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REGIONE SARDEGNA



DIABETE UNA PATOLOGIA
COMPLESSA A VALENZA
MULTIDISCIPLINARE

ALGHERO, Hotel Catalunya

30 NOVEMBRE / 1 DICEMBRE 2018

Diabete e disturbi cognitivi

Jacopo Salvatore Bulla

Il Dott. Bulla dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

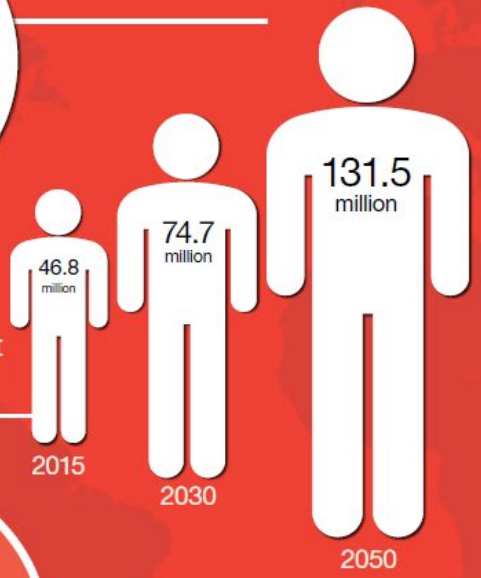
INFOGRAPHIC

The global impact of dementia



Around the world, there will be 9.9 million new cases of dementia in 2015,

one every 3 seconds

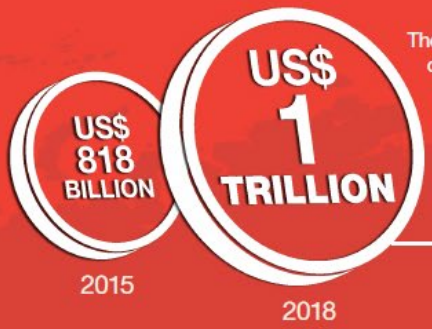


46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.



Much of the increase will take place in low and middle income countries (LMICs):
in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.



The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google







(source: Forbes 2015 ranking).



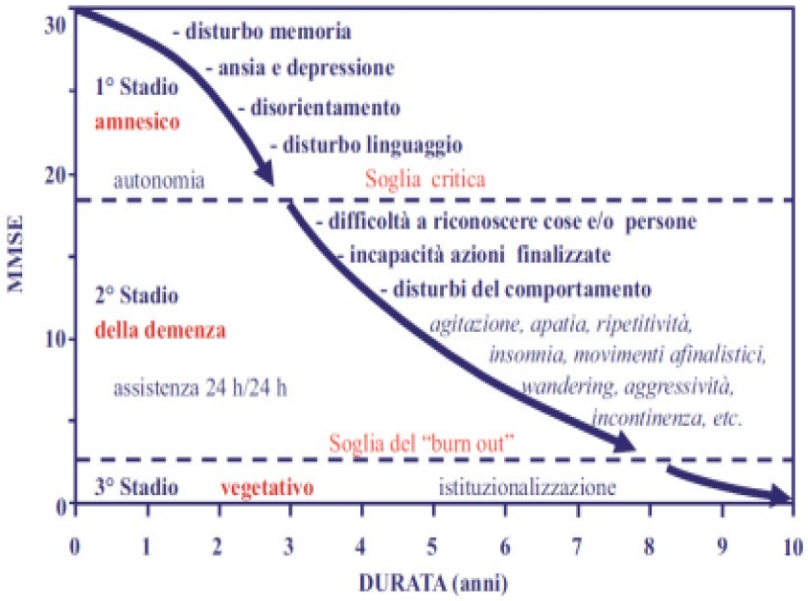
This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.

World Alzheimer report, WHO 2015



Disturbo neurocognitivo maggiore



Progressiva **compromissione delle funzioni corticali superiori e della dipendenza nelle attività della vita quotidiana.**

5 cluster sintomatologici:

1. **Psicosi** (Allucinazioni, delusioni e misidentificazioni);
2. **Depressione** (Tristezza, pianto, disperazione, scarsa autostima, ansia, colpa);
3. **Apatia** (Ritiro sociale, mancanza di interessi e demotivazione);
4. **Aggressività** (Resistenza aggressiva, aggressività fisica e verbale);
5. **Agitazione** (Affaccendamento, vagabondaggio, pedinamento, irrequietezza, grida, disinibizione, stereotipie, vestirsi/svestirsi, disturbi del sonno).

Criteri diagnostici per il desturbo neurocognitivo maggiore (DSM-5)

- *Significativo decadimento cognitivo in almeno uno dei seguenti domini funzionali:*
  - apprendimento e memoria
  - linguaggio
  - Funzioni esecutive
  - attenzione
  - Funzione motoria
  - Funzione sociale



- *Il decadimento deve essere: **acquisito**, **graduale** con evoluzione spesso **insidiosa** e rappresentare un significativo **declino** rispetto a una pregressa condizione di funzionalità cognitiva*

- *I deficit cognitive devono **compromettere l'autonomia nelle attività quotidiane***

- Deve essere eslusa la presenza di un disturbo mentale (depression maggiore e schizophrenia)

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

Deterioramento cognitivo lieve (MCI)

- Condizione clinica caratterizzata da una **sfumata difficoltà in uno o più domini cognitivi** (ad esempio memoria, attenzione, linguaggio) e oggettivata attraverso i test neuropsicologici, tale però da **non compromettere le normali attività quotidiane della persona.**

- I pazienti con MCI di solito incontrano qualche **difficoltà nella gestione delle IADL** (ad esempio gestione del denaro, preparare un pasto oppure fare la spesa), necessitando di **tempi più lunghi o facendo più errori rispetto al passato** nelle medesime attività, mantengono tuttavia la loro autonomia.

- Rappresenta uno stato di **transizione** tra il normale invecchiamento e la demenza lieve.

Delirium

In ospedale, circa 1 paziente anziano ogni 6 ne è affetto, presenta un'elevata prevalenza anche negli anziani ospiti di strutture per anziani.

Secondo il **DSM 5**, il delirium è definito dalla **coesistenza di 5 condizioni:**

1. disturbo dell'attenzione e dello stato di consapevolezza di sé nell'ambiente;
2. **insorgenza acuta o subacuta** e decorso fluttuante;
3. **coesistenza di altri deficit cognitivi** (disorientamento temporo-spaziale, disturbi del linguaggio, della memoria o della percezione);
4. **assenza di severa compromissione del livello di coscienza**;
5. **evidenza di patologia acuta in atto**, intossicazione da farmaci, sindrome da astinenza, esposizione a tossine o eziologia multipla.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013

Delirium

Forma ipercinetica o iperattiva: è caratterizzata da **agitazione psicomotoria**, aumentata sensibilità agli stimoli esterni, stato di iper-allerta. Si sviluppano spesso **illusioni e allucinazioni**;

Forma ipocinetica o ipoattiva: si presenta con **rallentamento psicomotorio**, tendenza all'assopimento fino alla letargia e ridotta risposta agli stimoli esterni

Forma mista: caratterizzata dall'alternanza di fasi di tipo ipercinetico e ipocinetico.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013

Delirium

PREDISPONENTI	PRECIPITANTI
Ridotta riserva cognitiva - Età avanzata - Declino cognitivo e demenza - Depressione Deprivazione sensoriale (visiva e/o uditiva) Comorbidità (problematiche acute e/o croniche riacutizzate cardiovascolari, polmonari, renali) e relativa classificazione ASA Abuso etilico Malnutrizione (BMI, albuminemia) Disidratazione Polifarmacoterapia Istituzionalizzazione e alterate capacità funzionali	Farmaci (polifarmacoterapia, introduzione nuovi farmaci o sospensione) - antidolorifici (FANS e oppioidi) - anticolinergici - miorilassanti - antistaminici - antiaritmici - corticosteroidi - antibiotici - psicotropi (antidepressivi, antiepilettici, antipsicotici, benzodiazepine) Dolore Tipo di anestesia (generale, spinale) Ipossiemia Infezioni Alterazioni elettrolitiche, anemia Catetere vescicale Mezzi di contenzione Ambiente ospedaliero Alterazioni ritmo sonno veglia

Clinical features of delirium versus dementia

	Delirium	Dementia
Onset	More abrupt decline in cognitive function over hours to days, with waxing and waning course	Typically insidious, progressive decline in cognition over months to years
Attention and orientation	Impaired	Generally preserved; can be altered in later stages
Level of consciousness	Fluctuating, sometimes reduced	Normal
Speech and language	Incoherent, disorganized speech	Variable impairments in word retrieval, naming, fluency, and comprehension
Memory for recent and past events	Variable, fluctuating impairments	Often impaired for recent events; memory for remote events becomes impaired in later stages

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Recognition and initial assessment of Alzheimer's disease and related dementias. Clinical Practice Guidelines, Number 19, AHCPR; U.S. Department of Health and Human Services Agency for Health Care Policy and Research, 1996

Pseudodemenza

1. È fondamentalmente soddisfatto della sua vita?	Sì	No
2. Ha abbandonato molte delle sue attività e dei suoi interessi?	Sì	No
3. Sente che la sua vita è vuota?	Sì	No
4. Si annoia spesso?	Sì	No
5. È di buon umore la maggior parte del tempo?	Sì	No
6. Ha paura che qualcosa di brutto stia per succederle?	Sì	No
7. Si sente più felice nella maggior parte del tempo?	Sì	No
8. Si sente spesso impotente?	Sì	No
9. Preferisce restare a casa piuttosto che uscire e fare cose nuove?	Sì	No
10. Ritiene di avere più problemi con la memoria della maggior parte delle persone?	Sì	No
11. Pensa che la vita sia meravigliosa?	Sì	No
12. Si sente piuttosto inutile così com'è?	Sì	No
13. Si sente pieno di energie?	Sì	No
14. Ha l'impressione che la sua situazione sia disperata?	Sì	No
15. Pensa che la maggior parte delle persone sia migliore di lei?	Sì	No
Punteggio: ___/15 Un punto per "No" alle domande 1, 5, 7, 11, 13 Un punto per "Sì" alle altre domande	Normale	3 ± 2
	Lievemente depresso	7 ± 3
	Molto depresso	12 ± 2

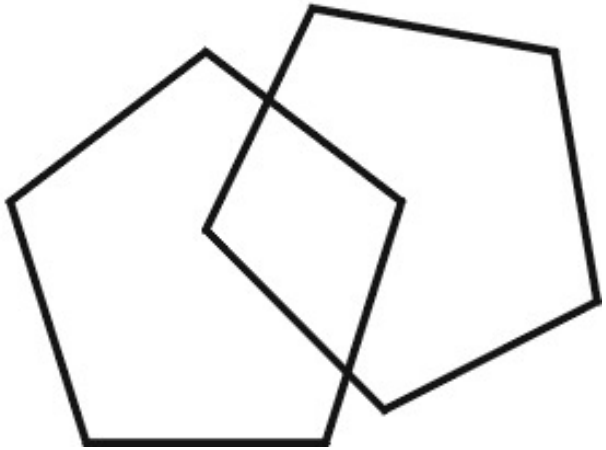
Condizione medica in cui la depressione si manifesta clinicamente con un importante deterioramento cognitivo al punto da essere "scambiata" per una demenza.

La pseudodemenza non è in realtà una condizione frequente, ma è importante riconoscerla in quanto potenzialmente reversibile una volta che la depressione venga trattata adeguatamente.

Al contrario, è stato successivamente osservato da più autori come la depressione, quando associata ad un deterioramento cognitivo, rappresenti molto spesso una **fase prodromica della demenza**.

La maggior parte degli autori considera la depressione come secondaria alla demenza e non viceversa.

Test cognitivi

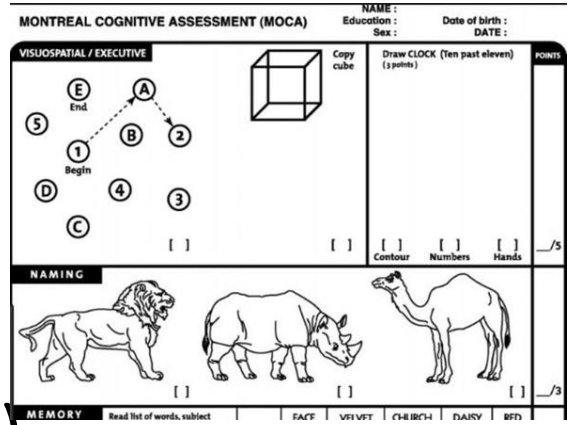


Mini-Mental State Examination

- L'MMSE è stato il test cognitivo più utilizzato per la demenza nella pratica clinica degli Stati Uniti
- Richiede circa sette minuti per essere completato.
- Mette alla prova un'ampia gamma di funzioni cognitive quali orientamento, richiamo, attenzione, calcolo, manipolazione della lingua e prassi costruttiva.
- Il punteggio massimo è di 30 punti. Un punteggio inferiore a 24 punti è indicativo di demenza o delirio, inferiore a 18 deterioramento cognitivo grave

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Test cognitivi

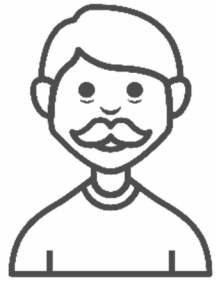


Montreal Cognitive Assessment (MoCA)

- Test di screening progettato per rilevare il deterioramento cognitivo negli anziani.
- Test a 30 punti che richiede circa 10 minuti per essere completato.
- Rispetto all'MMSE, il MoCA è **più sensibile per l'individuazione di un danno cognitivo lieve (MCI)** e include elementi che campionano una gamma più ampia di domini cognitivi, tra cui memoria, linguaggio, attenzione, visuo spaziale e funzioni esecutive.

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Test cognitivi



Clinical Dementia Rating (CDR)

- Progettato per valutare la gravità dell'AD in studi longitudinali e studi clinici
- **Intervista semistrutturata con il paziente e il caregiver** che valuta il grado di compromissione di sei domini cognitivi (memoria, orientamento, giudizio e risoluzione dei problemi, affari della comunità, casa e hobby, cura della persona).
- Il punteggio CDR globale viene assegnato in base a prestazioni in ciascun dominio, attribuendo particolare importanza al punteggio di memoria.

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Test cognitivi



Mini-Cog

Consiste in un **Clock-Drawing Task** e nel **ricordare tre parole** non correlate tra loro.
Il CDT è considerato normale se tutti i numeri sono presenti nella sequenza corretta e le lancette visualizzano l'ora corretta in modo leggibile. Il punteggio si basa su un semplice albero decisionale che segue tre regole:

- i soggetti che non ricordano nessuna delle parole sono classificati come dementi;
- i soggetti che richiamano tutte e tre le parole sono classificati come non dementi;
- I soggetti con richiamo intermedio (da uno a due) sono classificati in base al CDT.

I vantaggi del Mini-Cog includono un'**elevata sensibilità per la predizione dello stato di demenza, durata inferiore rispetto all'MMSE, facilità di somministrazione e valore diagnostico non limitato dall'istruzione del soggetto o al linguaggio.**

UpToDate®

Validity and reliability of the AD8 informant interview in dementia

James E. Galvin, MD, MPH; Catherine M. Roe, PhD; Chengjie Xiong, PhD; and John C. Morris, MD

***Table 1** AD8 questions asked of informants*

1. Problems with judgment (e.g., falls for scams, bad financial decisions, buys gifts inappropriate for recipients)
2. Reduced interest in hobbies/activities
3. Repeats questions, stories, or statements
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)
5. Forgets correct month or year
6. Difficulty handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)
7. Difficulty remembering appointments
8. Consistent problems with thinking and/or memory



The AD8 is a brief, sensitive measure that validly and reliably differentiates between nondemented and demented individuals.
It can be used as a general screening device to detect cognitive change regardless of etiology and with different types of informants.

NEUROLOGY 2006;67:1942–1948

Diabetes mellitus and the risk of dementia

The Rotterdam Study

A. Ott, MD, PhD; R.P. Stolk, MD, PhD; F. van Harskamp, MD; H.A.P. Pols, MD, PhD;
A. Hofman, MD, PhD; and M.M.B. Breteler, MD, PhD

Article abstract—*Objective:* To determine the influence of type 2 diabetes mellitus on the risk of dementia and AD. *Background:* Both dementia and diabetes are frequent disorders in elderly people. *Methods:* Prospective population-based cohort study among 6,370 elderly subjects. At baseline study participants were examined for presence of diabetes mellitus. Nondemented participants were followed up, on average, for 2.1 years. Incident dementia was diagnosed using a three-step screening and comprehensive diagnostic workup. To complete the follow-up, medical files were studied of persons who could not be reexamined. We estimated relative risks with proportional hazard regression, adjusting for age, sex, and possible confounders. *Results:* During the follow-up, 126 patients became demented, of whom 89 had AD. Diabetes mellitus almost doubled the risk of dementia (relative risk [RR] 1.9 [1.3 to 2.8]) and AD (RR 1.9 [1.2 to 3.1]). Patients treated with insulin were at highest risk of dementia (RR 4.3 [1.7 to 10.5]). *Conclusion:* The diabetes attributable risk for dementia of 8.8% suggests that diabetes may have contributed to the clinical syndrome in a substantial proportion of all dementia patients. **Key words:** AD—Dementia—Diabetes mellitus—Epidemiology—Incidence.

NEUROLOGY 1999;53:1937–1942

Table 1 – Risk of dementia in patients with diabetes.

Study	Nation Population Mean age Follow-up year	Dementia RR (95% CI)		
		All	Alzheimer's disease	Vascular dement
Ott et al. [66]*	Netherlands 6370 elderly persons from the community-based Rotterdam Study 11% with DM Mean age: 68.9 Follow-up year: 2.1	1.9 (1.3–2.8)	1.9 (1.2–3.1)	2.0 (0.7–5.6)
Luchsinger et al. [67]*	USA 1262 healthy Medicare beneficiaries residing in northern Manhattan 20% with DM Mean age: 75.6 Follow-up year: 4.3	–	1.3 (0.84–1.88)	3.4 (1.20–6.91)
Peila et al. [68]*	USA Japanese-American 2574 Japanese-American elderly men from the fourth exam cohort (1991–1993) of the Honolulu-Asia aging study 35% with DM Mean age: 77 Follow-up year: 3	1.5 (1.01–2.2)	1.8 (1.1–2.9)	2.3 (1.1–5.0)
Hassing et al. [69]*	Sweden 702 elderly individuals from the population-based Origins of Variance in the Old-Old study (OCTO-Twin Study) 15% with DM Mean age: 83 Follow-up year: 6–8	–	0.85 (0.36–2.02)	3.63 (1.35–9.76)
MacKnight et al. [70]*	Canada 5574 elderly participants from the Canadian study of health and aging 9% with DM Mean age: 74 Follow-up year: 5	1.26 (0.90–1.76)	1.30 (0.83–2.03)	2.03 (1.15–3.57)
Xu et al. [71]*	Sweden 1301 community elderly dwellers from the Kungsholmen project 8.8% with DM Mean age: 81 Follow-up year: 4.7	1.5 (1.0–2.1)	1.3 (0.9–2.1)	2.6 (1.2–6.1)
Akomolafe et al. [72]*	USA 2210 community-dwelling dementia-free elders from Framingham study original cohort 9.1% with DM Mean age: 70 Follow-up year: 12.7	1.20 (0.74–1.96)	1.15 (0.65–2.05)	0.81 (0.18–3.70)
Hayden et al. [73]*	USA 3264 aged 65 or older adults from the community-based cohort of Cache County Study of Memory Health and Aging (CCSMHA) 10.5% with DM Mean age: 70 Follow-up year: 12.7	1.56 (0.90–2.56)	1.33 (0.66–2.46)	2.23 (0.88–5.17)
Irie et al. [74]	USA 2547 dementia-free participants in the CHS (Cardiovascular Health Study) cognition study cohort 12.6% with DM Mean age: 74.7 Follow-up year: 5.4	1.44 (1.03–2.01)	1.62 (0.98–2.67)	0.80 (0.30–2.09)

Archives of Gerontology and Geriatrics 72 (2017) 39–44

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Longitudinal association between diabetes and cognitive decline: The National Health and Aging Trends Study

Alexandra M.V. Wennberg[a,*], Clinton E. Hagen[a], Rebecca F. Gottesman[b], Vadim Zipunnikov[c], Christopher N. Kaufmann[d], Marilyn S. Albert[b], George W. Rebok[e,f], Judith D. Kasper[f,g], Adam P. Spira[e,f,h]

ABSTRACT

Type II diabetes mellitus (DM) is associated with increased risk of dementia; however, few studies have examined the longitudinal association between DM and cognitive outcomes in large nationally representative cohorts. We investigated these associations in 7605 participants enrolled in the National Health and Aging Trends Study, a nationally representative prospective study of Medicare beneficiaries ≥65, from 2011 to 2015. Participants or proxy respondents reported DM and dementia diagnosis, and participants completed immediate and delayed recall word list learning tests and the Clock Drawing Test. In multivariable-adjusted generalized linear mixed models, baseline DM diagnosis was associated with decline on immediate and delayed word recall and the Clock Drawing Test. In Cox proportional hazards models, DM also predicted incident dementia in older age groups at baseline. These findings further support the notion that DM is associated with cognitive outcomes, suggesting that treatment and prevention of DM may reduce the risk of these outcomes. However, more studies are needed to better understand whether DM treatments affect this relationship.

	N	B (95% CI)	p
	Immediate Word Recall		
ll ages	7177	−0.21 (−0.26, −0.15)	< 0.001
5–69	1358	−0.23 (−0.35, −0.12)	< 0.001
0–74	1509	−0.34 (−0.45, −0.24)	< 0.001
5–79	1439	−0.22 (−0.35, −0.09)	< 0.001
0–84	1421	0.02 (−0.13, 0.16)	0.825
5–89	873	−0.26 (−0.46, −0.07)	0.008
0+	577	−0.13 (−0.50, 0.24)	0.490
	Delayed Word Recall		
ll ages	7177	−0.24 (−0.31, −0.16)	< 0.001
5–69	1358	−0.21 (−0.36, −0.06)	0.005
0–74	1509	−0.46 (−0.59, −0.32)	< 0.001
5–79	1439	−0.21 (−0.37, −0.04)	0.014
0–84	1421	−0.02 (−0.20, 0.15)	0.783
85–89	873	−0.22 (−0.46, 0.01)	0.060
90+	577	−0.17 (−0.48, 0.13)	0.269
	Clock Drawing Test		
All ages	7177	−0.11 (−0.18, −0.04)	0.003
65–69	1358	−0.12 (−0.20, −0.04)	0.005
70–74	1509	−0.10 (−0.22, 0.02)	0.110
75–79	1439	−0.11 (−0.25, 0.03)	0.136
80–84	1421	−0.06 (−0.22, 0.11)	0.514
85–89	873	−0.15 (−0.41, 0.11)	0.248
90+	577	−0.22 (−0.64, 0.21)	0.316

Is the brain exclusively an insulin-insensitive organ?

Biochemical findings	FDG-PET
Presence of insulin Insulin receptors Neuronal expression of GLUT-4 in the brain	Insulin stimulates brain glucose metabolism in patients with impaired glucose tolerance Lowering insulin plasma concentrations below physiological levels decreases brain glucose metabolism
El Messari et al., 2002; Havrankova et al., 1978; Hill et al., 1986; Sankar et al., 2002	Bingham et al., 2002; Hirvonen et al., 2011).

Is the brain exclusively an insulin-insensitive organ?

- Organization and function of the brain, **including neuromodulatory and neurotrophic roles** (Cholerton et al., 2013; Correia et al., 2011; de la Monte and Tong, 2014;Kim and Feldman, 2012).

- **Synaptic plasticity** by modulating cell membrane expression of excitatory and inhibitory receptors

- Regulation of **neurotransmitter expression** (Cholerton et al., 2013)

- Triggering signal transduction cascades (Correia et al., 2011)

- **Increasing cortical cerebral glucose metabolism in brain regions important for learning and memory** (de la Monte and Tong, 2014; Kim and Feldman, 2012).

- **Intranasal insulin administration improves memory function** in both human and animal studies (Benedict et al., 2004, 2008; McNay et al., 2010).

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European Journal of Pharmacology 490 (2004) 5–12
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The source of cerebral insulin

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Accepted 27 February 2004

Abstract

Insulin and its receptor are found throughout the central nervous system (CNS). Insulin administered into the CNS can exert powerful effects, yet the consensus is that little or no insulin is produced in the CNS. Therefore, CNS insulin is essentially dependent on the ability of peripheral insulin to cross the blood–brain barrier (BBB). Insulin is known to cross the BBB by a saturable transport mechanism. This transporter shows some thematic similarities to other transporters for peptides or regulatory proteins. It is unevenly distributed throughout the CNS with the olfactory bulbs having the fastest transport rate of any brain region. It is partially saturated at euglycemic levels, suggesting that its main signaling function occurs at physiological blood levels, rather than as a brake to hypoglycemic events. One probable function of the BBB transporter is to allow CNS insulin to act as a counter-regulatory hormone to peripheral insulin. The transporter is regulated, with the transport rate of insulin being altered during development and by fasting, obesity, hibernation, diabetes mellitus and Alzheimer's disease. Enhancement of insulin transport by lipopolysaccharide could be the basis for the insulin resistance seen with bacterial infections. Inhibition of insulin transport across the BBB by dexamethasone could be the basis for the enhanced appetite seen with glucocorticoid treatments. Insulin itself also has effects on the BBB, altering enzymatic and transporter functions. Overall, BBB transport of insulin provides a mechanism for peripheral insulin to act within the CNS as a regulatory peptide.
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Biochimica et Biophysica Acta 1863 (2017) 1078–1089

Is Alzheimer's a Form of Diabetes?

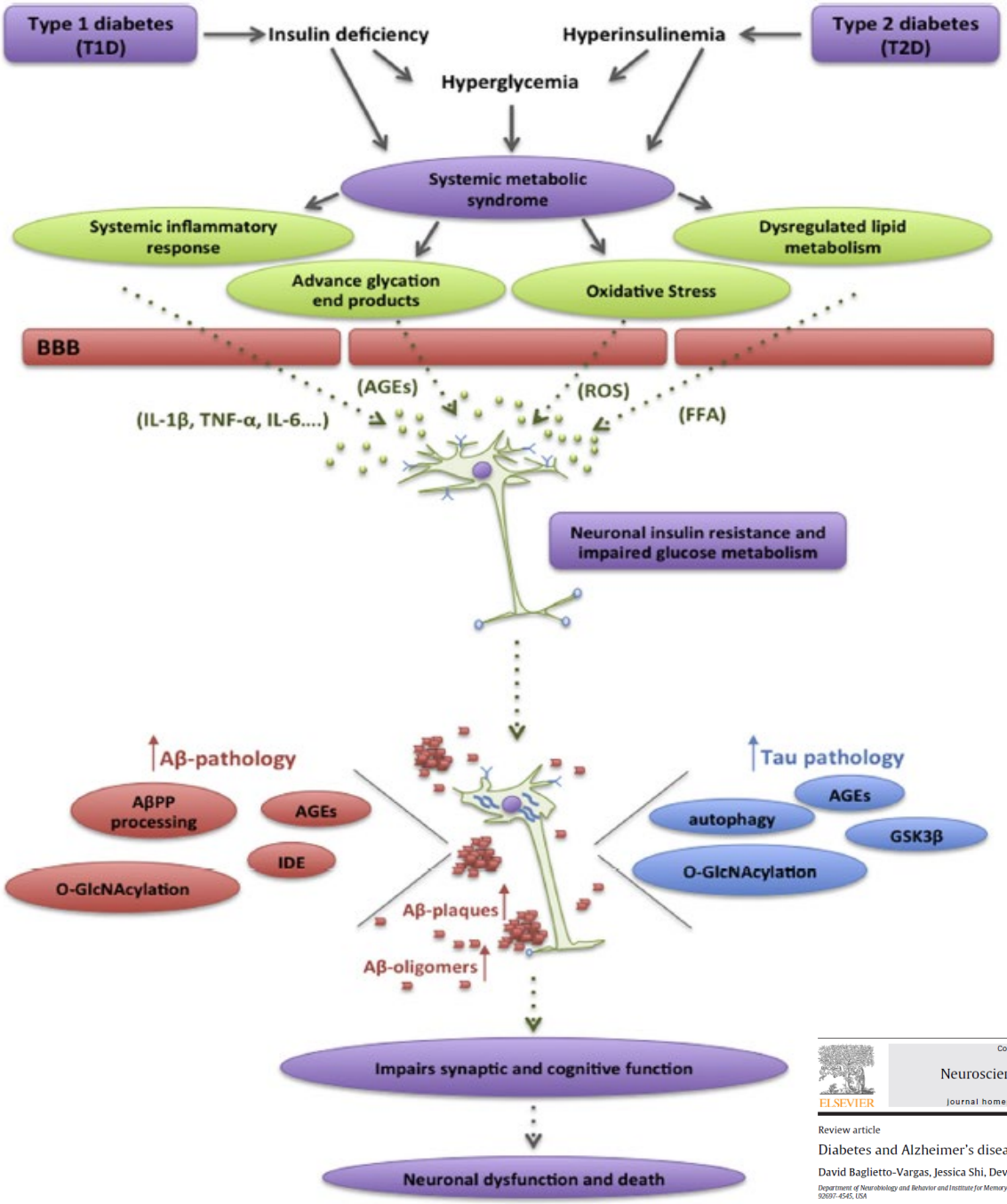
By Catherine Guthrie Thursday, Oct. 18, 2007

"Scientists report new evidence linking insulin to a disorder of the brain: when the brain prevents the hormone from acting properly, the ensuing chemical imbalance may help trigger Alzheimer's disease. **The correlation is so strong that some researchers are calling Alzheimer's disease "type 3" diabetes".**

Article history:
Received 29 June 2016
Received in revised form 7 August 2016
Accepted 17 August 2016
Available online 25 August 2016

Keywords:
Alzheimer's disease
Obesity
BMI
diabetes
Type-3-Diabetes
MCI amyloid beta
Tau
GSK3β

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Review article

Diabetes and Alzheimer's disease crosstalk

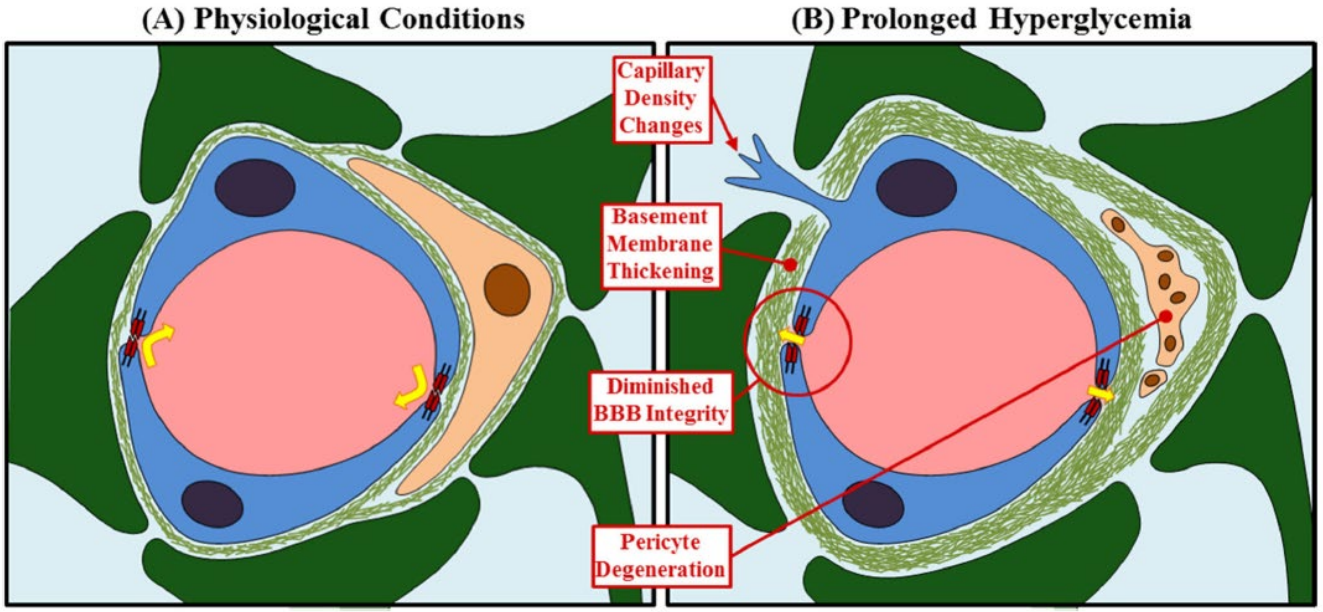
David Baglietto-Vargas, Jessica Shi, Devin M. Yaeger, Rahasson Ager, Frank M. LaFerla*
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J Neuroimmune Pharmacol (2017) 12:593–601
DOI 10.1007/s11481-017-9752-7

INVITED REVIEW

Blood Brain Barrier Injury in Diabetes: Unrecognized Effects on Brain and Cognition

Marina Bogush[1] · Nathan A. Heldt[1] · Yuri Persidsky[1,2]



Hyperglycemia induces thickening of the basement membrane, increases proliferation of endothelial cells, and promotes permeability.

These changes are associated with a greater incidence of encephalopathy and neurodegenerative disease, as well as worsened prognosis in comorbidities such as stroke.

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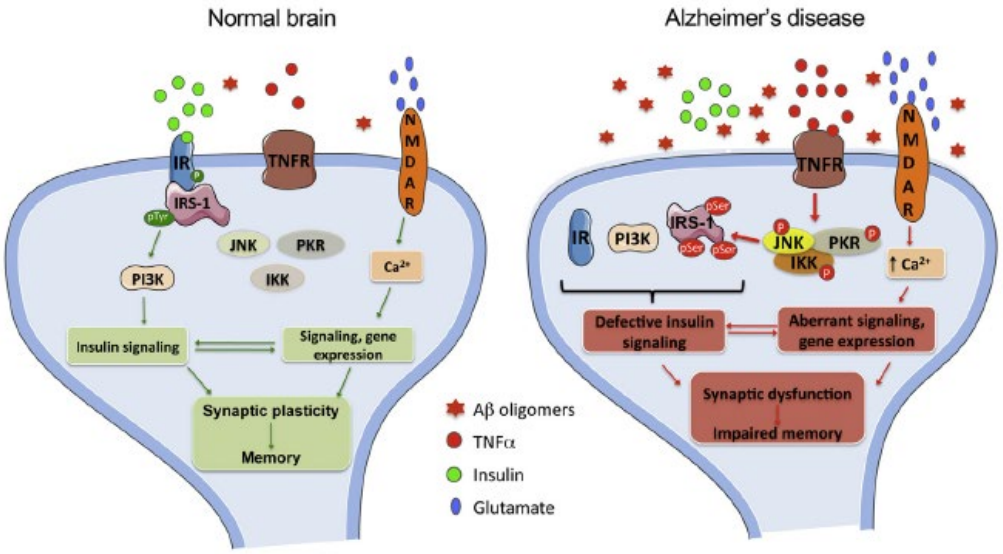
Alzheimer's & Dementia 10 (2014) S26–S32

Alzheimer's & Dementia

How does brain insulin resistance develop in Alzheimer's disease?

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Alzheimer's disease

Accumulation of amyloid-b (Ab) oligomers leads to increased TNF-a levels and activation of stress kinases, resulting in inhibitory serine phosphorylation of IRS-1.

Ab oligomers instigate additional removal of IRs from the cell surface and redistribution to the cell body. These combined events **block neuronal insulin signaling.**

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Diabetes Research and Clinical Practice

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Hypoglycemia is associated with dementia in elderly patients with type 2 diabetes mellitus: An analysis based on the Korea National Diabetes Program Cohort

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A B S T R A C T

Aim: Although hypoglycemia is associated with cognitive dysfunction, including dementia, in patients with type 2 diabetes mellitus (DM), the data are equivocal. The purpose of this study was to investigate the association between hypoglycemia, dementia, and other cognitive dysfunctions.

Methods: This was a prospective observational study based upon the Korea National Diabetes Program (KNDP). Among the 4540 participants in the KNDP cohort, individuals aged ⩾60 years without any history of hypoglycemia or cognitive dysfunction ($n = 1957$) were included. Nationally representative data from the Health Insurance Review and Assessment Service of Korea claim database were used to obtain a more precise determination of patient outcome.

Results: During a mean follow-up period of 3.4 ± 0.9 years, 118 subjects experienced hypoglycemia-related events. The incidence of dementia and cognitive dysfunction was 7.5 cases per 1000 person-years (PY) and 0.61 cases per 1000 PY, respectively. In the subjects who experienced hypoglycemic events (relative to those who did not), the incidence of dementia was significantly higher ($P = 0.0139$), but the incidence of cognitive dysfunction was not ($P = 0.1106$). Hypoglycemic events were associated with dementia (HR, 2.689; 95% CI, 1.080–6.694, $P = 0.0335$) following multiple adjustments. There was also a significant

Table 2 – Hypoglycemic episodes increase the risk of cognitive decline and dementia among T2DM patients.

Study	Population (Nation)	Impact of hypoglycemia
Clinical evidence of hypoglycemia and cognitive decline		
Duning et al. [38]	Germany N = 4635 patients in surgical intensive care unit, who were treated by tight glycemic control protocol	Hypoglycemia aggravate critical illness-induced neurocognitive dysfunction Hypoglycemia was associated with worse neurocognitive dysfunction test results
Aung et al. [25]	UK N = 1066 60–75 years old *Hypoglycemia over a person's lifetime and in the year prior to cognitive testing was assessed using a previously validated self-completion questionnaire	Self-reported history of severe hypoglycemia was associated with poorer late-life cognitive ability, and the cognitive ability decline was independent of prior/premorbid cognitive ability
Clinical evidence of hypoglycemia and dementia		
Bruce et al. [39]	Australia N = 302 Age more than 70	Sever hypoglycemia increase the risk of cognitive impairment (HR 3.00, 95% CI 1.06–8.48) inability to self-manage medications: (HR 4.17, 95% CI 1.43–12.13)
	Sex% male/female: 48.3/51.7 Follow-up: a median 1.6 (1.4–1.8) years later *Severe hypoglycemia was determined from self-reports, physician assessments and records of health service use for hypoglycemia	No significant associations between historical hypoglycemia and cognitive decline
Whitmer et al. [26]	USA N = 166,677 Mean age: 65 Sex% male/female: 54.5/45.5 22-year follow-up for hypoglycemia episode	A 2.39% increase in risk of dementia per year of follow-up for patients with history of hypoglycemia vs. patients without hypoglycemia 1 episode (HR, 1.26; 95% CI, 1.10–1.49) 2 episodes (HR, 1.80; 95% CI, 1.37–2.36) 3 or more episodes (HR, 1.94; 95% CI, 1.42–2.64).Fully adjusted HRs: 1 episode (HR, 1.42; 95% CI, 1.12–1.78) 2 or more episodes (HR, 2.36; 95% CI, 1.57–3.55)
Yaffe et al. [40]	USA N = 783 Mean age: 74 Sex% male/female: 52.4/47.6 12-year follow-up period	A 2-fold increased risk of dementia compared with those who without hypoglycemic event 34.4% vs. 17.6% (multivariate-adjusted HR, 2.1; 95% CI, 1.0–4.4)
Lin and Sheu [22]	Taiwan N = 15,404 Mean age:64.2 Sex% male/female: 45.1/54.9	A 3 times more likely to develop dementia (HR 2.76) in those who experienced hypoglycemic event Incidence rate of dementia Patients with hypoglycemia: 29.9 per 1000 person-years (95% CI 22.1–39.2) Patients without hypoglycemia: 11.1 per 1000 person-years (95% CI 10.3–11.8) Rate ratio (RR) values for dementia in subjects with hypoglycemia compared to those without hypoglycemia Crude RR: 2.76 (95% CI 2.06–3.70) age- and gender-adjusted RR: 1.60 (95% CI 1.19–2.14)

Diabetologia (2017) 60:971–979
DOI 10.1007/s00125-017-4233-3

ARTICLE

Cognitive deficits associated with impaired awareness of hypoglycaemia in type 1 diabetes

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Methods A total of 68 adults with type 1 diabetes were included: 33 had impaired and 35 had normal awareness of hypoglycaemia, as confirmed by formal testing. The groups were matched for age, sex and diabetes duration. Cognitive tests of verbal memory, object-location memory, pattern separation, executive function, working memory and processing speed were administered.

Conclusion

The present study has demonstrated significant impairments in learning, memory, pattern separation and aspects of executive function (specifically, planning ability) in adults with type 1 diabetes who have IAH. These findings suggest that recurrent SH may have a role in promoting cognitive deficits in people with impaired hypoglycaemia awareness.

Cognitive test	IAH group		NAH group		*p*	Cohen's *d* (95% CI)
	n[a]	Mean ± SD	*n*[a]	Mean ± SD		
Verbal memory test[b]						
Distraction recall	32	6.4 ± 2.3	35	8.3 ± 3.1	0.007	−0.70 (−1.18, −0.2)
Post-distraction recall	32	12.3 ± 2.6	35	13.2 ± 2.6	0.179	−0.34 (−0.83, 0.14)
Delayed recall	32	12.4 ± 2.2	32	13.7 ± 2.1	0.018	−0.62 (−1.11, −0.10)
Objects in grid[b]	30	7.9 ± 3.1	34	9.9 ± 4.7	0.043	−0.55 (−1.05, −0.05)
Pattern separation[b]	28	0.19 ± 0.20	33	0.35 ± 0.17	0.001	−0.86 (−1.39, −0.34)
Digit span backwards[b]	29	9.2 ± 2.7	33	9.9 ± 2.8	0.328	−0.25 (−0.76, 0.25)
Coding[b]	27	29.2 ± 8.1	34	34.4 ± 11.6	0.051	−0.52 (−1.02, 0.01)
Tower test[c]						
Total moves	24	57.5 ± 9.4	25	54.0 ± 6.6	0.142	0.43 (−0.13, 1.0)
Log illegal moves	24	0.46 ± 0.29	25	0.29 ± 0.31	0.057	0.57 (0, 1.14)

[a] Number of valid responses

[b] Higher scores indicate better performance

[c] Higher scores indicate poorer performance

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Diabetes Research and Clinical Practice

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International Diabetes Federation



Review

Association between hypoglycemia and dementia in patients with type 2 diabetes

Yi-Jing Sheen [a], Wayne H.H. Sheu [b,c,d,e,*]

- **Links between hypoglycemia and dementia:**
- post-hypoglycemic encephalopathy;
- synaptic dysfunction;
- permanent neuronal damage.

- **Specific structural changes after hypoglycemic brain injury:**
- MRI and CT findings report selective vulnerability to hypos in the hyppocampal area, temporal area, cerebral cortex, substantia nigra and basal ganglia.

- **Ischemic and cerebral vascular events caused by hypoglycemia:**
- hypos have been shown to induce transient ischemic and focal neurologic deficit, and may result in neuronal cell death
- Endothelial dysfunction during hypos may contribute to cerebral ischemia

Effect of a Long-Term Intensive Lifestyle Intervention on Cognitive Function: Action for Health in Diabetes Study

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OBJECTIVES: To assess whether randomization to 10 years of lifestyle intervention to induce and maintain weight loss improves cognitive function.

DESIGN: Randomized controlled clinical trial.
PARTICIPANTS: Individuals with T2DM aged 45 to 76 (N = 3,751).
INTERVENTION: Intensive lifestyle intervention (ILI) for weight loss through reduced caloric intake and increased physical activity compared with a control condition of diabetes support and education (DSE).
RESULTS: **Assignment to lifestyle intervention was not associated with significantly different cognitive function** than assignment to diabetes support and education.

Cochrane Library
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We found no good evidence that any specific treatment or treatment strategy for Type 2 diabetes can prevent or delay cognitive impairment.

Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia (Review)

Areosa Sastre A, Vernooij RWM, González-Colaço Harmand M, Martínez G

Metformin, Lifestyle Intervention, and Cognition in the Diabetes Prevention Program Outcomes Study

José A. Luchsinger,[1] Yong Ma,[2] Costas A. Christophi,[2] Hermes Florez,[3] Sherita H. Golden,[4] Helen Hazuda,[5] Jill Crandall,[6] Elizabeth Venditti,[7] Karol Watson,[8] Susan Jeffries,[7] Jennifer J. Manly,[1] and F. Xavier Pi-Sunyer,[1] for the Diabetes Prevention Program Research Group

https://doi.org/10.2337/dc16-2376

OBJECTIVE

We examined the association of the Diabetes Prevention Program (DPP) intervention arms (lifestyle intervention, metformin, and placebo) with cognition in the DPP Outcomes Study (DPPOS). We also examined metformin use, incident type 2 diabetes, and glycemia as exposures.

RESEARCH DESIGN AND METHODS

The DPP lasted 2.8 years, followed by a 13-month bridge to DPPOS. Cognition was assessed in DPPOS years 8 and 10 (12 and 14 years after randomization) with the Spanish English Verbal Learning Test (SEVLT), letter fluency and animal fluency tests, Digit Symbol Substitution Test (DSST), and a composite cognitive score.

RESULTS

A total of 2,280 participants (749 lifestyle, 776 metformin, and 755 placebo) aged 63.1 ± 10.7 years underwent cognitive assessments; 67.7% women, 54.6% non-Hispanic white, 20.7% non-Hispanic black, 14.6% Hispanic, 5.5% American Indian, and 4.6% Asian; 26.6% were homozygous or heterozygous for APOE-ε4. At the time of cognitive assessment, type 2 diabetes was higher in the placebo group (57.9%; $P < 0.001$) compared with lifestyle (47.0%) and metformin (50.4%). Metformin exposure was higher in the metformin group (8.72 years; $P < 0.001$) compared with placebo (1.43 years) and lifestyle (0.96 years). There were no differences in cognition across intervention arms. Type 2 diabetes was not related to cognition, but higher glycated hemoglobin at year 8 was related to worse cognition after confounder adjustment. Cumulative metformin exposure was not related to cognition.

Diabetes Care Publish Ahead of Print, published online May 12, 2017

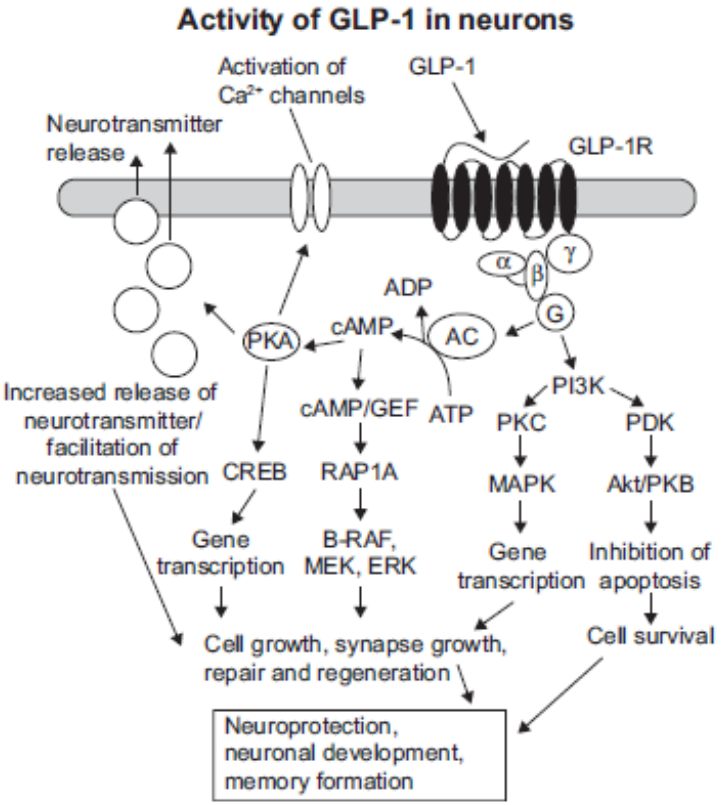
Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases

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Abstract

The incretin hormone glucagon-like peptide 1 (GLP-1) has many effects in the body. It is best known for the 'incretin effect', facilitating insulin release from the pancreas under hyperglycaemic conditions. Building on this, GLP-1 mimetics have been developed as a treatment for type 2 diabetes. In the course of monitoring of patients, it has become apparent that GLP-1 mimetics have a range of other physiological effects in the body. In preclinical trials, a substantial body of evidence has been built that these mimetics have neuroprotective and anti-inflammatory effects. GLP-1 also has very similar growth-factor-like properties to insulin, which is presumably the underlying basis of the neuroprotective effects. In preclinical studies of Alzheimer's disease (AD), Parkinson's disease (PD), stroke and other neurodegenerative disorders, it has been shown that most GLP-1 mimetics cross the blood–brain barrier and show impressive neuroprotective effects in numerous studies. In animal models of AD, GLP-1 mimetics such as exendin-4, liraglutide and lixisenatide have shown protective effects in the CNS by reducing β-amyloid plaques, preventing loss of synapses and memory impairments, and reducing oxidative stress and the chronic inflammatory response in the brain. In animal models of PD, exendin-4 showed protection of dopaminergic neurons in the substantia nigra and prevention of dopamine loss in the basal ganglia while preserving motor control. These encouraging findings have spawned several clinical trials, some of which have shown encouraging initial results. Therefore, GLP-1 mimetics show great promise as a novel treatment for neurodegenerative conditions.



Statins and their effect on cognition: Let's clear up the confusion

Jérémie M. Gauthier, BScPharm; Anne Massicotte, BPharm, MSc

A meta-analysis of 4 cohort trials (*n* > 4019) demonstrated a lower risk for mild cognitive impairment associated with statin use in patients with intact cognition at baseline (relative risk [RR],0.66; 95% confidence interval [CI], 0.51-0.86).

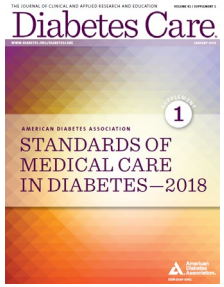
One RCT (*n* = 20,536) from the systematic review revealed no difference in incidence of cognitive impairment between statin and placebo
use (RR, 0.98; 95% CI, 0.93 to 1.03).

Three RCTs (*n* = 38,360) in patients with normal cognition at baseline did not find a significant difference between the statins and placebo groups for the development
of cognitive impairment.

KNOWLEDGE INTO PRACTICE



- Despite some case reports of statin-induced memory loss and confusion, statins do not appear to be associated with an increased risk of cognitive impairment.
- If cognitive impairment is suspected in a patient taking a statin, look for other medications that may be contributing.
- It is important to highlight the cardiovascular benefits of statins in patients concerned about cognitive impairment effects.
- With the current level of evidence, especially from the analyses of randomized controlled trials, statins cannot be recommended for the prevention or treatment of dementia.



11. Older Adults: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S119–S125 | https://doi.org/10.2337/dc18-S011

Consider the **assessment of medical, psychological functional, and social geriatric domains** to provide a framework to determine targets and therapeutic approaches for diabetes management.

Screening for geriatric syndromes may be appropriate in older adults experiencing **limitations in their basic and instrumental activities of daily living** as they may affect diabetes self-management and be related to health-related quality of life.

Hypoglycemia should be avoided in older adults with diabetes.

When clinicians are managing patients with cognitive dysfunction, it is critical to **simplify drug regimens** and to **involve caregivers** in all aspects of care.

11. Older Adults: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S119–S125 | https://doi.org/10.2337/dc18-S011

Different patient categories have been proposed for diabetes management:

1. **A stable patient**: continue with the patient's previous regimen, with a focus on the prevention of **hypoglycemia** and the management of hyperglycemia using blood

Table 11.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes (2)

Patient characteristics/health status	Rationale	Reasonable A1C goal†	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

values in the upper level of the desired target range.

3. **A dying patient**: for patients with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as patients are unlikely to have any oral intake. In patients with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

Standards of medical care in diabetes – 2018, ADA



Il regime basal-bolus può esser appropriato nei soggetti anziani con conservate capacità funzionali e cognitive.

Particolare importanza nel soggetto anziano riveste l'educazione del paziente o del *caregiver* alla gestione della terapia insulinica.

Vi è evidenza che pazienti anziani con decadimento cognitivo non sappiano che cosa fare in caso di ipoglicemia e dimostrino una minor capacità di gestione della malattia diabetica (Hewitt J 2011).

2015 American Geriatrics Society **Beers Criteria** for Potentially Inappropriate Medication Use in Older Adults

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting; refers to sole use of short- or rapid-acting insulins to manage or avoid hyperglycemia in absence of basal or long-acting insulin; does not apply to titration of basal insulin or use of additional short- or rapid-acting insulin in conjunction with scheduled insulin (i.e., correction insulin)	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long-duration Chlorpropamide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion	Avoid	High	Strong
Glyburide	Glyburide: higher risk of severe prolonged hypoglycemia in older adults			

European Geriatric Medicine 1 (2010) 45–51

Available online at ScienceDirect www.sciencedirect.com

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Pharmacology applied to geriatric medicine

STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age

D. O'Mahony [a,*,b], P. Gallagher [a], C. Ryan [c], S. Byrne [c], H. Hamilton [a], P. Barry [a], M. O'Connor [a], J. Kennedy [c]



STOPP (Screening Tool of Older People's Potentially inappropriate Prescriptions)

Endocrine system

Glibenclamide or chlorpropamide with type 2 diabetes mellitus *(risk of prolonged hypoglycaemia)*

Betablockers in those with diabetes mellitus and frequent hypoglycaemic episodes i.e. ≥1 episode per month *(risk of masking hypoglycaemic symptoms)*

Oestrogens with a history of breast cancer or venous thromboembolism *(increased risk of recurrence)*

Oestrogens without progestogen in patients with intact uterus *(risk of endometrial cancer)*

START (Screening Tool to Alert to Right Treatment)

Endocrine system

Metformin with type 2 diabetes ± metabolic syndrome (in the absence of renal impairment[a])

ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy i.e. overt urinalysis proteinuria or micoralbuminuria (>30 mg/24 hours) ± serum biochemical renal impairment[a]

Antiplatelet therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present (hypertension, hypercholesterolaemia, smoking history)

Statin therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present

[a] Estimated GFR < 50 ml/minute.

Punti chiave

L'encefalo non è totalmente insulino-indipendente

Gestione **multidisciplinare** del paziente diabetico anziano

Garantire una buona **QoL**

Indispensabile una **valutazione multidimensionale geriatrica** e una valutazione delle sindromi geriatriche se riscontro di:

1. non aderenza alla terapia;

2. frequenti episodi di ipoglicemia;

3. deterioramento del compenso glicemico in assenza di una causa evidente

Interagire con il **caregiver effettivo**

Evitare le **ipoglicemie**



Grazie per l’attenzione

