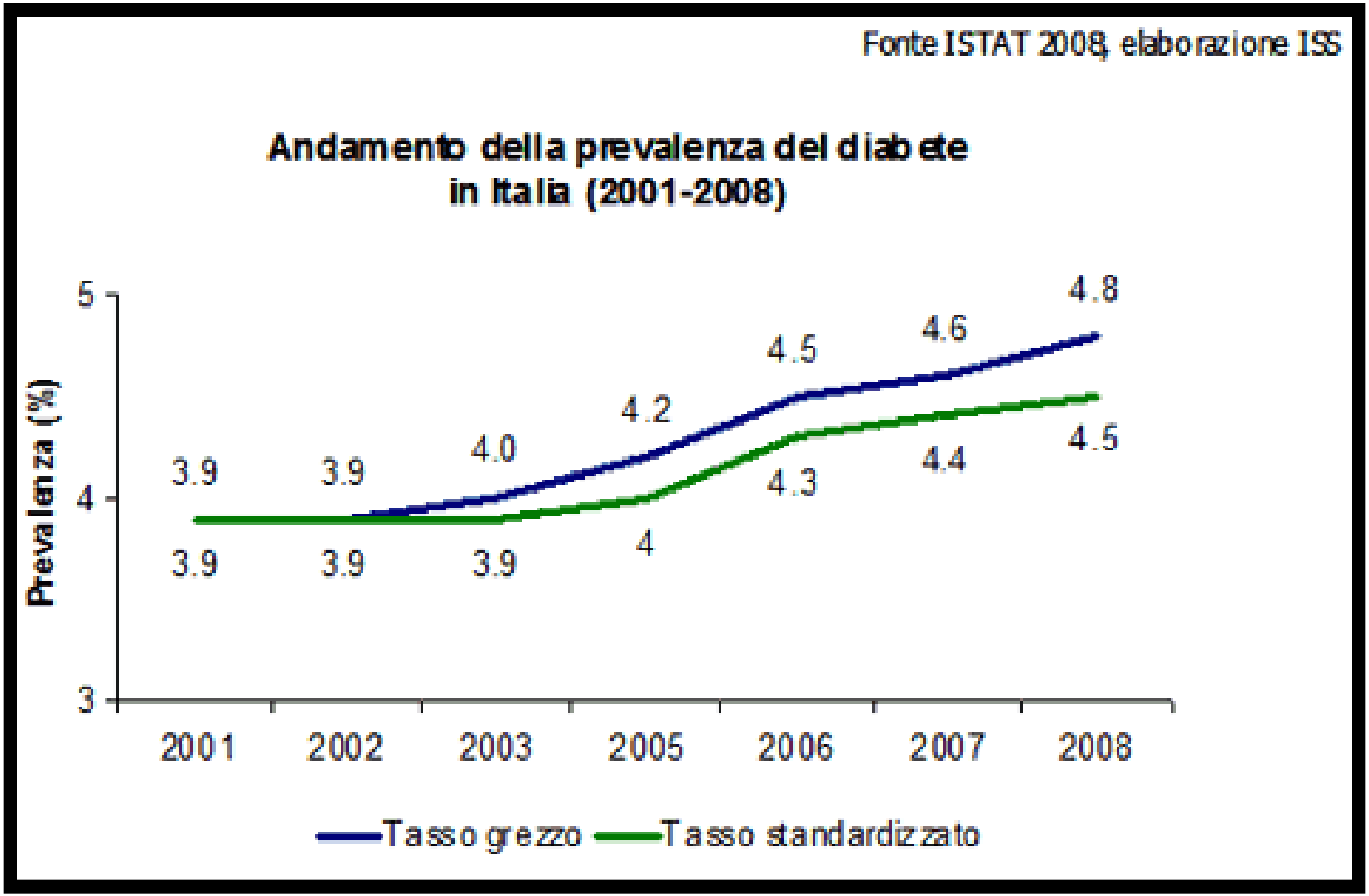
Rapporto tra diabete e demenza: il punto

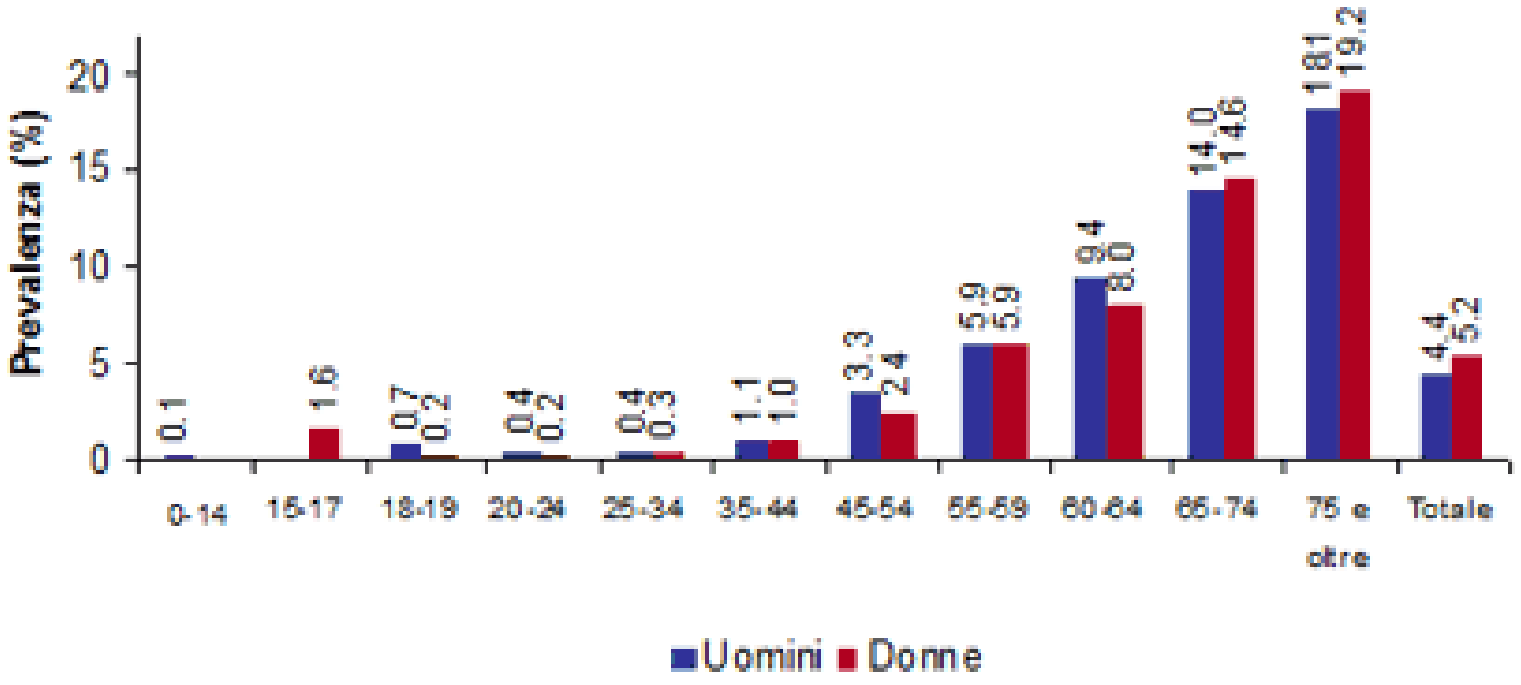
Luca ROZZINI

Fonte ISTAT 2008, elaborazione ISS

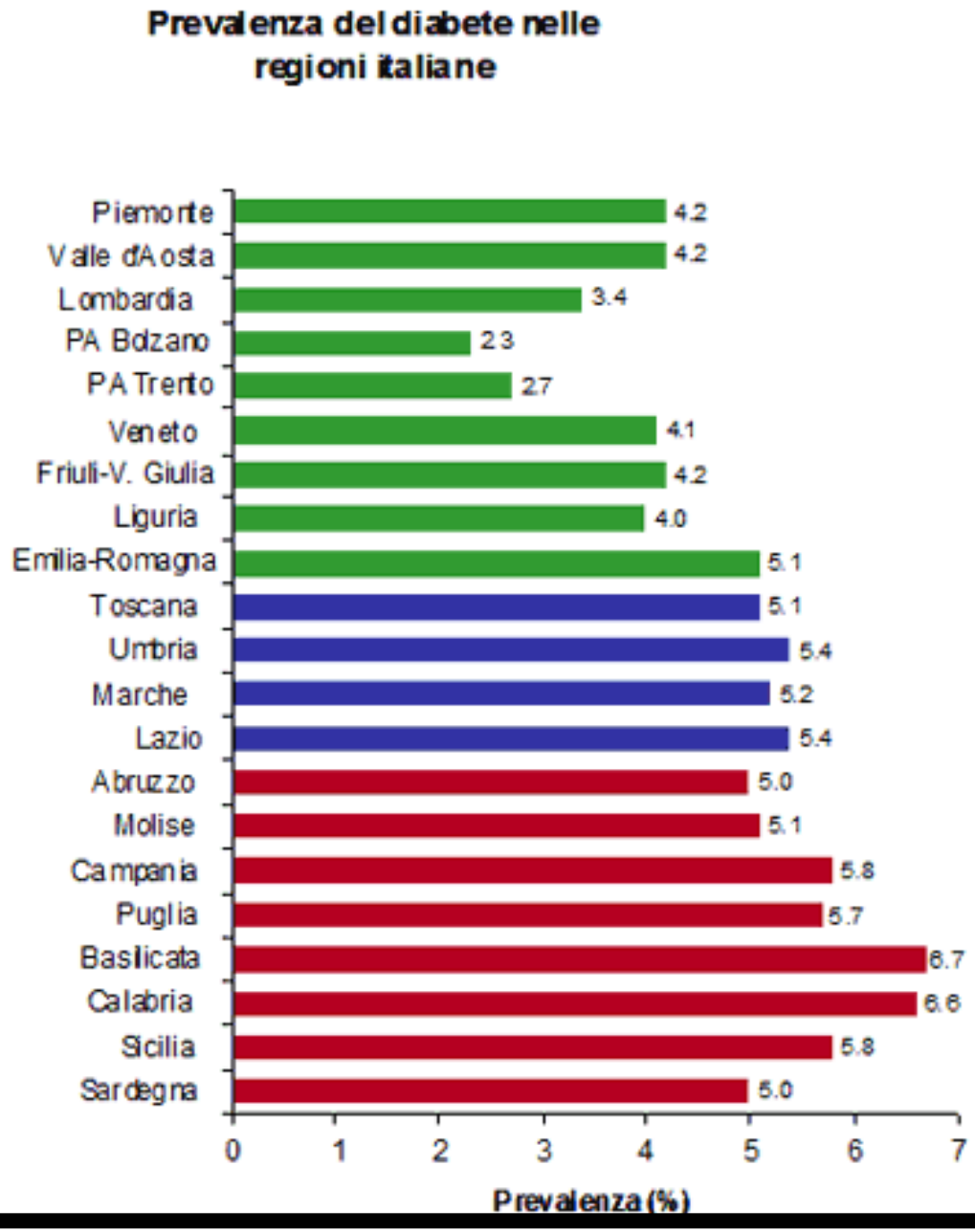


Fonte ISTAT 2008, elaborazione ISS

Prevalenza del diabete per sesso e fasce di età



Fonte ISTAT 2008, elaborazione ISS



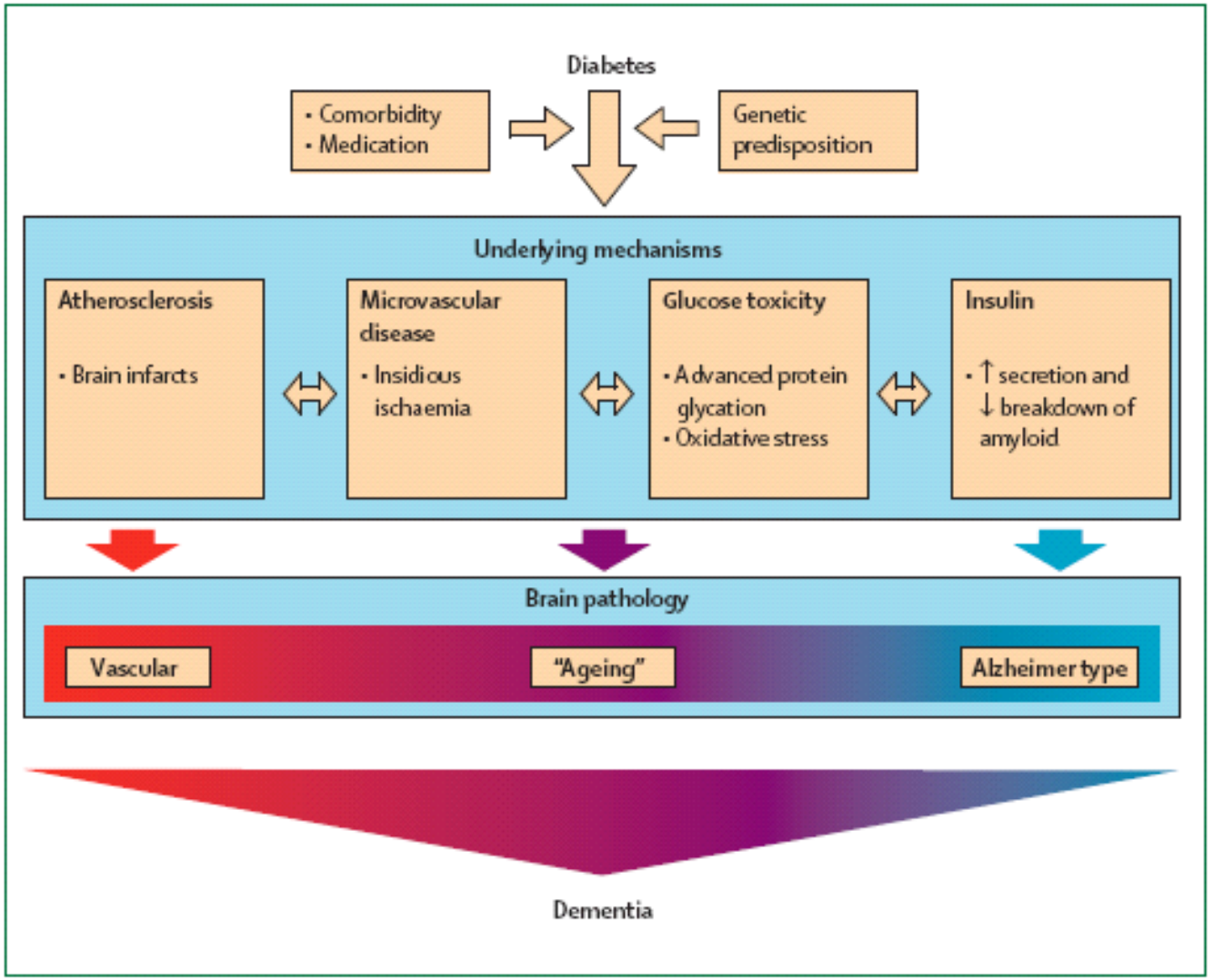


Figure 1: **Proposed pathophysiological mechanisms linking diabetes to changes in the brain and dementia**
Diabetes and its comorbid conditions are associated with an increased risk of atherosclerosis and stroke, leading to vascular pathology in the brain. Glucose-mediated toxicity can lead to microvascular abnormalities and more widespread changes in cognition and brain structure, referred to as accelerated brain ageing. Additionally diabetes and its treatment might interfere with amyloid metabolism, giving rise to Alzheimer's type pathology.

Gender differences in memory and learning in children with insulin-dependent diabetes mellitus (IDDM) over a 4-year follow-up interval.

Fox MA, et al. J Pediatr Psychol 2003; 28:569-78.

CONCLUSIONS: Subtle difficulties were found in learning related to longer disease duration for a predominantly middle-class group of children with diabetes over a 4-year follow-up interval.

The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function.

Awad N et al J Clin Exp Neuropsychol 2004; 26:1044-80.

Cognitive deficits are observed in older people with **glucose intolerance** or **untreated diabetes** but these deficits appear to be attenuated by treatments that improve glycemic control. Cognitive decrements in treated type 2 diabetic patients are most consistently observed on measures of **verbal memory** (35% of the measures) and **processing speed** (45% of the measures) while preserved function is observed on measures of visuospatial, attention, semantic and language function.

Type 2 diabetes mellitus, cognitive impairment and dementia.

Stewart R and Liolitsa D. *Diabet Med 1999; 16:93-112*

RESULTS: We found evidence of cross-sectional and prospective associations between Type 2 DM and cognitive impairment, probably both for **memory and executive function.**

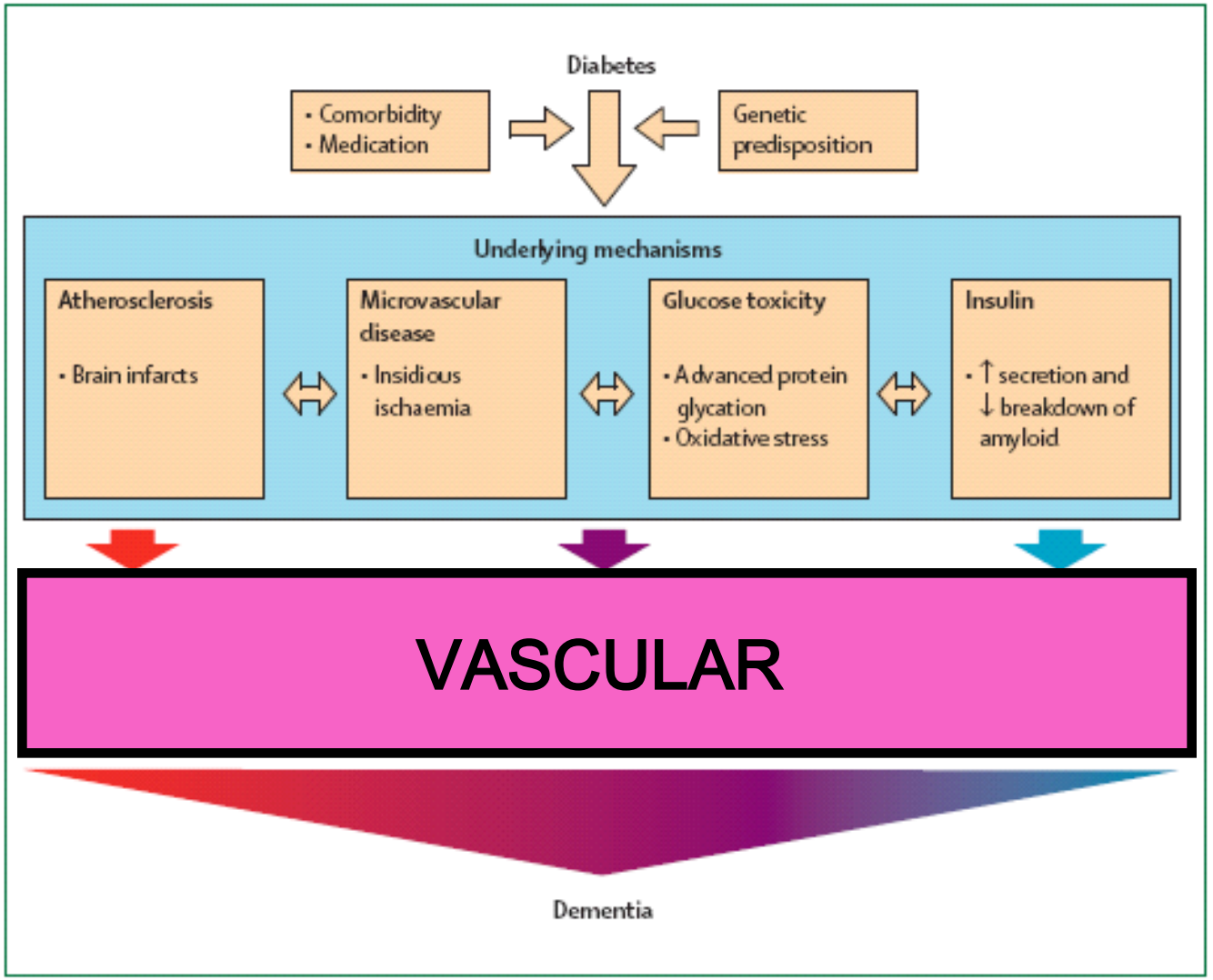


Figure 1: Proposed pathophysiological mechanisms linking diabetes to changes in the brain and dementia
Diabetes and its comorbid conditions are associated with an increased risk of atherosclerosis and stroke, leading to vascular pathology in the brain. Glucose-mediated toxicity can lead to microvascular abnormalities and more widespread changes in cognition and brain structure, referred to as accelerated brain ageing. Additionally diabetes and its treatment might interfere with amyloid metabolism, giving rise to Alzheimer's type pathology.

Il diabete si associa ad alterazioni neuropatologiche nei circuiti microvascolari che includono l'angiopatia amiloide e l'ispessimento della membrana basale.

Thickened cerebral cortical capillary basement membranes in diabetics.
Johnson PC, Brenedel K, Meezan E.
Arch Pathol Lab Med 1982; 106: 214–17.

Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu- Asia Aging Study.
Peila R, Rodriguez BL, Launer LJ. Diabetes 2002; 51: 1256–62.

Effect of vascular lesions on cognition in Alzheimer's disease: a community- based study.

Riekse RG, Leverenz JB, McCormick W et al. J Am Geriatr Soc 2004; 52: 1442–8.

On cerebral magnetic resonance imaging (MRI), white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). These lesions are frequently concomitant with Alzheimer-related neuropathology (senile plaques and NFTs) and contributes to cognitive impairment in AD subjects

Cognition and diabetes: a lifespan perspective.

Lancet Neurology 2008; 7:184-190.
Biessels GJ et al.

Structural brain imaging studies in adults (**without dementia**) with type 1 diabetes report subtle abnormalities, in particular lower density of the cortical grey matter and lower total cerebral volume compared with age-matched controls.

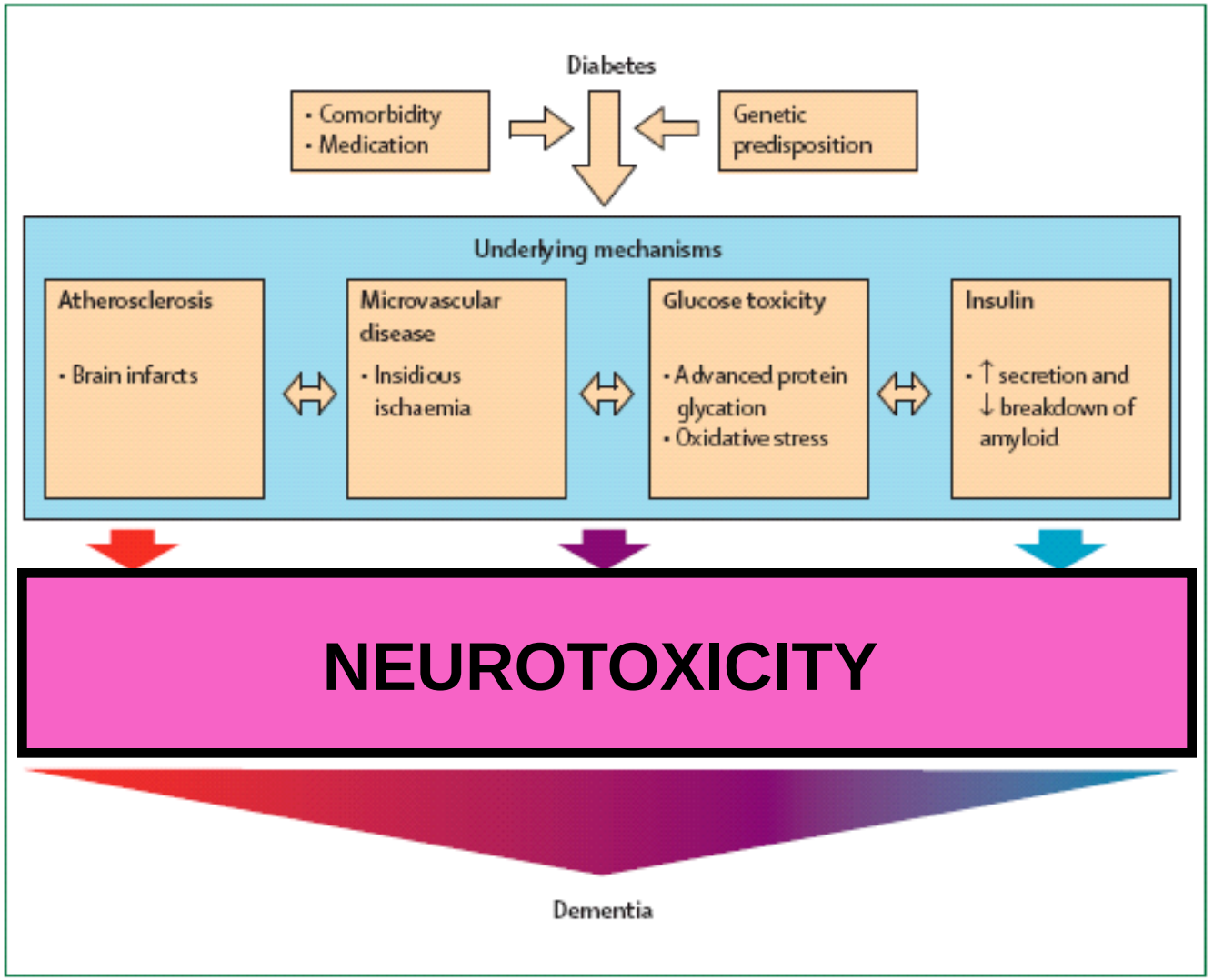


Figure 1: Proposed pathophysiological mechanisms linking diabetes to changes in the brain and dementia
Diabetes and its comorbid conditions are associated with an increased risk of atherosclerosis and stroke, leading to vascular pathology in the brain. Glucose-mediated toxicity can lead to microvascular abnormalities and more widespread changes in cognition and brain structure, referred to as accelerated brain ageing. Additionally diabetes and its treatment might interfere with amyloid metabolism, giving rise to Alzheimer's type pathology.

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

Hiroyuki Umegaki, Age and Ageing 2010; 39: 8–10

High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation end products, which have potentially toxic effects on neurons.

Diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic.

In assenza di patologie i livelli di glucosio nel sangue sono mantenuti entro uno stretto intervallo; questo equilibrio è regolato soprattutto dagli ormoni pancreatici: in particolare all'aumento della glicemia si associa conseguente rilascio in circolo di insulina. L'aumento di insulina a sua volta stimola il trasporto e l'utilizzazione del glucosio da parte dei tessuti periferici (in particolar modo il fegato, i muscoli scheletrici e il tessuto adiposo).
L'iperglicemia persistente stimola il pancreas a secernere quantità maggiori di insulina, determinando così iperinsulinemia.
L'insulino-resistenza è una condizione caratterizzata da una diminuzione degli effetti biologici dell'insulina; in altri termini, è una condizione nella quale le quantità fisiologiche di insulina producono una risposta biologica ridotta, specie a livello dell'omeostasi glicemica.

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

Hiroyuki Umegaki, Age and Ageing 2010; 39: 8–10

T2DM, especially in conjunction with obesity, is characterized by insulin resistance and/or hyperinsulinaemia.
Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiological effects of circulating insulin, and often is accompanied by raised insulin levels.

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

Hiroyuki Umegaki, Age and Ageing 2010; 39: 8–10

- Iperinsulemia: aumenta la produzione di beta amiloide (Aβ).
- Diminuisce la produzione di insulin-degrading enzyme (IDE).
- IDE: degrada insulina e beta amiloide.
- Accumulo beta amiloide.

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

Hiroyuki Umegaki, Age and Ageing 2010; 39: 8–10

-Iperinsulemia: aumenta la produzione di tau fosforilata.
- Aumenta l'attività di glycogen synthase kinase-3β, che porta ad aumentata fosforilazione di proteina tau e alla formazione di neurofibrillary tangles (NFTs).

High glucose concentration: toxic effects on neurons in the brain through osmotic insults and oxidative stress.

Diabetes is associated with an increased release of inflammatory cytokines: neurotoxic.

The insulin resistance, reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE) that degrades Aβ.

Less insulin signaling may also induce increased activity of glycogen synthase kinase-3β, which leads to the enhanced phosphorylation of tau protein.

Insulin resistance syndrome and Alzheimer Disease: pathophysiologic mechanism and therapeutic implications.

Suzanne Craft. Alzheimer Dis Assoc Disord 20:298-301

Insulina normalmente non media l'ingresso di glucosio nelle cellule cerebrali ma ne modula l'ingresso in alcune specifiche aree (ippocampo, corteccia entorinale e frontale).

Insulina può influire inoltre sul rilascio di neurotrasmettitori quali acetilcolina, noradrenalina e dopamina…

Il diabete mellito risulta fattore di rischio per Demenza Vascolare, Demenza di Alzheimer e Demenza mista.

Risulta un fattore di rischio modificabile.

The paradox

Diabetes is associated with a slower rate of cognitive decline in Alzheimer disease

Sanz C. Neurology 73 October 27, 2009

Conclusions: in a cohort of community-dwelling patients with Alzheimer disease (AD), the presence of diabetes mellitus (DM) was associated **with a lower rate of cognitive decline.**

Pharmachological explanation

A possible explanation of the slower decline observed with DM is that elderly diabetic patients may have more frequently received cardiovascular medications (i.e., antihypertension drugs, low-dose aspirin, or a statin) than nondiabetic counterpart.

Notably, hypertension treatments that inhibit the renin-angiotensin system have been reported to decrease cognitive decline in diabetic patients who do not have dementia.

But…

Within the diabetic group, the rate of cognitive decline did not differ between insulin users (0.11, *p =0.68 in multivariate adjusted model) and* nonusers and patients with diet-controlled diabetes (0.12, *p = 0.65 in multivariate adjusted* model) compared with those taking antidiabetic medications.

Neuropathological explanation

Il rallentamento del declino cognitivo può essere spiegato da differenza neuropatologiche tra il paziente affetto da demenza diabetico e non.

Neuropathological explanation

Atrofia e lesioni vascolari rivelano l'eziologia mista (vascolare neurodegenerativa) del danno cerebrale in diabete tipo 2.

Studi clinici recenti evidenziano una progressione più lenta del declino cognitivo nei pazienti in AD + CVD e più veloce nei pazienti AD.

Alzheimer disease with cerebrovascular disease and vascular dementia: clinical features and course compared with Alzheimer disease

Bruandet A. et al. J Neurol Neurosurg Psychiatry 2009 80: 133-139

Cognitive decline, assessed with both MMSE and DRS scores, was significantly faster for AD than for VaD patients. The rate of decline was essentially intermediate for those who had AD+CVD.

This lower cognitive decline (measured with MMSE) is however not surprising because the decline in VaD patients is more likely to affect executive functions, which are estimated instead with an activity of daily living scale.

Neuropatologia

Atrofia e lesioni vascolari rivelano l'eziologia mista (vascolare neurodegenerativa) del danno cerebrale in diabete tipo 2.

Different Patterns of Cerebral Injury in Dementia With or Without Diabetes

Sonnen, J.A. et al Arch Neurol. 2009 66(3):315-322

Objective: To test the hypothesis that DM promotes specific neuropathologic processes that contribute to dementia and that these processes may be suppressed by antidiabetic therapy.

Design: A comprehensive neuropathologic assessment of all cases from a community-based study of incident dementia (Adult Changes in Thought Study) that underwent autopsies (n=259) and had information on DM status (n=196). Biochemical analysis was conducted on a subset of these cases with rapidly frozen brain tissue (n=57).

Demenza senza diabete (AD puro): maggiore quantità di placche di beta amiloide.

Demenza con diabete:
maggiore presenza di infarti microvascolari e concentrazione corticale di IL-6 (interleukin 6).

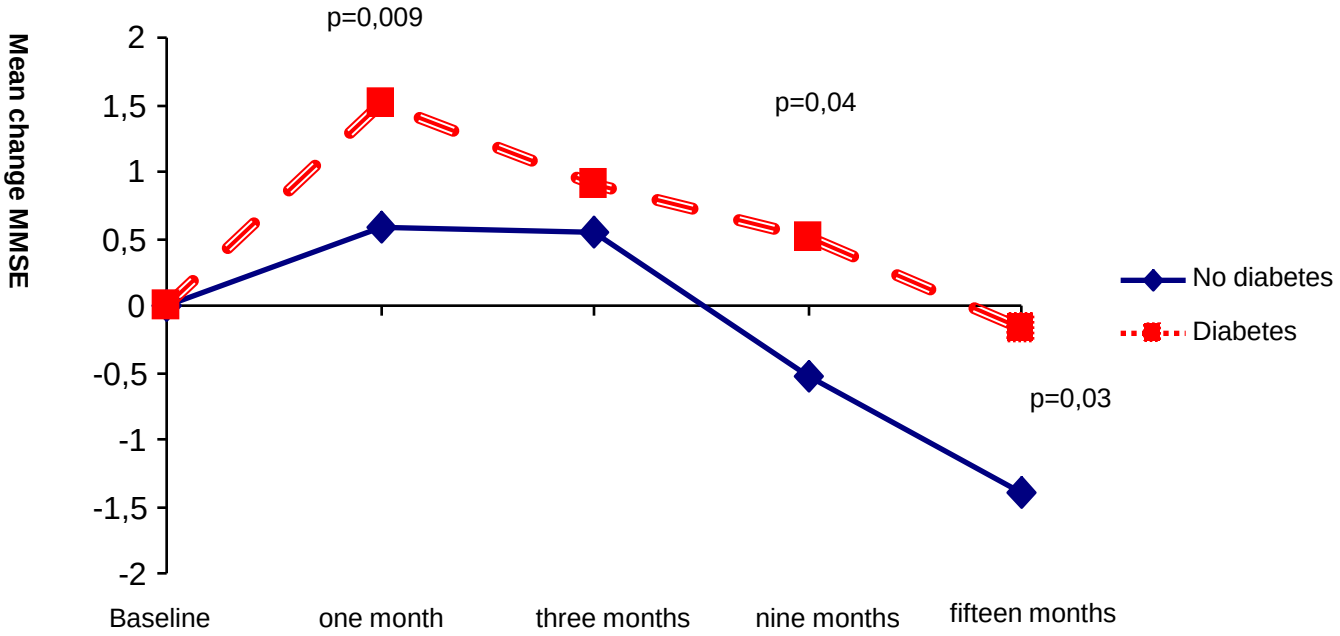
Antidiabetic drugs may delay the progression of Alzheimer's disease in diabetic patients.

Methods: At baseline, 58 patients affected by AD had diabetes mellitus treated with antidiabetic drugs, while 315 patients affected by AD were not diabetics. The evolution of cognitive decline over 15 months was evaluated by mean change in Mini Mental State Examination (MMSE) score. Demographic characteristics, comorbidity and pharmacological treatments were assessed at the first visit and the cognitive status was evaluated at baseline, after one (T1), three (T3), nine (T9) and fifteen months (T15) at the study entry. At baseline all patients started taking donepezil at different dosages as per judgement of physicians.

Table 1. Characteristics of AD patients (N=373) grouped in diabetics treated with oral antidiabetic medications (N=58) or not diabetics (N=315).

	No diabetes N=315			Diabetes N=58			
	Mean	SD	%	Mean	SD	%	*p.*
Sex, female			74			90	0,05
Age, years	76,3	7,2		77,5	6,7		NS
Education, years	5,5	2,6		4,8	2,1		NS
Duration of the disease, months	25,9	12,9		23,6	14,7		NS
MMSE	20,1	4,3		18,7	4,1		0,02
CDR	0,9	0,4		0,9	0,2		NS
IADL (functions maintained)	4,2	2,8		3,8	2,2		NS
BADL (functions maintained)	4,3	2,1		4,1	2,4		NS
NPI	14,5	12,2		18,9	11,6		0,02
GDS	3,8	3,1		3,7	2,4		NS
Number of drugs*	1,7	1,9		2,0	2,1		NS
Number of diseases**	0,8	0,9		2,2	0,8		0,000
Cholesterol mg/dl	228,1	40,1		218,2	39,1		NS
Hypertension***			40			72	0,000
Cardiovascular diseases****			18			21	NS

Mean change of MMSE after 15 months in two different groups: diabetic patients treated with oral antidiabetic medications (N=58) and non diabetic patients (N=315).



The association between cognitive evolution and its potential determinants (age, sex, MMSE at baseline, NPI, number of disease, hypertension and use or antidiabetic medications) was calculated with a linear regression model: being diabetics and utilizing antidiabetic drugs (95% CI: 0,26 to 2,55; p=0,016) was independently associated with the slowing down of cognitive decline.

For example **sulfonylureas**, widely prescribed insulin-sensitizing drugs, could share with cholinesterase inhibitors an important pharmacological property: both act as inhibitors of ATP-sensitive potassium channels (Landi *et al.*, 1997). Even if this effect of sulfonylureas on extra-pancreatic cells has not yet a clear explanation, this hypothesis has been supported by the observation that K channels may be a possible site of AD pathology (Kim *et al.*, 1995).

Furthermore, both experimental (Correia et al., 2008) and clinical studies (Mazziotti et al., 2009) showed the positive cognitive effects of **metformin**; even if recently authors (Chen et al., 2009) raised some concerns about a potentially harmful consequence of **metformin** when used as a monotherapy, in combined use with insulin it seems to reduce the densities of neuritic plaques and neurofibrillary tangles.