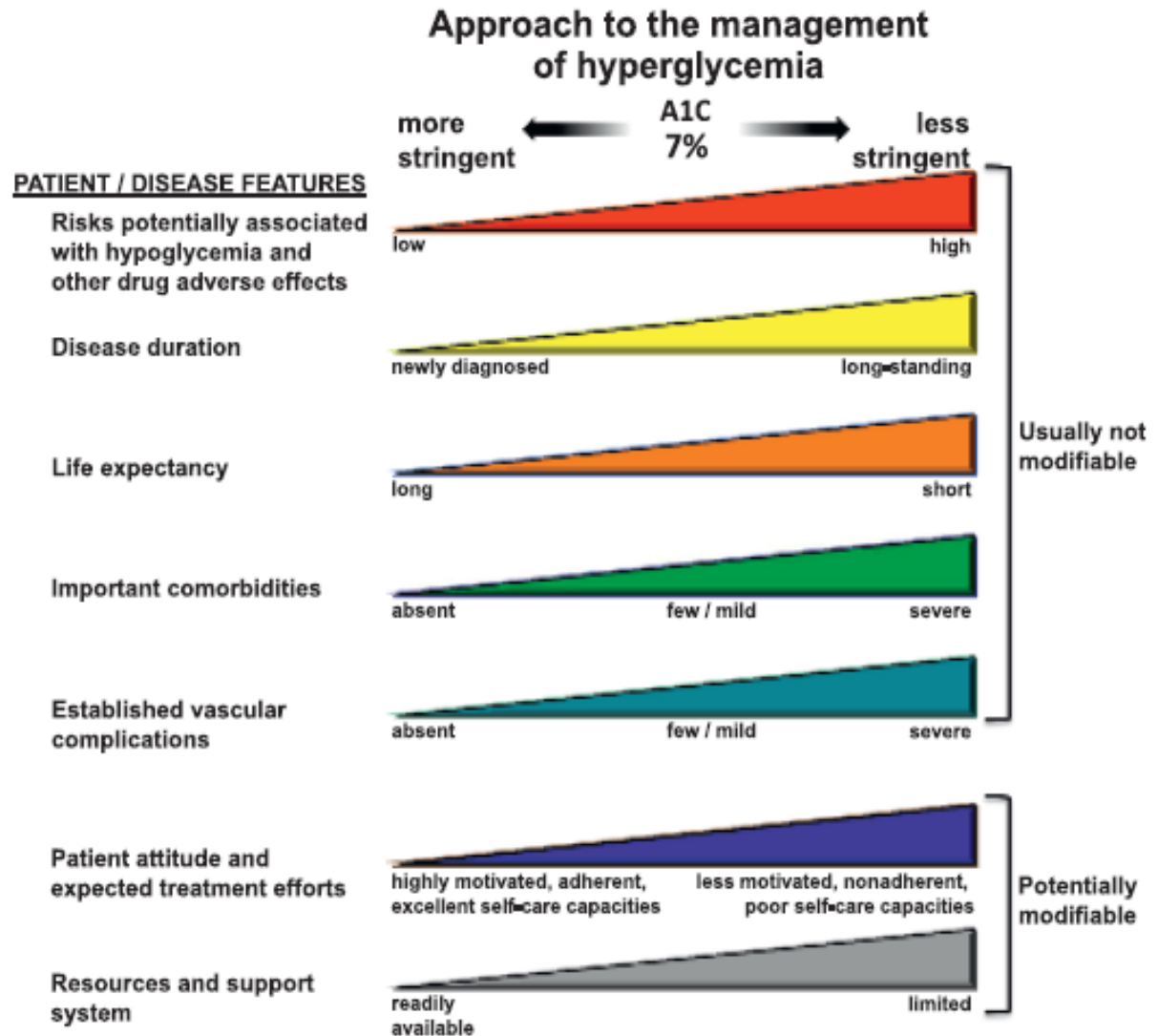


Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (45).

Decadimento cognitivo e diabete

Diversi studi hanno dimostrato che il DMT2 è associato ad un elevato rischio di avere un decadimento cognitivo o demenza

Table 1 T2DM and risk of dementia, AD, or VD

Study	Participants	Number of participants	Age at baseline (years) mean \pm SD	Major findings
Rotterdam study ⁶	Older persons over 55-years-old living in a suburb of Rotterdam	6,370 (692 diabetics)	T2DM: 72.6 \pm 8.8, non-T2DM: 68.4 \pm 8.6	T2DM increased all dementia (RR: 1.9, 95% CI: 1.3–2.8) and AD (RR: 1.9, 95% CI: 1.2–3.1)
Religious orders study ⁷	Catholic nuns, priests, and brothers in the US	824 (127 diabetics)	T2DM: 74.4 \pm 6.1, non-T2DM: 75.2 \pm 7.1	T2DM increased AD incidence (HR: 1.65, 95% CI: 1.10–2.47)
Honolulu Asia Aging Study ⁸	Japanese American men in Hawaii	2,574 (900 diabetics)	T2DM: 77.0 \pm 4.1, non-T2DM: 76.9 \pm 4.0	T2DM increased all dementia (RR: 1.5, 95% CI: 1.01–2.2), AD (RR: 1.8, 95% CI: 1.1–2.9), and VD (RR: 2.3, 95% CI: 1.1–5.0)
Hisayama study ⁹	Japanese community dwellers in a suburb of a metropolitan area in Japan	1,017 (150 diabetics)	T2DM: 69 \pm 6, non-T2DM: 68 \pm 6	T2DM increased all dementia (HR: 1.74, 95% CI: 1.19–2.53), AD (HR: 2.05, 95% CI: 1.18–3.57), and VD (HR: 1.82, 95% CI: 0.89–3.71)

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; AD, Alzheimer's disease; HR, hazard ratio; RR, relative risk; T2DM, type 2 diabetes mellitus; VD, vascular dementia.

Decadimento cognitivo e diabete

- **Il diabete mellito tipo 2 è un fattore di rischio per lo sviluppo di decadimento cognitivo e demenza**
- **Un paziente con DMT2 ha un rischio di 50%-150% di sviluppare demenza, fattore di rischio indipendente**
- **Una review sistematica ha dimostrato come il diabete sia associato con un rischio del 50%-100% di sviluppare demenza di Alzheimer e con un rischio del 100-150% di demenza vascolare**

Decadimento cognitivo e diabete

Livelli elevati di glucosio sono associati ad un maggior rischio di sviluppo di demenza anche nei pazienti non diabetici (NEJM 2013).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Levels and Risk of Dementia

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Ge Li, M.D., Ph.D., David M. Nathan, M.D., Hui Zheng, Ph.D.,
Sebastien Haneuse, Ph.D., Suzanne Craft, Ph.D., Thomas J. Montine, M.D., Ph.D.,
Steven E. Kahn, M.B., Ch.B., Wayne McCormick, M.D., M.P.H.,
Susan M. McCurry, Ph.D., James D. Bowen, M.D., and Eric B. Larson, M.D., M.P.H.

Risk of dementia in diabetes mellitus: a systematic review

Geert Jan Biessels, Salka Staekenborg, Eric Brunner, Carol Brayne, Philip Scheltens

The relation between diabetes and major types of dementia is controversial. This systematic review examines the incidence of dementia in people with diabetes mellitus. We identified 14 eligible longitudinal population-based studies of variable methodological quality. The incidence of “any dementia” was higher in individuals with diabetes than in those without diabetes in seven of ten studies reporting this aggregate outcome. This high risk included both Alzheimer’s disease and vascular dementia (eight of 13 studies and six of nine studies respectively). Detailed data on modulating and mediating effects of glycaemic control, microvascular complications, and comorbidity (eg, hypertension and stroke) were generally absent. The findings of mechanistic studies suggest that vascular disease and alterations in glucose, insulin, and amyloid metabolism underlie the pathophysiology, but which of these mechanisms are clinically relevant is unclear. Further high quality studies need to be initiated, with objective diabetes assessment, together with reliable methods to establish the contribution of vascular disease and other comorbidity to dementia.

Lancet Neurol 2006; 5: 64–74

Diabetes, Alzheimer disease, and vascular dementia

A population-based neuropathologic study



ABSTRACT

Objective: To investigate the relation of diabetes to dementia, Alzheimer disease (AD), and vascular dementia (VaD), through analyses of incidence, mortality, and neuropathologic outcomes in a prospective population-based study of the oldest old.

Methods: The Vantaa 85+ study included 553 residents living in the city of Vantaa, Finland, and aged ≥ 85 years on April 1, 1991. Survivors were reexamined in 1994, 1996, 1999, and 2001. Autopsies were performed in 291 persons who died during the follow-up (48% of total population). Diabetes was assessed according to self-report, medical record of physician-diagnosed diabetes, or use of antidiabetic medication. Macroscopic infarcts were identified from 1-cm coronal slices of cerebral hemispheres, 5-mm transverse brainstem slices, and sagittal cerebellum slices. Methenamine silver staining was used for β -amyloid, methenamine silver-Bodian staining for neurofibrillary tangles, and modified Bielschowsky method for neuritic plaques. Cox proportional hazards and multiple logistic regression models were used to analyze the association of diabetes with dementia and neuropathology, respectively.

Results: Diabetes at baseline doubled the incidence of dementia, AD, and VaD, and increased mortality. Individuals with diabetes were less likely to have β -amyloid (hazard ratio [HR] [95% confidence interval (CI)] was 0.48 [0.23–0.98]) and tangles (HR [95% CI] 0.72 [0.39–1.33]) but more likely to have cerebral infarcts (HR [95% CI] 1.88 [1.06–3.34]) after all adjustments.

Conclusion: Elderly patients with diabetes develop more extensive vascular pathology, which alone or together with AD-type pathology (particularly in APOE $\epsilon 4$ carriers) results in increased dementia risk. *Neurology*® 2010;75:1195–1202

Progression of brain atrophy and cognitive decline in diabetes mellitus

A 3-year follow-up

ABSTRACT

Objective: To investigate progression of MRI-assessed manifestations of cerebral degeneration related to cognitive changes in a population of elderly patients with diabetes mellitus (DM) compared to age-matched control subjects.

Methods: From a randomized controlled trial (PROSPER study), a study sample of 89 patients with DM and 438 control subjects without DM aged 70–82 years were included for brain MRI scanning and cognitive function testing at baseline and reexamination after 3 years. Changes in brain atrophy, white matter hyperintensities (WMHs), number of infarctions, and cognitive function test results were determined in patients with DM and subjects without DM. Linear regression analysis was performed with correction for age, gender, hypertension, pravastatin treatment, educational level, and baseline test results. In patients with DM, baseline MRI parameters were correlated with change in cognitive function test result using linear regression analysis with covariates age and gender.

Results: Patients with DM showed increased progression of brain atrophy ($p < 0.01$) after follow-up compared to control subjects. No difference in progression of WMH volume or infarctions was found. Patients with DM showed increased decline in cognitive performance on Stroop Test ($p = 0.04$) and Picture Learning Test ($p = 0.03$). Furthermore, in patients with DM, change in Picture Learning Test was associated with baseline brain atrophy ($p < 0.02$).

Conclusion: Our data show that elderly patients with DM without dementia have accelerated progression of brain atrophy with significant consequences in cognition compared to subjects without DM. Our findings add further evidence to the hypothesis that diabetes exerts deleterious effects on neuronal integrity. *Neurology*® 2010;75:997–1002

Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review

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Accepted 12 February 2008

Available online 4 March 2008

Abstract

Vascular risk factors, such as type 2 diabetes, hypertension, obesity and dyslipidaemia often co-occur. Each of these factors has been associated with an increased risk of dementia, but it is uncertain which factor imposes the greatest risk. Moreover, the effect of age at time of exposure may differ across factors. This paper systematically reviews the evidence for the association of each of these risk factors with dementia. Longitudinal population-based studies that assessed the incidence of dementia in relation to diabetes ($n=14$), hypertension ($n=13$), dyslipidaemia ($n=8$) or obesity ($n=9$) were included. All four risk factors were indeed associated with an increased risk of dementia, but the results of studies on diabetes and obesity were most consistent. The magnitude of the effects was comparable across the risk factors, with odds ratios for 'any dementia' around 1.5. For hypertension, obesity and dyslipidaemia age appeared to modulate the association: the risk of dementia was generally largest in studies that measured the risk factor in midlife (compared to late life) and had a long follow-up time. At midlife, the population attributable risk of dementia was highest for hypertension, up to 30% of cases of late life dementia. Later in life diabetes appears to convey the highest risk of dementia. This review shows that vascular risk factors should be regarded as a major target for preventive measures, but that timing of such measures appears to be critical.

Decadimento cognitivo e diabete

- Non è tuttavia chiaro se un miglior controllo metabolico indichi miglior performance cognitive, esistono infatti lavori discordanti

Am J Med. 2015 Jan;128(1):46-55

Glycemia and cognitive function in metabolic syndrome and coronary heart disease.

Avadhani R, et al

Cognitive Dysfunction Is Associated With Poor Diabetes Control in Older Adults

OBJECTIVE — To evaluate the association between cognitive dysfunction and other barriers and glycemic control in older adults with diabetes.

RESEARCH DESIGN AND METHODS — Patients over the age of 70 years presenting to a geriatric diabetes clinic were evaluated for barriers to successful diabetes management. Patients were screened for cognitive dysfunction with the Mini Mental State Examination (MMSE) and a clock-drawing test (CDT) scored by 1) a method validated by Mendez et al. and 2) a modified CDT (clock in a box [CIB]). Depression was evaluated with the Geriatric Depression Scale. Interview questionnaires surveyed activities of daily living (ADLs) and instrumental ADLs (IADLs), as well as other functional disabilities.

RESULTS — Sixty patients (age 79 ± 5 years, diabetes duration 14 ± 13 years) were evaluated. Thirty-four percent of patients had low CIB (≤ 5), and 38% of patients had low CDT (≤ 13). Both CIB as well as CDT were inversely correlated with HbA_{1c}, suggesting that cognitive dysfunction is associated with poor glycemic control ($r = -0.37$, $P < 0.004$ and $r = -0.38$, $P < 0.004$, respectively). Thirty-three percent of patients had depressive symptoms with greater difficulty completing the tasks of the IADL survey (5.7 ± 1.7 vs. 4.6 ± 2.0 ; $P < 0.03$). These older adults with diabetes had a high incidence of functional disabilities, including hearing impairment (48%), vision impairment (53%), history of recent falls (33%), fear of falls (44%), and difficulty performing IADLs (39%).

CONCLUSIONS — Older adults with diabetes have a high risk of undiagnosed cognitive dysfunction, depression, and functional disabilities. Cognitive dysfunction in this population is associated with poor diabetes control.

Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy

Lenore J Launer, Michael E Miller, Jeff D Williamson, Ron M Lazar, Hertzell C Gerstein, Anne M Murray, Mark Sullivan, Karen R Horowitz, Jingzhong Ding, Santica Marcovina, Laura C Lovato, James Lovato, Karen L Margolis, Patrick O'Connor, Edward W Lipkin, Joy Hirsch, Laura Coker, Joseph Maldjian, Jeffrey L Sunshine, Charles Truwit, Christos Davatzikos, R Nick Bryan, for the ACCORD MIND investigators*

Summary

Background People with type 2 diabetes are at risk of cognitive impairment and brain atrophy. We aimed to compare the effects on cognitive function and brain volume of intensive versus standard glycaemic control.

Methods The Memory in Diabetes (MIND) study was done in 52 clinical sites in North America as part of Action to Control Cardiovascular Risk in Diabetes (ACCORD), a double two-by-two factorial parallel group randomised trial. Participants (aged 55–80 years) with type 2 diabetes, high glycated haemoglobin A_{1c} (HbA_{1c}) concentrations (>7.5%; >58 mmol/mol), and a high risk of cardiovascular events were randomly assigned to receive intensive glycaemic control targeting HbA_{1c} to less than 6.0% (42 mmol/mol) or a standard strategy targeting HbA_{1c} to 7.0–7.9% (53–63 mmol/mol). Randomisation was via a centralised web-based system and treatment allocation was not masked from clinic staff or participants. We assessed our cognitive primary outcome, the Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 months. We assessed total brain volume (TBV), our primary brain structure outcome, with MRI at baseline and 40 months in a subset of participants. We included all participants with follow-up data in our primary analyses. In February, 2008, raised mortality risk led to the end of the intensive treatment and transition of those participants to standard treatment. We tested our cognitive function hypotheses with a mixed-effects model that incorporated information from both the 20 and 40 month outcome measures. We tested our MRI hypotheses with an ANCOVA model that included intracranial volume and factors used to stratify randomisation. This study is registered with ClinicalTrials.gov, number NCT00182910.

Findings We consecutively enrolled 2977 patients (mean age 62.5 years; SD 5.8) who had been randomly assigned to treatment groups in the ACCORD study. Our primary cognitive analysis was of patients with a 20-month or 40-month DSST score: 1378 assigned to receive intensive treatment and 1416 assigned to receive standard treatment. Of the 614 patients with a baseline MRI, we included 230 assigned to receive intensive treatment and 273 assigned to receive standard treatment in our primary MRI analysis at 40 months. There was no significant treatment difference in mean 40-month DSST score (difference in mean 0.32, 95% CI –0.28 to 0.91; $p=0.2997$). The intensive-treatment group had a greater mean TBV than the standard-treatment group (4.62, 2.0 to 7.3; $p=0.0007$).

Interpretation Although significant differences in TBV favoured the intensive treatment, cognitive outcomes were not different. Combined with the non-significant effects on other ACCORD outcomes, and increased mortality in participants in the intensive treatment group, our findings do not support the use of intensive therapy to reduce the adverse effects of diabetes on the brain in patients with similar characteristics to those of our participants.

L'iperglicemia determina:

- minori performance nel calcolo,
- minor velocità psicomotoria e scarsa capacità di concentrazione

Lenore J. Launer, et al. The action to control cardiovascular risk in diabetes memory in diabetes study (ACCORD-MIND): Rationale, Design, and Methods. *Am J Cardiol* 2007

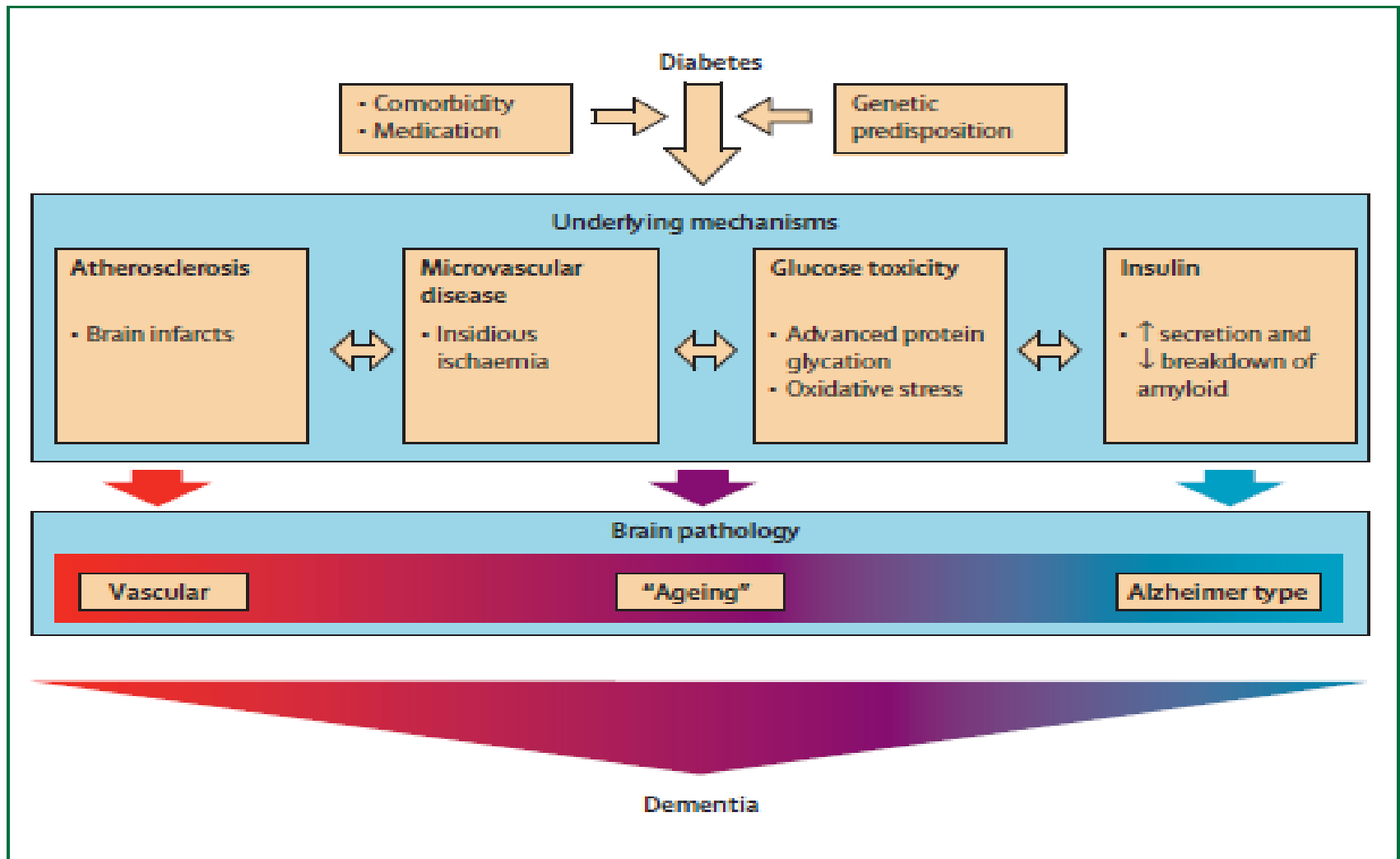
- peggioramento della memoria e della fluenza verbale

Messier C, et al., *Effect of age and glucoregulation on cognitive performance*. *Neurobiol Aging* 2003

- disfunzioni esecutive

• Gregg EW, Yaffe K, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174–180

Meccanismi fisiopatologici



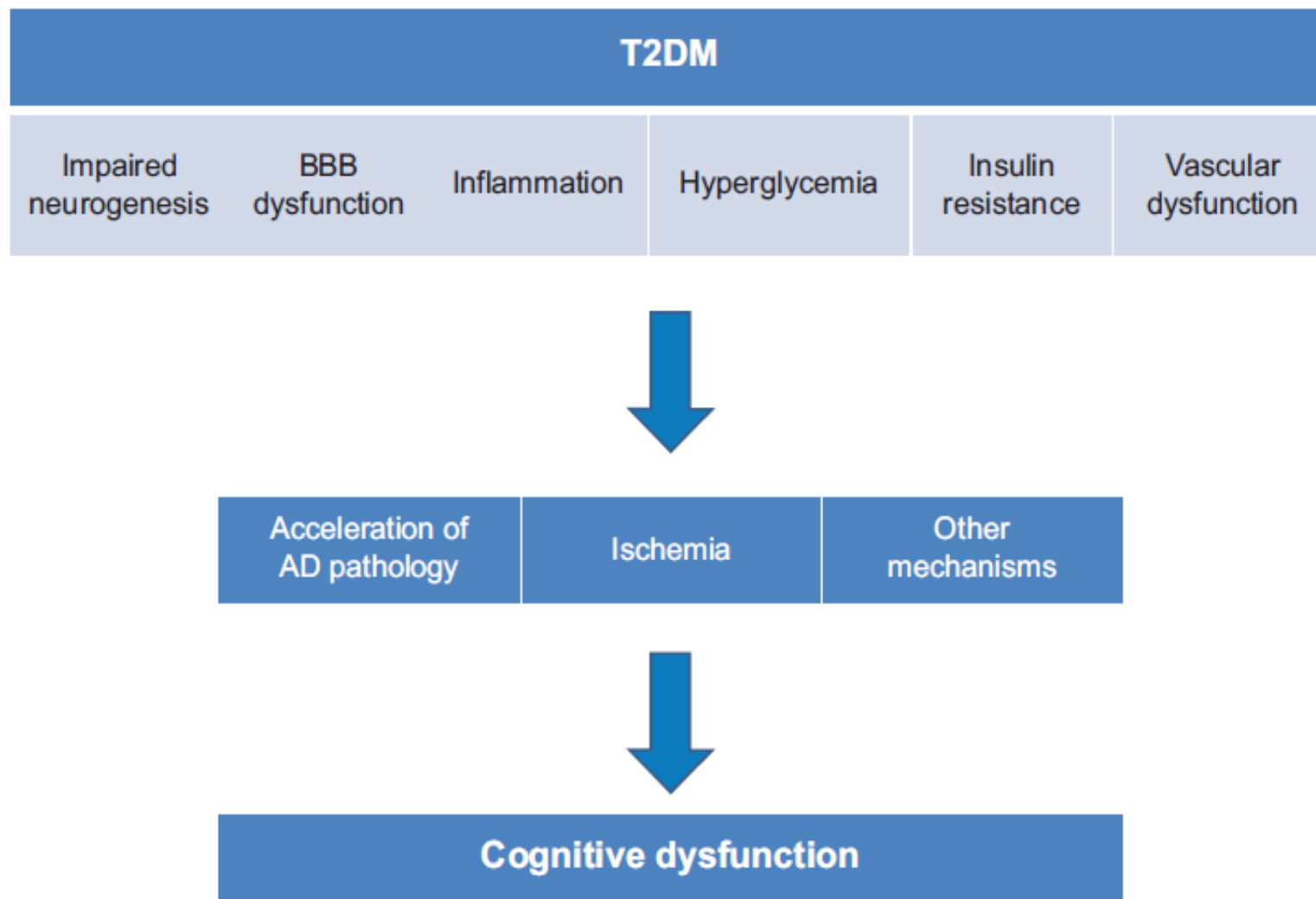


Figure 1 Mechanism of T2DM-associated cognitive dysfunction.

Abbreviations: AD, Alzheimer's disease; BBB, blood-brain barrier; T2DM, type 2 diabetes mellitus.

Meccanismi fisiopatologici

- **NEUROGENESI:**

L'ippocampo ha un ruolo principe nell'apprendimento e nella memoria, l'iperglicemia stimola la proliferazione neuronale ma non la sopravvivenza

> ridotta neurogenesi (deficit cognitivo e atrofia cerebrale)

Lang BT, Yan Y, Dempsey RJ, Vemuganti R. Impaired neurogenesis in adult type-2 diabetic rats. *Brain Res.* 2009;1258:25–33.

Meccanismi fisiopatologici

- **BARRIERA EMATOENCEFALICA:**

Nell' AD dimostrate alterazioni BEE

> alterazione nelle membrane, perdita di mitocondri, alterazioni del microcircolo, presenti anche nel diabete

Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. *Nat Neurosci.* 2007;10(11):1369–1376.

- **INFIAMMAZIONE:**

citochine proinfiammatorie (TNF alfa) sono implicate sia nella patogenesi di AD sia di DMT2 , TGF beta potente

antiinfiammatorio cerebrale è minore nei pz affetti da AD e in quelli con DMT2

Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. *Biochim Biophys Acta.* 2009;1792(5):482–496.

Meccanismi fisiopatologici

- **IPERGLICEMIA:**

**se cronica provoca alterazioni strutturali dell'ippocampo
attraverso diversi meccanismi:**

- **Osmosi**
- **Stress ossidativo**
- **Formazione dei prodotti di glicosilazione avanzata (AGEs) >
alterazione della microglia, danno ossidativo (trovati nelle
placche amiloidee e neurofibrillari)**
- **Danno endoteliale nel microcircolo**

Meccanismi fisiopatologici

- **IPERGLICEMIA:**

L'iperglicemia cronica modifica l'omeostasi cellulare

- **conversione di glucosio intracellulare a sorbitolo da parte di aldoso reduttasi, ciò porta ad un alterato potere ossido riduttivo cellulare**
- **produzione dei prodotti finali della glicosilazione avanzata (AGEs) che danneggiano le cellule endoteliali contribuendo al danno vascolare**
- **produzione di diacilglicerolo e attivazione di Protein Chinasi C che ha effetti negativi sul flusso sanguigno e sulla permeabilità vascolare, in particolar modo favorisce uno stato protrombotico**
- **formazione dell' esosamina che porta ad un' alterazione della trascrizione proteica con un incremento della sintesi di proteoglicani e glicoproteine, che contribuisce al danno vascolare**

Meccanismi fisiopatologici

- **EFFETTI DELL' INSULINA NELL' ENCEFALO:**
 - **Controllo dell' introito di cibo > recettori nel talamo e bulbo olfattivo**
 - **Effetto sulle funzioni cognitive > regola l' espressione di Ach transferasi**
 - **Degradata da Insulin-degrading enzime (IDE) che degrada anche la beta amiloide cerebrale > l' insulina compete con la beta amiloide che si accumula in uno stato di iperinsulinemia (studio istopatologico ha dimostrato che IDE è inferiore nell' ippocampo di pz affetti da AD)**

Meccanismi fisiopatologici

- **EFFETTI DELL' INSULINA NELL' ENCEFALO (2):**
 - **Aumenta la fosforilazione della proteina tau > alterato segnale dell'insulina può causare inibizione of PI3K/Akt e attivazione di glicogeno sintetasi chinasi 3b che aumenta la fosforilazione della proteina Tau**

Meccanismi fisiopatologici

- **DISFUNZIONE VASCOLARE:**
 - **Deficit endoteliale altera la funzione vascolare di autoregolazione del flusso cerebrale in corso di attività neuronale > maggior suscettibilità ad ipossia e ischemie**
 - **Disfunzione vascolare sembra correlarsi all'accumulo di beta amiloide > ridotta clearance AB**
 - **Alterazioni microvascolari a livello retinico e renale sembrano essere correlati ad alterazione microcircolo cerebrale e quindi indicatori di deficit cognitivo**

Meccanismi fisiopatologici

- **IPOGLICEMIA:**
 - **Diversi studi dimostrano come l' ipoglicemia peggiori le performance cognitive, chi ha frequenti episodi di ipoglicemia grave ha un aumentato rischio di sviluppare demenza**
 - **L'ipoglicemia sembra causare la morte neuronale soprattutto in aree specifiche (ippocampo)**

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Context Although acute hypoglycemia may be associated with cognitive impairment in children with type 1 diabetes, no studies to date have evaluated whether hypoglycemia is a risk factor for dementia in older patients with type 2 diabetes.

Objective To determine if hypoglycemic episodes severe enough to require hospitalization are associated with an increased risk of dementia in a population of older patients with type 2 diabetes followed up for 27 years.

Design, Setting, and Patients A longitudinal cohort study from 1980-2007 of 16 667 patients with a mean age of 65 years and type 2 diabetes who are members of an integrated health care delivery system in northern California.

Main Outcome Measure Hypoglycemic events from 1980-2002 were collected and reviewed using hospital discharge and emergency department diagnoses. Cohort members with no prior diagnoses of dementia, mild cognitive impairment, or general memory complaints as of January 1, 2003, were followed up for a dementia diagnosis through January 15, 2007. Dementia risk was examined using Cox proportional hazard regression models, adjusted for age, sex, race/ethnicity, education, body mass index, duration of diabetes, 7-year mean glycated hemoglobin, diabetes treatment, duration of insulin use, hyperlipidemia, hypertension, cardiovascular disease, stroke, transient cerebral ischemia, and end-stage renal disease.

Results At least 1 episode of hypoglycemia was diagnosed in 1465 patients (8.8%) and dementia was diagnosed in 1822 patients (11%) during follow-up; 250 patients had both dementia and at least 1 episode of hypoglycemia (16.95%). Compared with patients with no hypoglycemia, patients with single or multiple episodes had a graded increase in risk with fully adjusted hazard ratios (HRs): for 1 episode (HR, 1.26; 95% confidence interval [CI], 1.10-1.49); 2 episodes (HR, 1.80; 95% CI, 1.37-2.36); and 3 or more episodes (HR, 1.94; 95% CI, 1.42-2.64). The attributable risk of dementia between individuals with and without a history of hypoglycemia was 2.39% per year (95% CI, 1.72%-3.01%). Results were not attenuated when medical utilization rates, length of health plan membership, or time since initial diabetes diagnosis were added to the model. When examining emergency department admissions for hypoglycemia for association with risk of dementia (535 episodes), results were similar (compared with patients with 0 episodes) with fully adjusted HRs: for 1 episode (HR, 1.42; 95% CI, 1.12-1.78) and for 2 or more episodes (HR, 2.36; 95% CI, 1.57-3.55).

Conclusions Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes was associated with a greater risk of dementia. Whether minor hypoglycemic episodes increase risk of dementia is unknown.

Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus

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Importance: Hypoglycemia commonly occurs in patients with diabetes mellitus (DM) and may negatively influence cognitive performance. Cognitive impairment in turn can compromise DM management and lead to hypoglycemia.

Objective: To prospectively evaluate the association between hypoglycemia and dementia in a biracial cohort of older adults with DM.

Design and Setting: Prospective population-based study.

Participants: We studied 783 older adults with DM (mean age, 74.0 years; 47.0% of black race/ethnicity; and 47.6% female) who were participating in the prospective population-based Health, Aging, and Body Composition Study beginning in 1997 and who had baseline Modified Mini-Mental State Examination scores of 80 or higher.

Main Outcome Measures: Dementia diagnosis was determined during the follow-up period from hospital records indicating an admission associated with dementia or the use of prescribed dementia medications. Hy-

poglycemic events were determined during the follow-up period by hospital records.

Results: During the 12-year follow-up period, 61 participants (7.8%) had a reported hypoglycemic event, and 148 (18.9%) developed dementia. Those who experienced a hypoglycemic event had a 2-fold increased risk for developing dementia compared with those who did not have a hypoglycemic event (34.4% vs 17.6%, $P < .001$; multivariate-adjusted hazard ratio, 2.1; 95% CI, 1.0-4.4). Similarly, older adults with DM who developed dementia had a greater risk for having a subsequent hypoglycemic event compared with participants who did not develop dementia (14.2% vs 6.3%, $P < .001$; multivariate-adjusted hazard ratio, 3.1; 95% CI, 1.5-6.6). Further adjustment for stroke, hypertension, myocardial infarction, and cognitive change scores produced similar results.

Conclusion and Relevance: Among older adults with DM, there seems to be a bidirectional association between hypoglycemia and dementia.

JAMA Intern Med.

Published online June 10, 2013.

doi:10.1001/jamainternmed.2013.6176

Effect of Depression and Diabetes Mellitus on the Risk for Dementia

A National Population-Based Cohort Study

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IMPORTANCE Although depression and type 2 diabetes mellitus (DM) may independently increase the risk for dementia, no studies have examined whether the risk for dementia among people with comorbid depression and DM is higher than the sum of each exposure individually.

OBJECTIVE To examine the risk for all-cause dementia among persons with depression, DM, or both compared with persons with neither exposure.

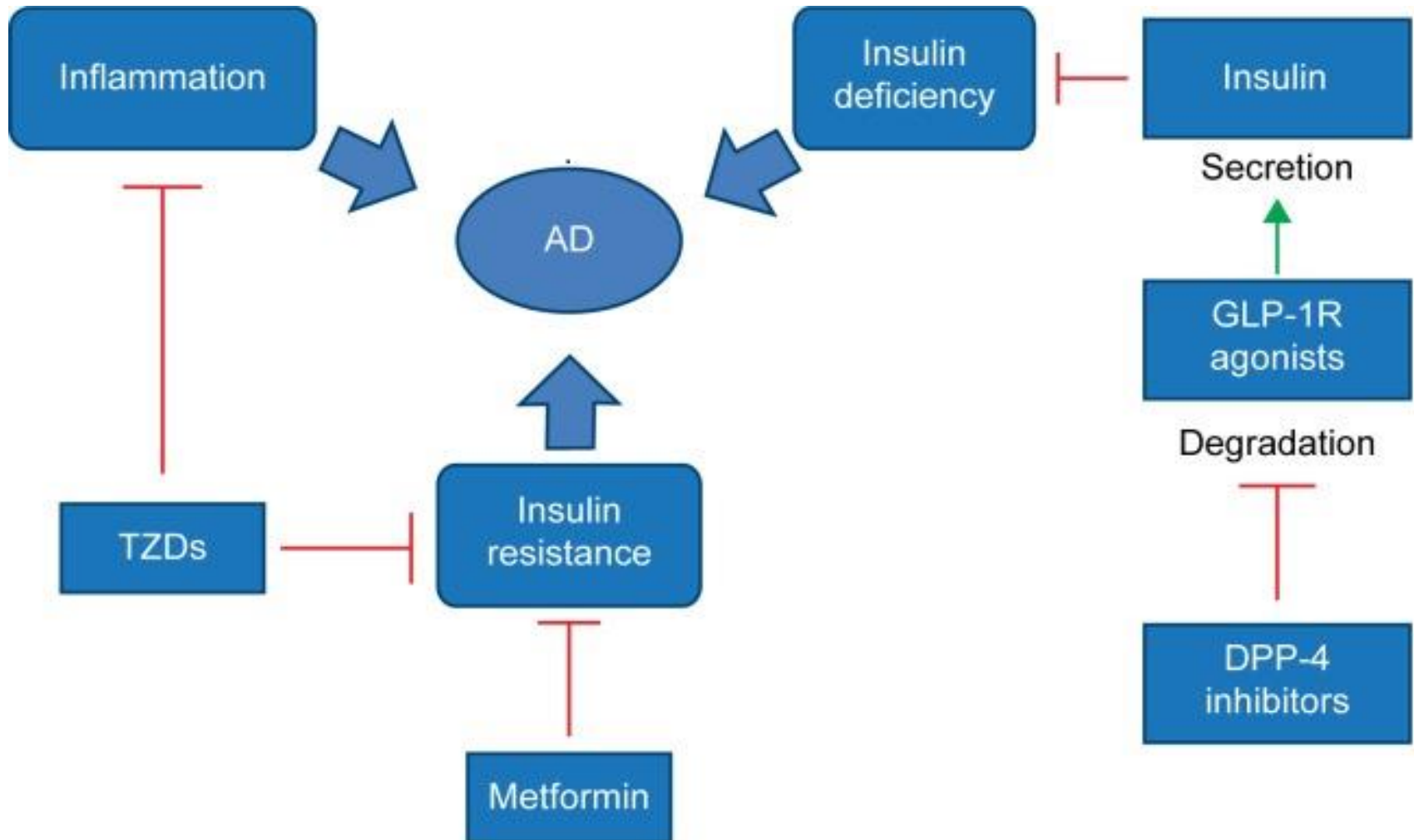
DESIGN, SETTING, AND PARTICIPANTS We performed a national population-based cohort study of 2 454 532 adults, including 477 133 (19.4%) with depression, 223 174 (9.1%) with DM, and 95 691 (3.9%) with both. We included all living Danish citizens 50 years or older who were free of dementia from January 1, 2007, through December 31, 2013 (followed up through December 31, 2013). Dementia was ascertained by physician diagnosis from the Danish National Patient Register or the Danish Psychiatric Central Register and/or by prescription of a cholinesterase inhibitor or memantine hydrochloride from the Danish National Prescription Registry. Depression was ascertained by psychiatrist diagnosis from the Danish Psychiatric Central Research Register or by prescription of an antidepressant from the Danish National Prescription Registry. Diabetes mellitus was identified using the National Diabetes Register.

MAIN OUTCOMES AND MEASURES We estimated the risk for all-cause dementia associated with DM, depression, or both using Cox proportional hazards regression models that adjusted for potential confounding factors (eg, demographics) and potential intermediates (eg, medical comorbidities).

RESULTS During 13 834 645 person-years of follow-up, 59 663 participants (2.4%) developed dementia; of these, 6466 (10.8%) had DM, 15 729 (26.4%) had depression, and 4022 (6.7%) had both. The adjusted hazard ratio for developing all-cause dementia was 1.83 (95% CI, 1.80-1.87) for persons with depression, 1.20 (95% CI, 1.17-1.23) for persons with DM, and 2.17 (95% CI, 2.10-2.24) for those with both compared with persons who had neither exposure. The excess risk for all-cause dementia observed for individuals with comorbid depression and DM surpassed the summed risk associated with each exposure individually, especially for persons younger than 65 years (hazard ratio, 4.84 [95% CI, 4.21-5.55]). The corresponding attributable proportion due to the interaction of comorbid depression and DM was 0.25 (95% CI, 0.13-0.36; $P < .001$) for those younger than 65 years and 0.06 (95% CI, 0.02-0.10; $P = .001$) for those 65 years or older.

CONCLUSIONS AND RELEVANCE Depression and DM were independently associated with a greater risk for dementia, and the combined association of both exposures with the risk for all-cause dementia was stronger than the additive association.

Possibili risvolti terapeutici



Possibili risvolti terapeutici

- **METFORMINA:**

Oltre all'effetto ipoglicemizzante e sull'insulino resistenza, riduce il rischio di sviluppare sindrome metabolica ed ha effetti antiinfiammatori

Nei pazienti affetti da AD con e senza DMT2 vi è un rallentamento del declino cognitivo rispetto a quelli non trattati

Un ampio studio inglese ha dimostrato come i pazienti affetti da DMT2 abbiano un rischio ridotto di sviluppare AD se in terapia con metformina, ma se usata per lungo tempo sembra aumentare il rischio di AD

Incidence of Dementia is Increased in Type 2 Diabetes and Reduced by the Use of Sulfonylureas and Metformin

Authors: Hsu, Chih-Cheng | Wahlqvist, Mark L. | Lee, Meei-Shyuan | Tsai, Hsin-Ni

Abstract: To determine incidence of dementia in type 2 diabetic (T2DM) patients, and whether there are adverse or favorable effects of oral agents (OA) in DM, we obtained a representative cohort of 800,000 from Taiwan's National Health Insurance database. Those who, as of on January 1, 2000, were 50 years or older and dementia free ($n = 127,209$) were followed until December 31, 2007, in relation to absence ($n = 101,816$) or presence ($n = 25,393$) of T2DM, and whether any OA was used. Dementia was ascertained by ICD9-CM or A-code. Dementia incidence densities (DID) and fully adjusted Cox proportional hazard models were used to estimate association between dementia, DM, and OA. Notably, DID (per 10,000 person-years) was markedly increased with DM (without medication), compared to DM free subjects (119 versus 46). Using non-DM as reference, the adjusted hazard ratios (HRs) (95% confidence interval) for DM without and with OA were 2.41 (2.17–2.66) and 1.62 (1.49–1.77), respectively. For T2DM, compared with no medication, sulfonylureas alone reduced the HR from 1 to 0.85 (0.71–1.01), metformin alone to 0.76 (0.58–0.98), while with combined oral therapy the HR was 0.65 (0.56–0.74). Adjustments included cerebrovascular diseases so that non-stroke related dementias were found to be decreased in DM with sulfonylurea and metformin therapy. T2DM increases the risk of dementia more than 2-fold. On the other hand, sulfonylureas may decrease the risk of dementia, as does metformin; together, these 2 OAs decrease the risk of dementia in T2DM patients by 35% over 8 years.

DOI: 10.3233/JAD-2011-101524

Journal: *Journal of Alzheimer's Disease*, vol. 24, no. 3, 2011

Metformin, Other Antidiabetic Drugs, and Risk of Alzheimer's Disease: A Population-Based Case–Control Study

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OBJECTIVES: To explore the risk of developing Alzheimer's disease (AD) in individuals with diabetes mellitus treated with metformin or other antidiabetic drugs.

DESIGN: Case–control study.

SETTING: The United Kingdom–based General Practice Research Database (GPRD), a well-established primary care database.

PARTICIPANTS: Seven thousand eighty-six individuals aged 65 and older with an incident diagnosis of AD identified between 1998 and 2008 and the same number of matched controls without dementia. Matching criteria were age, sex, general practice, calendar time, and years of history in the database.

MEASUREMENTS: Comparison of previous use of metformin or other antidiabetic drugs between cases and controls and calculation of corresponding odds ratios (ORs) with 95% confidence intervals (CIs), using conditional logistic regression. Risk estimates were stratified according to duration of use and adjusted for potential confounders.

RESULTS: As compared with nonusers, long-term users of 60 or more metformin prescriptions were at greater risk of developing AD (adjusted OR (AOR) = 1.71, 95% CI = 1.12–2.60), but there was no consistent trend with increasing number of prescriptions. Long-term use of other antidiabetic drugs such as sulfonylureas (AOR = 1.01, 95% CI = 0.72–1.42), thiazolidinediones (AOR = 0.87, 95% CI = 0.31–2.40), or insulin (AOR = 1.01, 95% CI = 0.58–1.73) was not related to an altered risk of developing AD.

CONCLUSION: Long-term use of sulfonylureas, thiazolidinediones, or insulin was not associated with an altered risk of developing AD. There was a suggestion of a slightly higher risk of AD in long-term users of metformin. *J Am Geriatr Soc* 60:916–921, 2012.

Possibili risvolti terapeutici

- **TIAZOLIDINEDIONI:**

Potenti insulino-sensibilizzatori con proprietà antiinfiammatorie

Alcuni studi hanno dimostrato come il loro utilizzo migliori le funzioni attentive e mnesiche, altri invece non hanno notato differenze

Uso limitato per la ritenzione idrica e l'edema che possono dare

Original Research Article

Dement Geriatr Cogn Disord 2010;30:131–146

DOI: [10.1159/000318845](https://doi.org/10.1159/000318845)

Accepted: June 21, 2010

Published online: August 21, 2010

Rosiglitazone Monotherapy in Mild-to-Moderate Alzheimer's Disease: Results from a Randomized, Double-Blind, Placebo-Controlled Phase III Study

Possibili risvolti terapeutici

- **GLP-1 AGONISTI e DPP4 INIBITORI:**

GLP1 è un' incretina prodotta dall'intestino e che stimola la produzione di insulina in presenza di glucosio, è rapidamente degradato da DPP4

I recettori di GLP1 sono presenti anche a livello cerebrale e si è visto come liraglutide e exendina4 abbiano delle proprietà neurotrofiche (migliorano il segnale insulinico, hanno effetto neuroprotettivo sui neuroni e sulle sinapsi, riducono l'accumulo di beta amiloide)

Sinagliptin e vidagliptin hanno effetti positivi sull'apprendimento e la memorizzazione

DPP-4 inhibitors improve cognition and brain mitochondrial function of insulin-resistant rats

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Abstract

Recent evidence has demonstrated that insulin resistance is related to the development of type 2 diabetes mellitus. Our previous study found that high-fat diet (HFD) consumption caused not only peripheral and brain insulin resistance but also brain mitochondrial dysfunction and cognitive impairment. Vildagliptin and sitagliptin, dipeptidyl-peptidase-4 inhibitors, are recently developed anti-diabetic drugs. However, the effects of both drugs on cognitive behaviors and brain mitochondrial function in HFD-induced insulin-resistant rats have not yet been investigated. Sixty male Wistar rats were divided into two groups to receive either normal diet or HFD for 12 weeks. Rats in each group were then further divided into three treatment groups to receive either vehicle, vildagliptin (3 mg/kg per day), or sitagliptin (30 mg/kg per day) for 21 days. The cognitive behaviors of the rats were tested using the Morris Water Maze test. Blood samples were collected to determine metabolic parameters and plasma oxidative stress levels. Upon completion of the study, the animals were killed and the brains were removed to investigate brain and hippocampal mitochondrial function as well as to determine oxidative stress levels. We demonstrated that both drugs significantly improved the metabolic parameters and decreased circulating and brain oxidative stress levels in HFD-induced insulin-resistant rats. In addition, both drugs completely prevented brain and hippocampal mitochondrial dysfunction and equally improved the learning behaviors impaired by the HFD. Our findings suggest that the inhibition of dipeptidyl-peptidase-4 enzymes with vildagliptin or sitagliptin in insulin-resistant rats not only increases peripheral insulin sensitivity but also decreases brain dysfunction.

Possibili risvolti terapeutici

- **INSULINA TRANSNASALE:**

E' stato dimostrato in diversi studi che la somministrazione di insulina transnasale migliora le funzioni cognitive e ha minori effetti collaterali (ridotte ipoglicemie) rispetto alla forma parenterale

Migliora l'attività cerebrale a livello parietotemporale e frontale alla PET

Intranasal insulin improves cognition and modulates β -amyloid in early AD

February 5, 2008 70:6 440-448; published ahead of print
October 17, 2007 1526-632X

Intranasal Insulin Therapy for Alzheimer Disease and Amnesic Mild Cognitive Impairment

A Pilot Clinical Trial

Suzanne Craft, PhD; Laura D. Baker, PhD; Thomas J. Montine, MD, PhD; Satoshi Minoshima, MD, PhD; G. Stennis Watson, PhD; Amy Claxton, PhD; Matthew Arbuckle, BA; Maureen Callaghan, MD; Elaine Tsai, MD; Stephen R. Plymate, MD; Paitie S. Green, PhD; James Leverenz, MD; Donna Cross, PhD; Brooke Gerton, MD

*Arch Neurol. 2012;69(1):29-38. Published online
September 12, 2011. doi:10.1001/archneurol.2011.233*

Diabete, decadimento cognitivo e careving

- **Quale obiettivo?**
- **Quale terapia?**
- **Gestione della malattia, delle complicanze, del follow-up**
- **Educazione del caregiver**

GRAZIE DELL' ATTENZIONE