Torino, 28 Novembre 2013

INIBITORI DEL DPP- 4 E MILD COGNITIVE IMPAIRMENT IN PAZIENTI DIABETICI ANZIANI

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Numbers of adults with diabetes by World Bank income group in 2011 and 2030, according to age

Contents available at Sciverse ScienceDirect
Diabetes Research and Clinical Practice
journal homepage: www.elsevier.com/locate/diabres
ELSEVIER
International Diabetes Federation
Diabetes Atlas

IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030

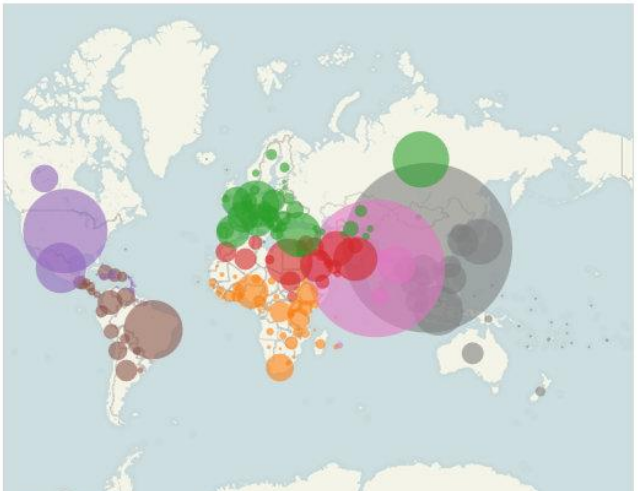
David R. Whiting [a,*], Leonor Guariguata [a], Clara Weil [a], Jonathan Shaw [b]

2011: 360 milioni

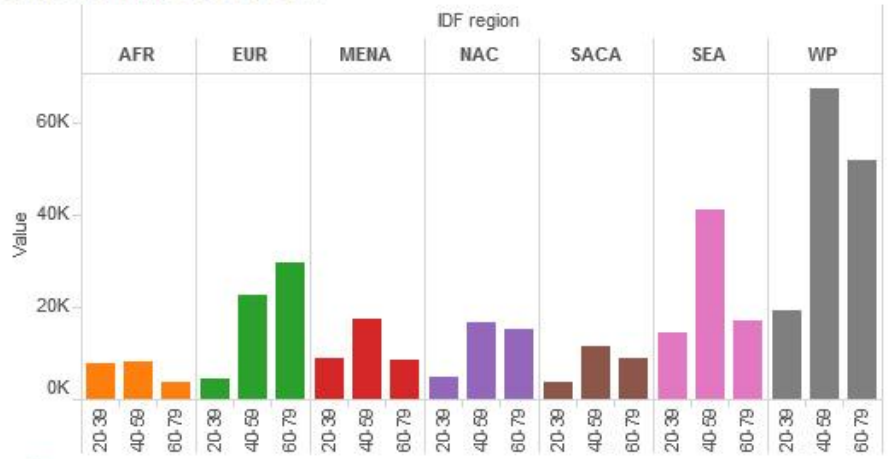
95% DM 2

2030: 552 milioni

Number of people with diabetes (20-79 years), 2013



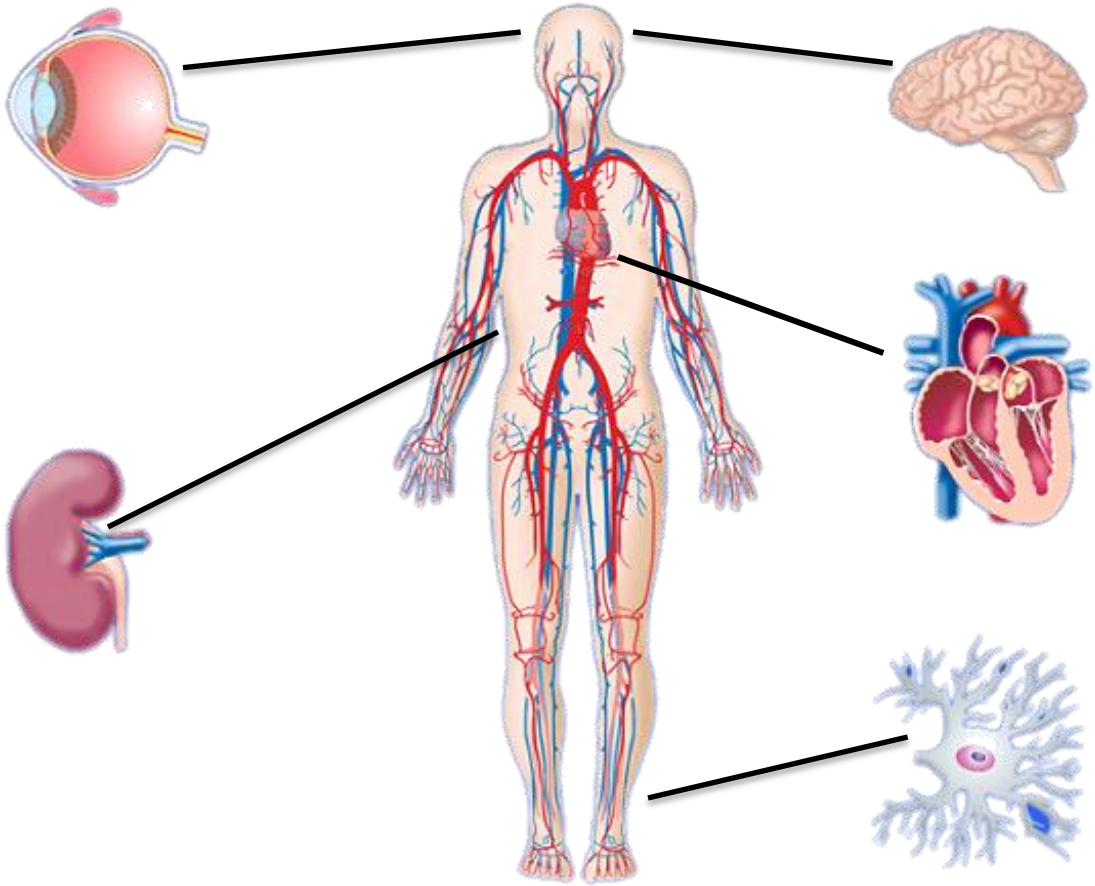
Cases of diabetes by age



International Diabetes Federation

Source: IDF Diabetes Atlas 6th edn. Brussels, Belgium, 2013.

Diabete e complicanze



Retinopatia diabetica

Stroke

Infarto

Nefropatia diabetica

Neuropatia diabetica

DECLINO COGNITIVO

[1]Fong DS [illegible] ME, *et al. Diabetes Care* 2003;26 (Suppl. 1):S94–S98.
[3]Kannel WB, *et al. Am Heart J* 1990;120:672–676. [4]Gray RP & Yudkin JS. In *Textbook of Diabetes* 1997.
[5]Mayfield JA, *et al. Diabetes Care* 2003;26 (Suppl. 1):S78–S79.

Risk of dementia in diabetes mellitus: a systematic review

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

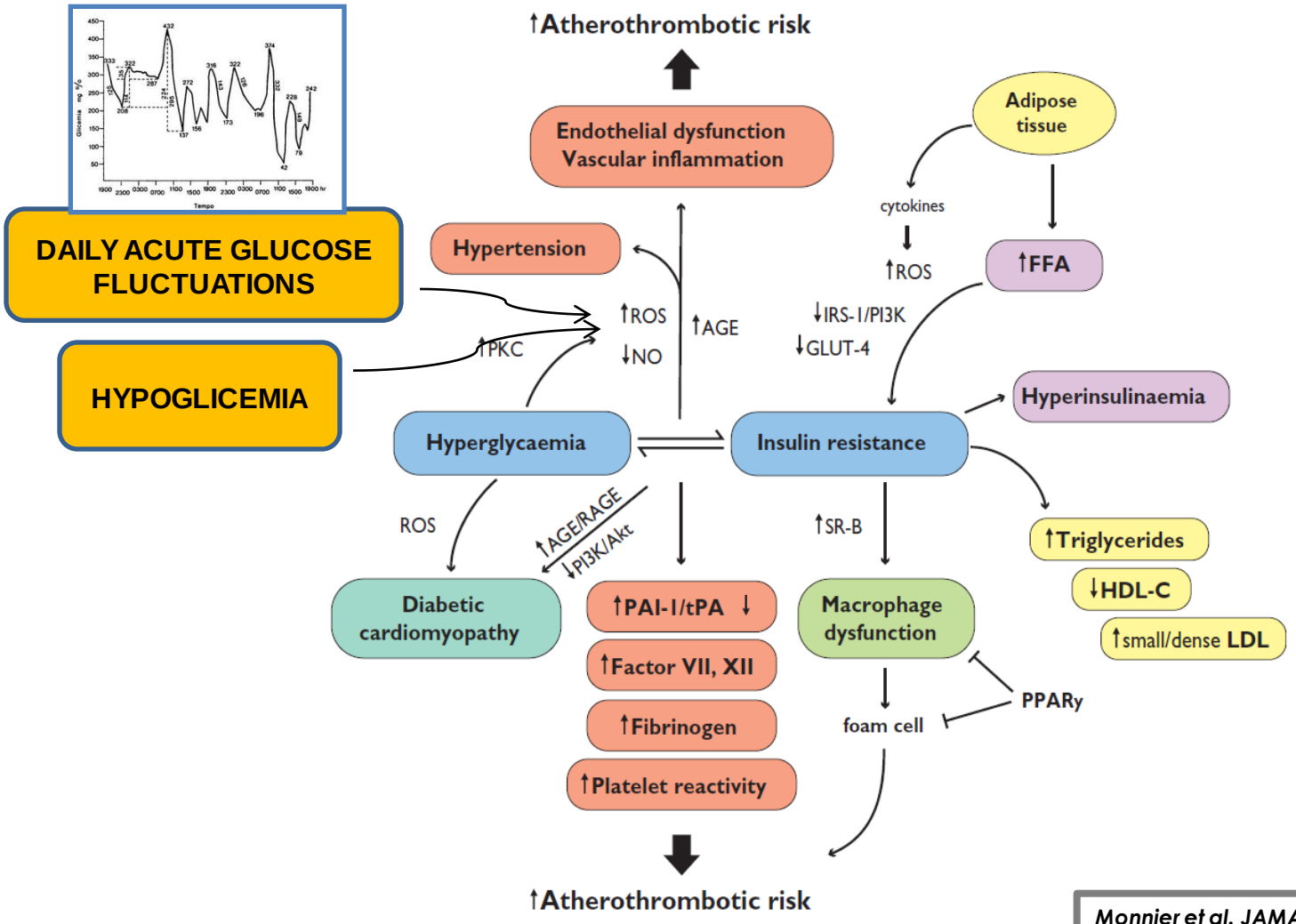
thelancet.com Vol 5 January 2006

Risk of incident dementia in diabetes mellitus –longitudinal studies with late-life assessment

	Reference	Quality rating	Results (95% CI)	Additional adjustment for vascular risk factors
Any dementia	Ott[18]	9	1·9 (1·3–2·8)	
	Brayne[17]	7	OR 2·6 (0·9–7·8)	
	Peila[22]	7	1·5 (1·0–2·2)	1·5 (1·0–2·2)
	MacKnight[23]	7	1·2 (0·9–1·7)	1·3 (0·9–1·8)
	Xu[27]	7	HR 1·5 (1·1–2·1)	HR 1·5 (1·0–2·1)
	Leibson[36]	6	SMR 1·6 (1·3–2·0)	
	Hassing[21]	4		1·2 (0·8–1·7)
Alzheimer's disease	Ott[18]	9	1·9 (1·2–3·1)	
	Brayne[17]	7	OR 1·4 (1·1–17·0)	
	Yoshitake[35]	7	2·2 (1·0–4·9)	
	Peila[22]	7	1·7 (1·0–2·8)	1·8 (1·1–2·9)
	MacKnight[23]	7	1·2 (0·8–1·8)	1·3 (0·8–2·0)
	Xu[27]	7	HR 1·3 (0·8–1·9)	HR 1·3 (0·9–2·1)
	Leibson[36]	6	SMR 1·6 (1·3–2·0)	
	Luchsinger[28]	6	HR 2·4 (1·8–3·2)	HR 2·0 (1·4–2·9)
	Arvanitakis[25]	6	HR 1·7 (1·1–2·5)	
	Katzman[14]	5	OR 0·5 (0·1–2·3)	
	Hassing[21]	4		0·8 (0·5–1·5)
Vascular dementia	Ott[18]	9	2·0 (0·7–5·6)	
	Yoshitake[35]	7	2·8 (2·6–3·0)	
	Peila[22]	7	2·2 (1·1–4·7)	2·3 (1·1–5·0)
	MacKnight[23]	7	2·2 (1·3–3·6)	2·0 (1·2–3·6)
	Xu[27]	7	HR 2·2 (1·1–5·0)	HR 2·6 (1·2–6·1)
	Luchsinger[28]	6	HR 4·2 (2·2–8·3)	HR 3·4 (1·7–6·9)
	Hassing[21]	4		2·5 (1·4–4·8)

Risk of dementia in people with diabetes relative to those without diabetes. Results were adjusted for age and sex (except the Katzman study), mostly for education, and vascular risk factors (eg, history of stroke, hypertension, and heart disease). Diagnoses were made using DSM III[40] (dementias), NINCDS-ADRDA[41] (Alzheimer's disease), and NINCDS-AIREN[43] or California criteria[42] (vascular dementia). All results are expressed as relative risks unless otherwise stated. OR=odds ratio; HR=hazard ratio; SMR=standard morbidity ratio.

Impairment cognitivo e DM: Meccanismi fisiopatologici



Monnier et al. JAMA 2006

Diabetes Care 33:2169–2174, 2010

Relationships Between Daily Acute Glucose Fluctuations and Cognitive Performance Among Aged Type 2 Diabetic Patients

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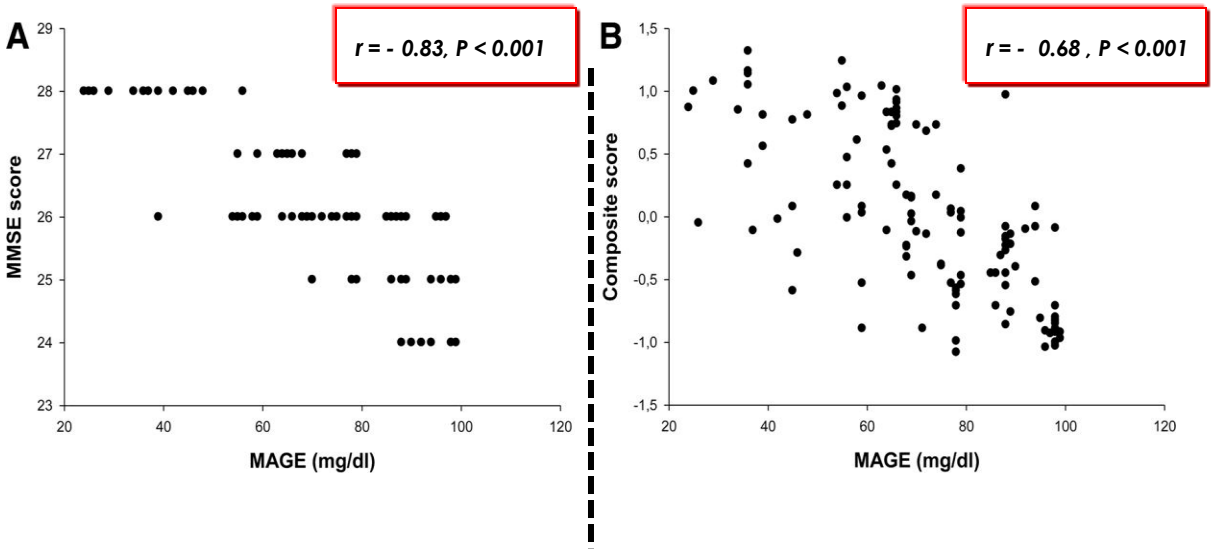
Relationship between MMSE, cognitive composite score and MAGE



Composite score TMTA; TMTB; DIFFBA; DSP FORWARD; DSP BACKWARD; VERBAL FLUENCY

Z score: individual value – mean value/SD

Impairment cognitivo e DM: Nuovi meccanismi fisiopatologici

↑ Secrezione insulinica

↓ Glucagone

Attraversa la Barriera Emato-Encefalica

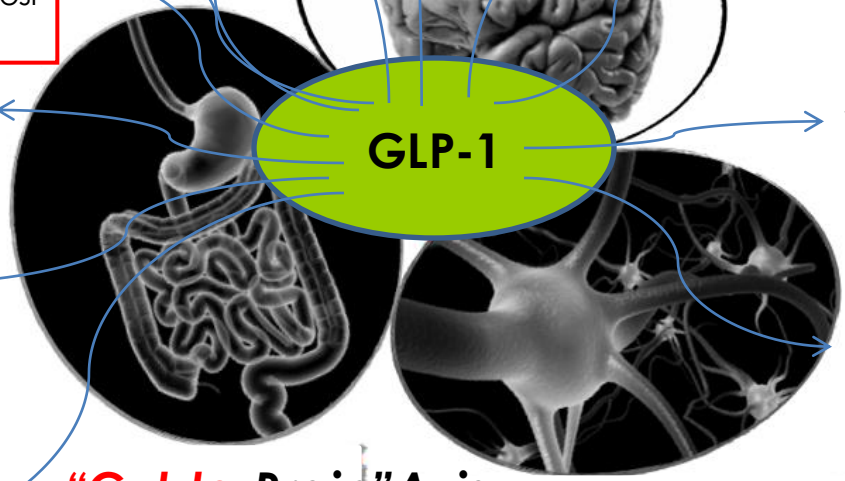
Aumenta il senso di sazietà

Regola il metabolismo glucidico intracerebrale riducendo le fluttuazioni glicemiche in fase post-prandiale

Migliora funzioni di memoria e apprendimento

Protegge dalla morte cellulare programmata

Rallentato svuotamento gastrico



Stimola la neurogenesi e la plasticità neuronale

Modula i processi infiammatori nel CNS

Effetto neuroprotettivo contro lo stress ossidativo e la morte cellulare

"Gut-to-Brain" Axis

Riduce la sintesi di frammenti Aβ amiloidogenici in modelli sperimentali di Alzheimer disease

Marfella R. et al. J Diabetes Complications 2010

Mossello E. et al.. Exp Diabetes Res. 2011

Ipoglicemizzanti orali e performance cognitiva

Journal of the AMERICAN GERIATRICS SOCIETY

Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus.

Gradman et al. Am Geriatr Soc, 1993, 41:1305-1312

THE AMERICAN JOURNAL OF GERIATRIC PSYCHIATRY

INCRETINE

Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study

Watson GS et al. Am Geriatr Psyciatry; 2005, 13:950-958

Rosiglitazone and Cognitive Stability in Older Individuals With Type 2 Diabetes and Mild Cognitive Impairment

Abbatecola et al. Diabetes Care, 2010, Aug: 33(8):1706-11

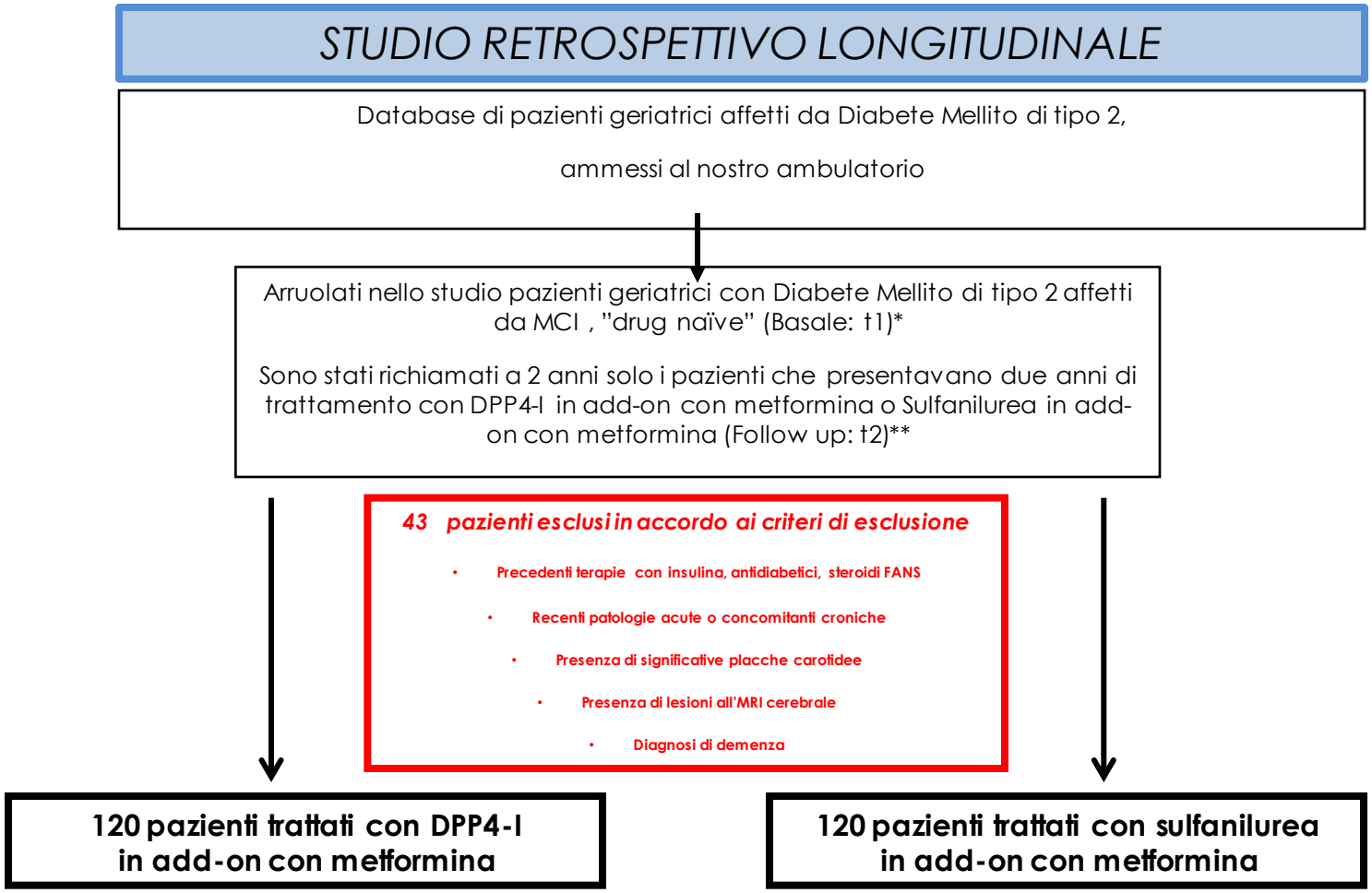
Scopo dello studio

- Indagare l'effetto del compenso glicemico con gli Inibitori del DPP-4 sulla performance cognitiva nei pazienti anziani con DM2 ed Mild Cognitive Impairment

- Valutare un possibile effetto indipendente degli Inibitori del DPP-4 sulla performance cognitiva

- Valutare il ruolo potenziale di episodi ipoglicemici sintomatici, ma soprattutto, asintomatici sulla funzione cognitiva

Disegno dello studio



** I dati si riferiscono a: CSGM (Continuous Subcutaneous Glucose Monitoring), valutazione clinica, laboratoristica, antropometrica e cognitiva prima della terapia ipoglicemizzante*

*** Al follow-up, tutti i pazienti sono stati sottoposti a CSGM, valutazione clinica, laboratoristica, antropometrica e cognitiva*

Materiali e metodi

PARAMETRI ANTROPOMETRICI:

- BMI (Kg/m^2)
- WHR (Whaist to Hip Ratio)

PROFILO GLICEMICO *(prelievi venosi e CSGM per 48h)*

- FPG (Fasting Plasma Glucose Level)
- 2hPPG (2h Post Prandial Glucose)
- HbA1c (Glycated Hemoglobin)
- MAGE (Mean Amplitude of Glycemic Excursions)
- SD (Standard Deviation)per le ipoglicemie asintomatiche

VALUTAZIONE NEUROPSICOLOGICA

- Mini Mental State Examination Test
- Trail making test A, Trail Making test B, DIFF B-A :
  valuta le funzioni esecutive; un ↑ nello score indica un peggioramento
- Forward e Backword DIGIT SPAN, Verbal Fluency Test:
  valuta le funzioni attentive; un ↑ indica un miglioramento
- GDS short version

VALUTAZIONE FUNZIONALE

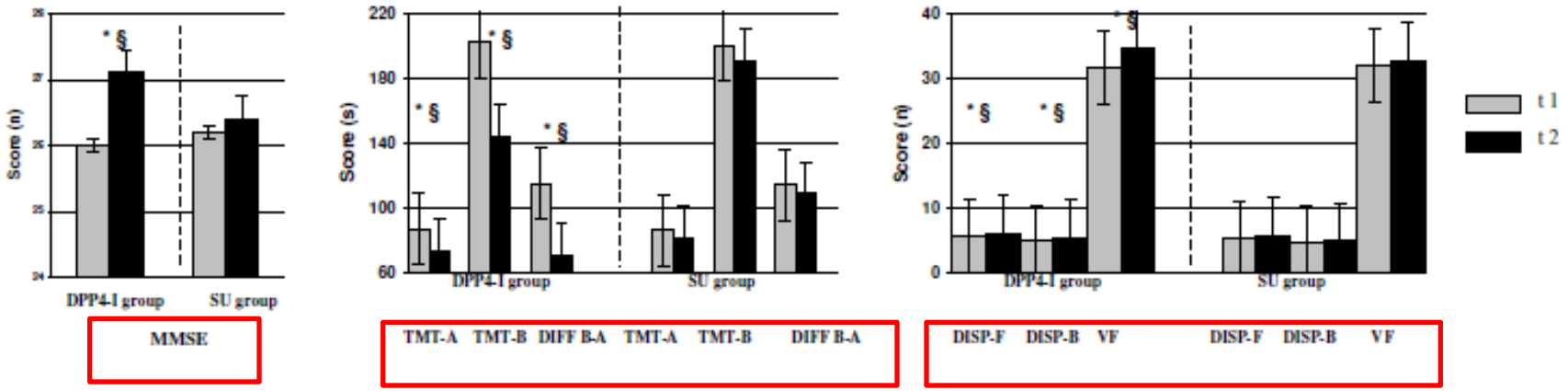
- ADL
- IADL

Caratteristiche cliniche e metaboliche dei pazienti

	DPP4-I group			SU group			
	n=120 t1	p	n=120 t2	n=120 t1	p	n=120 t2	p*
Variables							
Age (years)	73.1 ± 4.2		75.4 ± 4.1	72.5 ± 4.5		74.8 ± 4.6	
Male/Females sex	49/71		49/71	45/75		45/75	
BMI (Kg/m2)	27.1 ± 3	**0.002**	26 ± 2.8	27.8 ± 2.9	**00:03**	27.3 ± 2.7	**0.001**
WHR	0.91 ± 0.07	**0.03**	0.89 ± 0.07	0.92 ± 0.06	ns	0.91 ± 0.06	**0.01**
Systolic blood pressure (mmHg)	130 ± 6	**0.001**	123 ± 5	129 ± 7	**0.001**	122 ± 5	ns
Diastolic blood pressure (mmHg)	85 ± 5	**0.001**	80 ± 3	85 ± 4	**0.001**	80 ± 4	ns
Metabolic profile							
FPG (mg/dl)	152 ± 13	**0.001**	109 ± 12	153 ± 14	ns	150 ± 14	**0.01**
2h PPG (mg/dl)	173 ± 35	**0.01**	142 ± 9	171 ± 39	ns	164 ± 21.4	**0.01**
HbA1c (%)	7.9 ± 0.5	**0.01**	7.2 ± 0.4	8.0 ± 0.5	ns	7.9 ± 0.4	**0.01**
MAGE (mg/dl)	73.5 ± 6.3	**0.001**	47.4 ± 11.4	72.3 ± 5.4	ns	70.9 ± 6.1	**0.001**
SD for asymptomatic hypoglicemia	37.3 ± 2.8	**0.001**	18.3 ± 3.1	37.9 ± 2.1	ns	37.6 ± 1.8	**0.001**

Data are means± SD. P*= DPP4-I group vs SU group; DPP4-I: *dipeptidyl peptidase-4 inhibitors*; SU: *sulfanylurea*; BMI: *Body Mass Index*; WHR: *Waist Hip to Ratio*; FPG: *Fasting Plasma Glucose*; PPG: *Post Prandial Glucose*; MAGE: *Mean Amplitude of Glycemic Excursions*; SD for asymptomatic hypoglicemia: *Standard Deviation for asymptomatic hypoglicemia*; MMSE: *Mini Mental State Examination*; TMT: *Trail Making Test*; DIFF B-A: *Difference between TMT-B and TMT-A*; DSP–Forward: *Forward Digit Span*; DSP–Backward: *Backward Digit Span*.

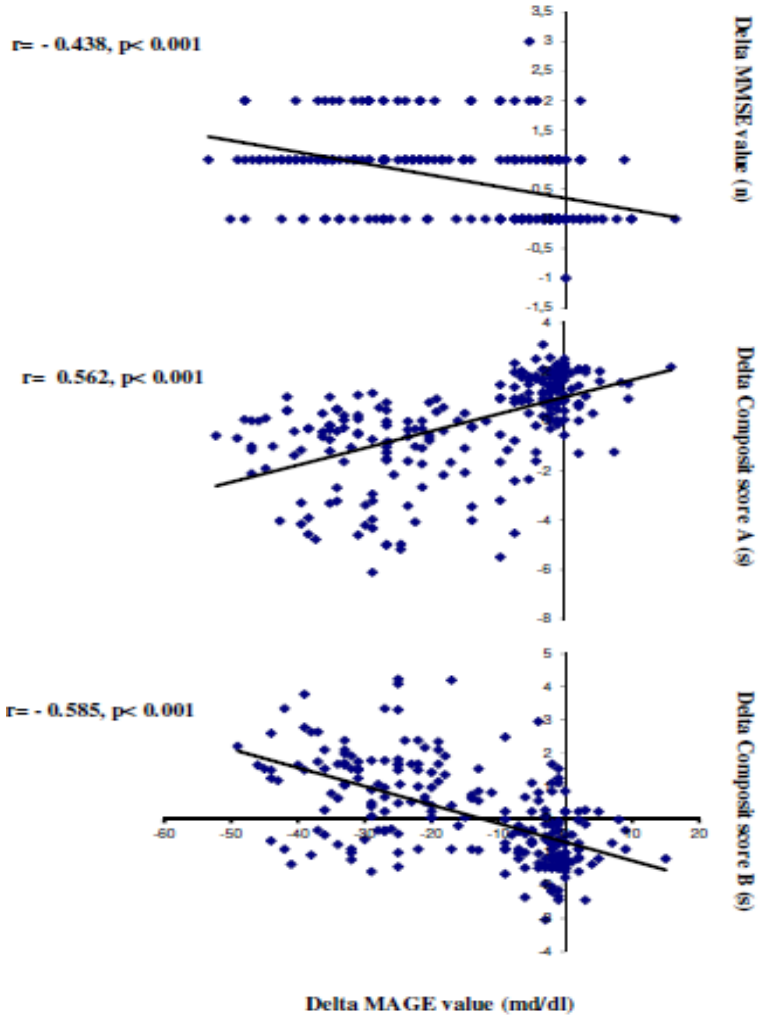
Funzione cognitiva in rapporto al trattamento ipoglicemizzante in basale (t1) e dopo terapia (t2)



* p <0.05= baseline vs therapy (t1 vs t2);
§ p <0.05= DPP4-I group vs SU group after therapy (t2 vs t2);

DPP4-I: *Dipeptidyl Peptidase-4 Inhibitors*; SU: *sulfanylurea;* MMSE: *Mini Mental State Examination*; TMT: *Trail Making Test*; DIFF B-A: *Difference between TMT-B and TMT-A*; DSP–F: *Forward Digit Span*; DSP–B: *Backward Digit Span*; *VF: Verbal Fluency*

Relazione tra MAGE e parametri psicometrici



Relazione tra MAGE e parametri psicometrici

	MMSE			Composite score A			Composite score B		
	B	**β**	**p**	**B**	**β**	**p**	**B**	**β**	**p**
Δ FPG	-0.004	-0.082	0.703	0.008	0.061	0.765	0.044	0.403	0.051
Δ 2h PPG	0.006	0.199	**0.002**	-0.018	-0.219	**0.001**	-1.236	-0.207	**0.010**
Δ HbA1c	-0.167	-0.071	0.432	-0.757	-0.109	0.202	-0.003	-0.040	0.500
Δ DS	0.029	0.307	0.346	-0.031	-0.113	0.713	-0.003	-0.138	0.640
Δ MAGE	-0.018	-0.294	**0.008**	0.027	0.304	**0.004**	-0.093	-0.601	**0.001**
Therapy*	0.646	0.362	0.371	-3.106	-0.588	0.124	-0.018	-0.004	0.991

For MMSE: R^2=0.20; For Composite score A: R^2=0.29; For Composite score B: R^2=0.32.
**DPP4-I therapy calculated as 1 and Sulfanylurea therapy calculated as 2.*

Predittività dei parametri glico-metabolici sulla performance cognitiva al basale

(MMSE < 25)

R^2= 72.9%

	OR	95% IC	p	
Age	1.05	0.97-1.21	0.12	
WHR	0.92	0.01-16.9	0.82	
BMI	1.11	1.03-1.21	0.03	←
FPG	1.02	0.98-1.05	0.62	
2hPPG	1.04	1.00-1.09	0.04	←
HbA1c	1.13	0.46-2.80	0.87	
SD for asymptomatic hypoglicemia	1.22	0.95-1.57	0.20	
MAGE value	1.37	1.11-1.69	0.008	←

WHR: *Waist Hip to Ratio*; BMI: *Body Mass Index*; FPG: *Fasting Plasma Glucose*; PPG: *Post Prandial Glucose*; SD for asymptomatic hypoglicemia: *Standard Deviation for asymptomatic hypoglicemia*; MAGE: *Mean Amplitude of Glycemic Excursions.*

Predittività dei parametri glico-metabolici sulla performance cognitiva a 2 anni di terapia

(MMSE > 26)

R^2= 69.2%

	OR	95% IC	p
Age	0.97	0.90-1.07	0.37
Δ WHR	0.93	0.05-17.1	0.62
Δ BMI	1.03	0.73-1.44	0.86
Δ FPG	1.01	0.94-1-14	0.89
Δ 2hPPG	1.02	0.98-1.05	0.09
Δ HbA1c	2.08	0.62-6.09	0.23
Δ SD for asymptomatic hypoglicemia	1.02	0.85-1.21	0.86
Δ MAGE value	**0.86**	**0.76-0.97**	**0.009**
Therapy	**0.88**	**0.45-0.99**	**0.03**

*DPP4-I therapy calculated as 1 and SU therapy calculated as 2. WHR: *Waist Hip to Ratio*; BMI: *Body Mass Index*; FPG: *Fasting Plasma Glucose*; PPG: *Post Prandial Glucose*; SD for asymptomatic hypoglicemia: *Standard Deviation for asymptomatic hypoglicemia*; MAGE: *Mean Amplitude of Glycemic Excursion*

Conclusioni

- La terapia con Inibitori del DPP-4 in pazienti anziani con DM2 ed MCI rappresenta un fattore predittivo indipendente di miglioramento della funzione cognitiva in assenza di episodi ipoglicemici sintomatici o asintomatici

- La correlazione tra MAGE e performance cognitiva, indipendentemente dai principali parametri antropometrici e glico-metabolici (compresa l'HbA1c), suggerisce una possibile rivalutazione della variabilità glicemica quale target fondamentale di trattamento in pazienti anziani con DM2

- Sono necessari ulteriori studi, su più ampia casistica, per chiarire il meccanismo neuroprotettivo, diretto e/o indiretto, degli Inibitori del DPP-4