

Physiopathologie de la polyneuropathie diabétique

6^{ème} symposium annuel SFNM
Nice, 8 octobre 2022

Pierre Lozeron

Polyneuropathie diabétique

- Diabète

- **Prévalence** x 1,5 d'ici 2045 (<https://solidarites-sante.gouv.fr>)

- Neuropathie

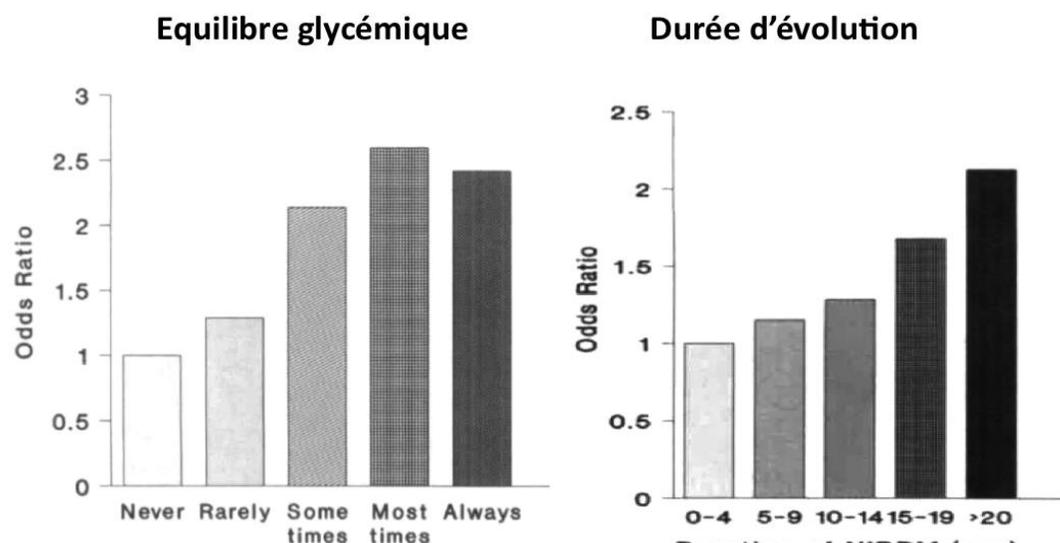
- Prévalence **50% au cours de la vie**

- **Cout annuel** (Sadosky, J Diab Complic 2015)

- Diabète \$ 6,632
- Diabète + neuropathie douloureuse \$ 12,492 à \$ 30,755
- Plaies des pieds (Gordoïs Diab care 2003) \$ 10,907

Glycémie et neuropathie

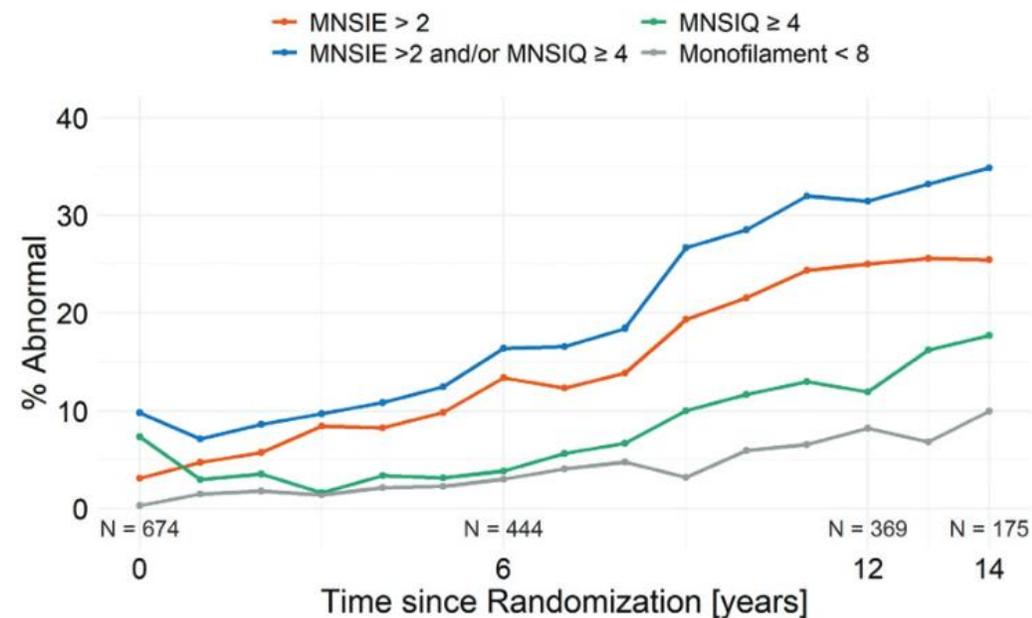
Adultes



Neuropathie corrélée à l'équilibre glycémique et durée d'évolution

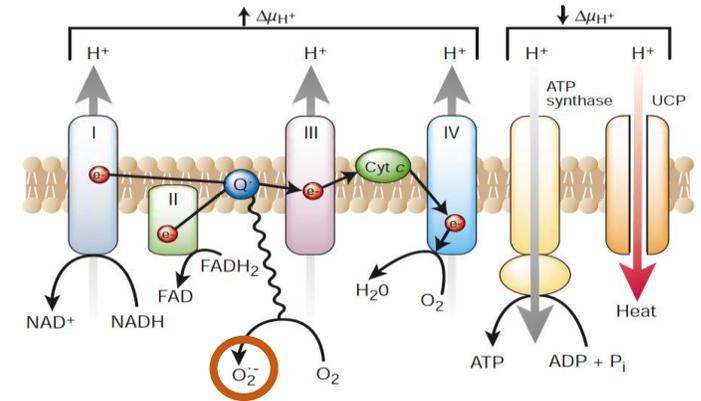
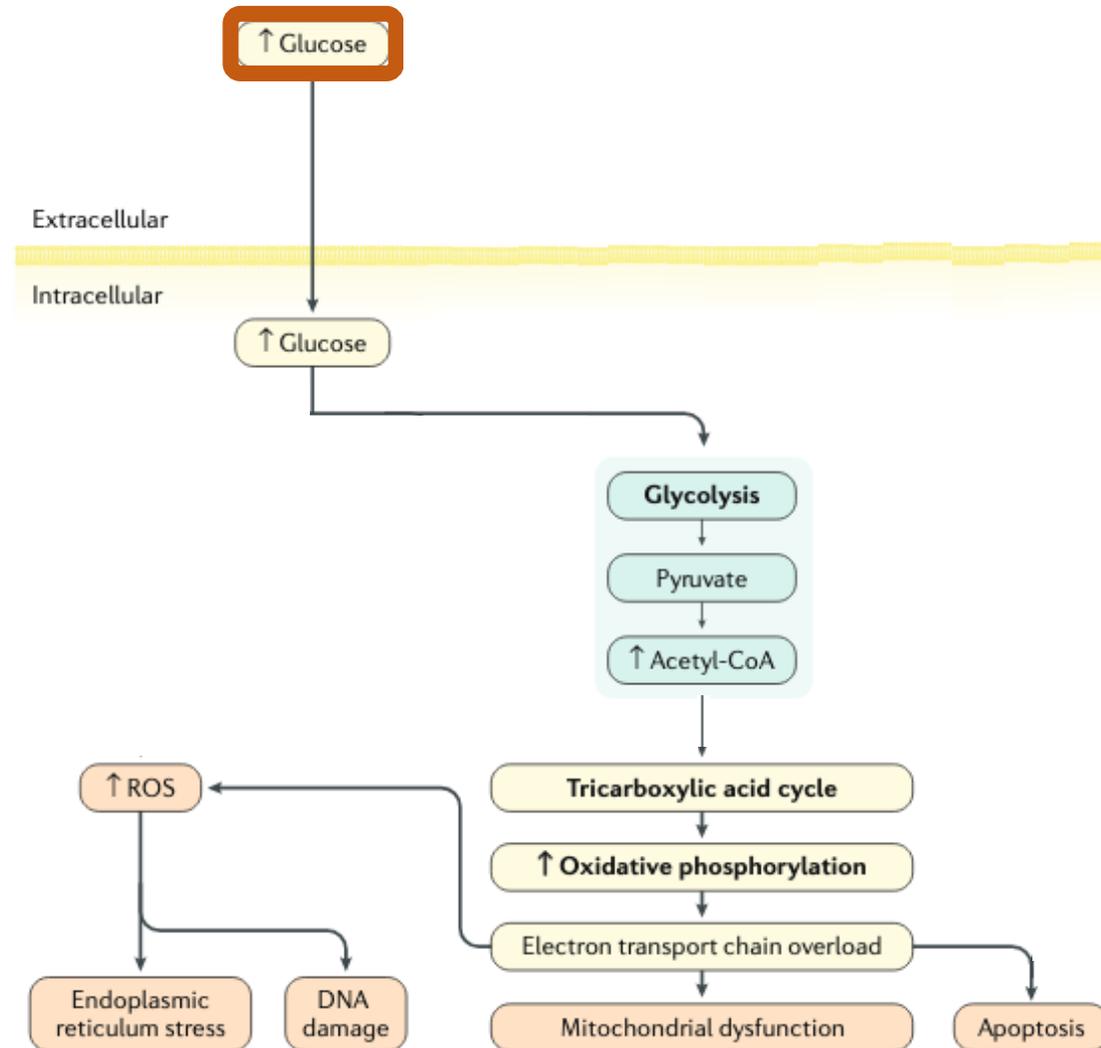
Adolescents DT2

Longitudinale
N= 674
Age 14 ans
Diabète <2 ans
Suivi 10 ans



Neuropathie corrélée à l'HbA1c

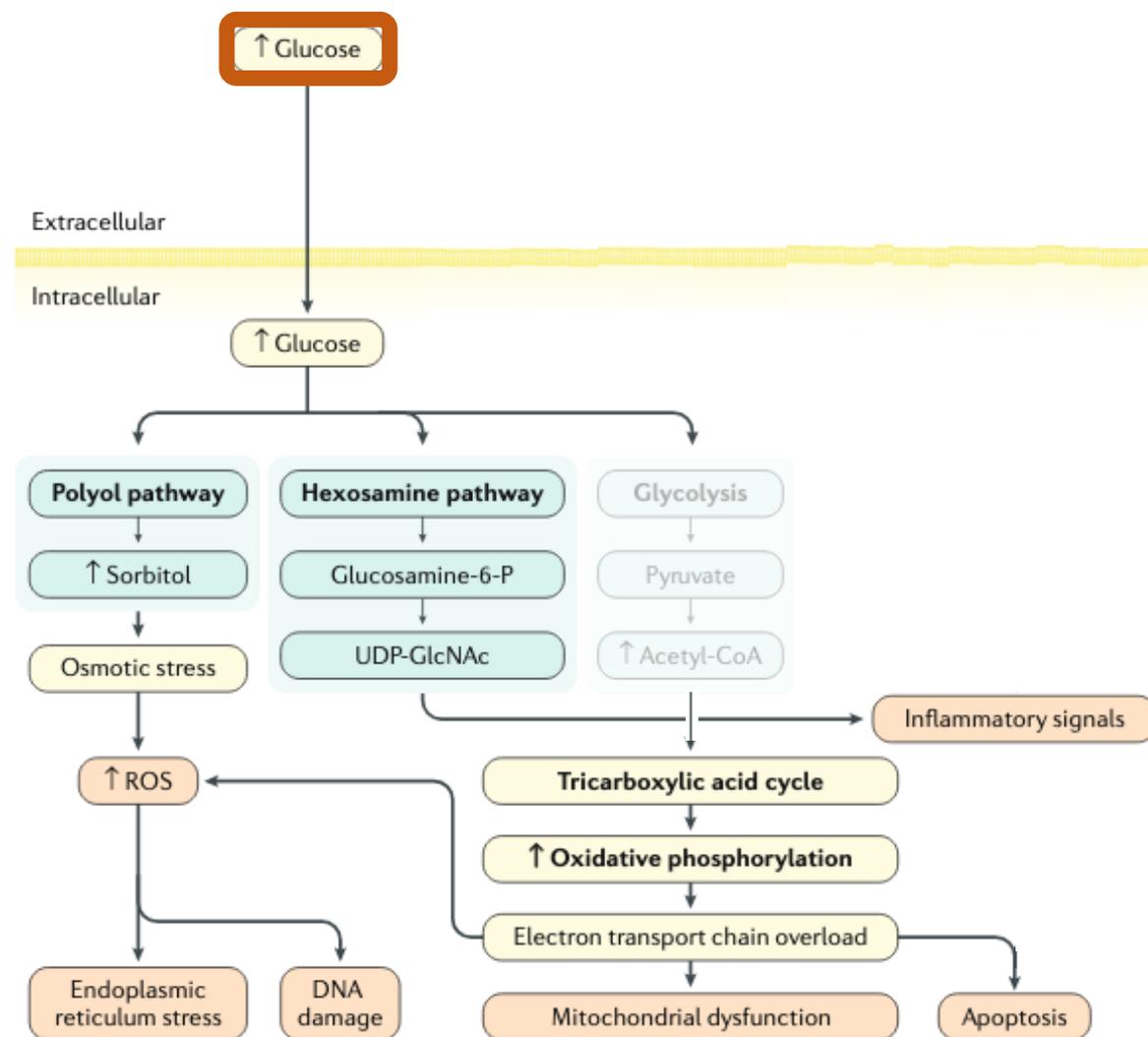
Physiopathologie



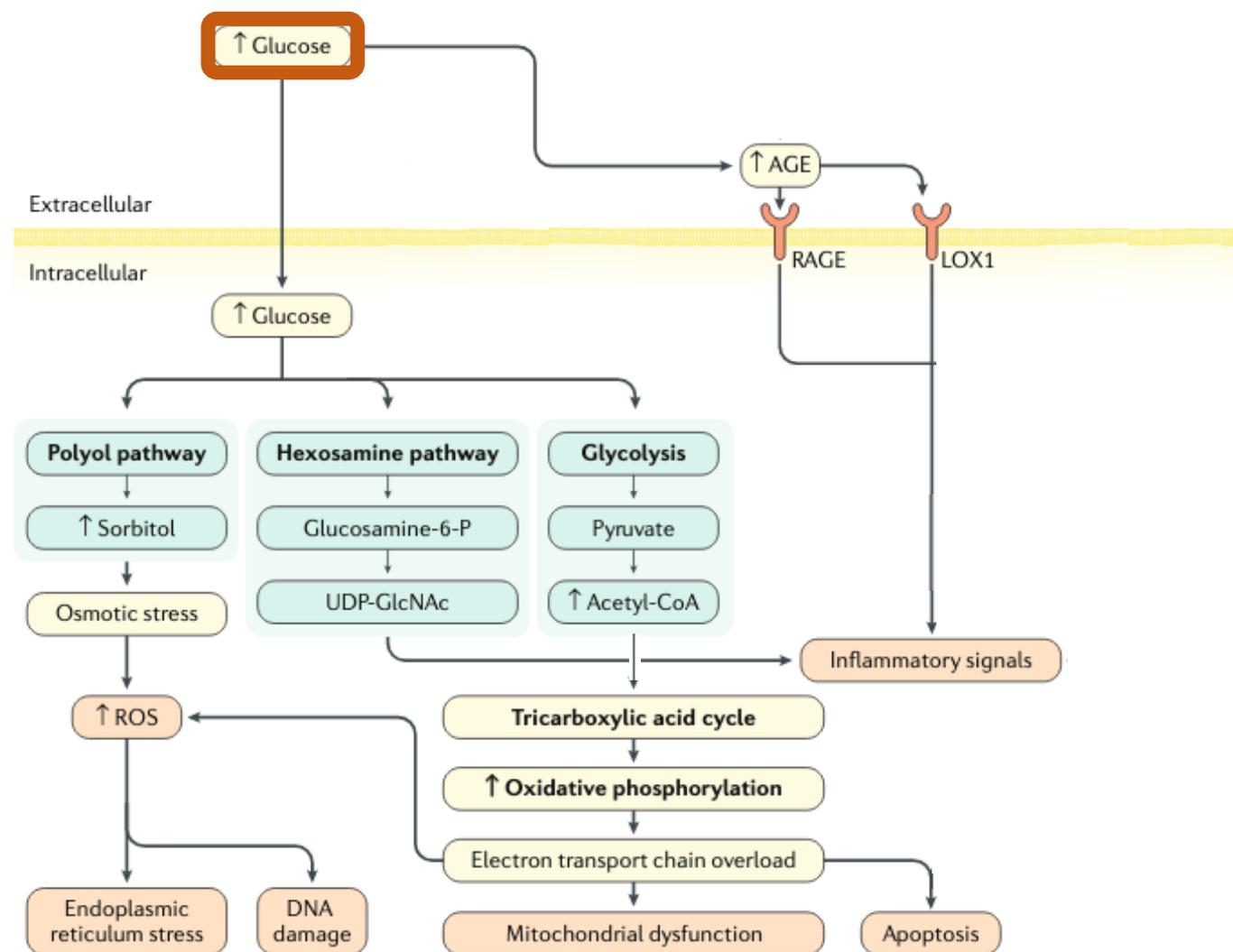
Ion superoxyde

Brownlee, Nature 2001

Physiopathologie

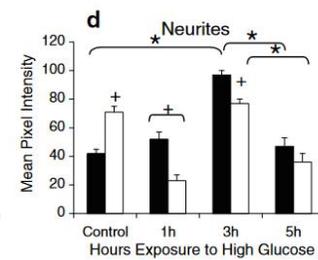
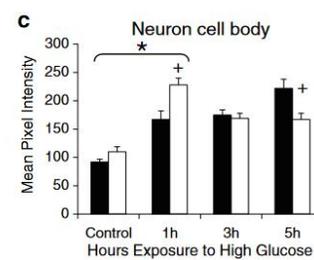
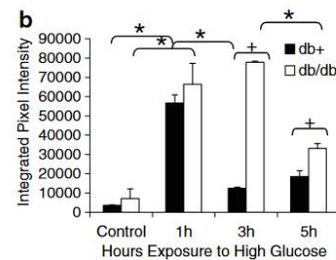
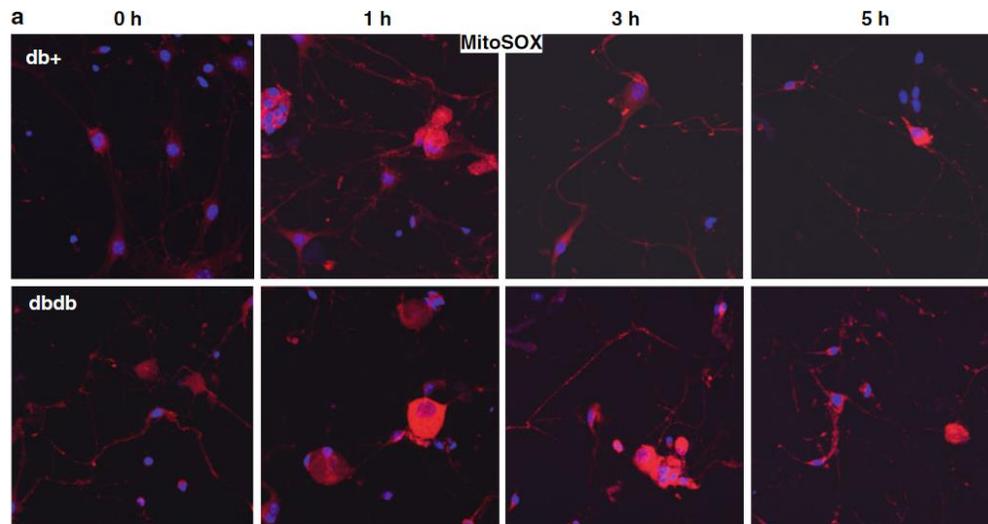


Physiopathologie

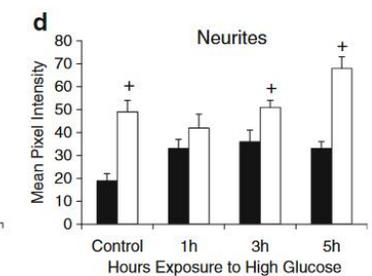
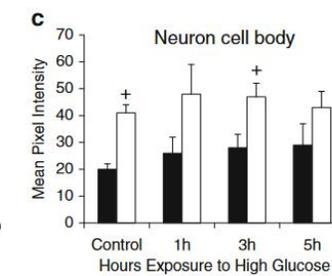
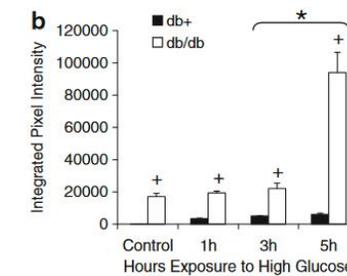
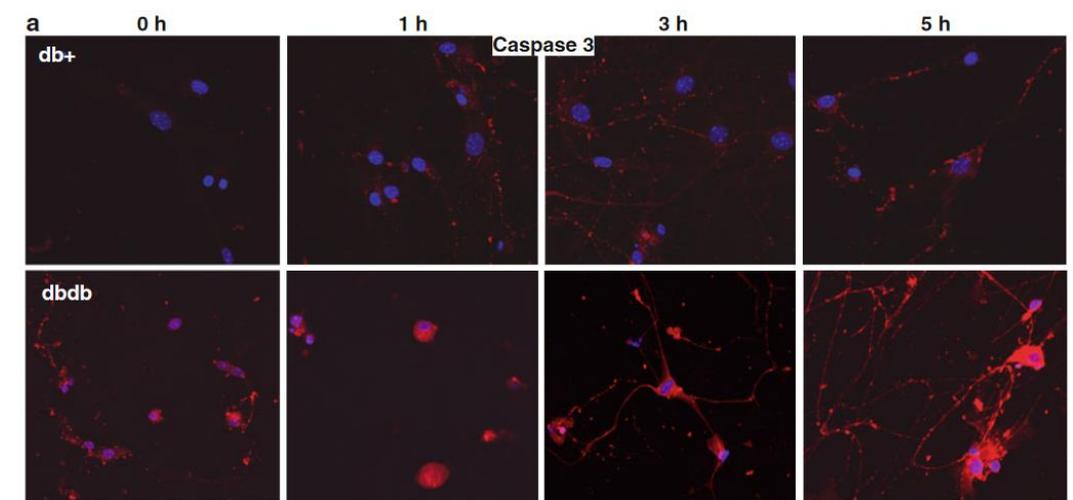


Effets de l'hyperglycémie

↗ production de superoxyde



↗ apoptose



Régénération avec normo glycémie?

Prospective (acetyl-L-carnitine)
2 biopsies nerveuses à 1 an d'intervalle (sural droit et gauche)

	Degen	Inter	Regen	Fisher exact test or t test P value			
				Three groups	Degen vs. Regen	Inter vs. Degen	Inter vs. Regen
Total subjects	67	290	67				
ALC treatment				0.69	1	1	1
ALC	43	201	47				
Placebo	24	89	20				
Sex				0.12	0.21	1	0.35
Female	18	94	29				
Male	49	196	38				
Insulin treatment				0.06	1	0.11	0.64
Yes	32	181	36				
No	35	109	31				
Diabetes type				0.31	0.82	0.43	1
Type 1	10	68	16				
Type 2	57	222	51				
Age (years)	55.0 ± 9.7	52.7 ± 10.8	53.6 ± 10.0	0.25	0.25	1	1
BMI (kg/cm ²)	30.2 ± 5.7	29.5 ± 5.8	29.5 ± 5.1	0.66	1	1	1
Diabetes duration (years)	10.5 ± 8.1	12.7 ± 8.1	12.6 ± 9.5	0.15	0.15	0.50	1
HbA _{1c} , % (mmol/mol)	9.2 ± 1.8 (76.7 ± 20.0)	8.8 ± 1.7 (73.1 ± 18.9)	8.3 ± 1.6 (66.9 ± 17.7)	0.01*	0.01*	0.54	0.04*
Triglyceride (mmol/L)	3.6 ± 6.6	2.5 ± 2.7	2.6 ± 2.1	0.07	0.70	0.57	1
Cholesterol (mmol/L)	5.7 ± 1.7	5.6 ± 1.3	5.6 ± 1.3	0.86	1	1	1
Albumin (mmol/L)	42.6 ± 2.6	42.2 ± 2.8	42.5 ± 3.3	0.41	1	0.59	1
Hematocrit (fraction)	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.82	1	1	1
O'Brien neuropathy score	2,839.8 ± 1,167.5	3,563.4 ± 1,119.7	3,427.6 ± 1,132.7	1.88E-05*	0.01*	3.77E-05*	1

Présence de signes de régénération associée à HbA_{1c} plus basse

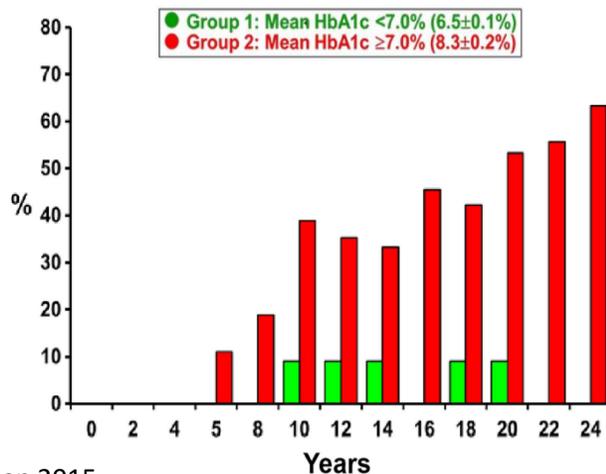
Correction de la glycémie: DT1

DCCT

Dyck, NEJM 1993

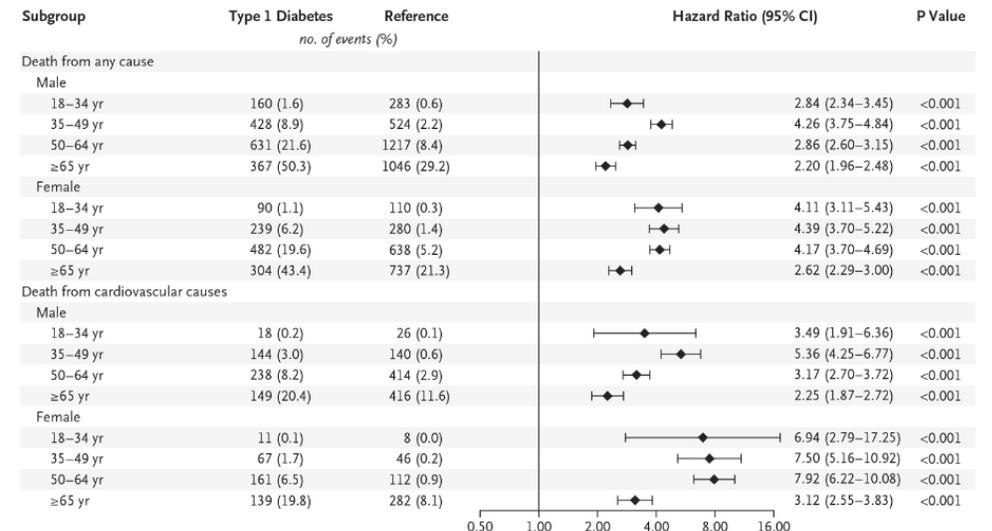
COMPLICATIONS	PRIMARY PREVENTION			SECONDARY INTERVENTION			BOTH COHORTS†
	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	RISK REDUCTION
	rate/100 patient-yr		% (95% CI)	rate/100 patient-yr		% (95% CI)	% (95% CI)
Clinical neuropathy at 5 yr**	9.8	3.1	69 (24-87)¶	16.1	7.0	57 (29-73)‡	60 (38-74)‡

Arrêt d'évolution?



Etude prospective observationnelle 24 ans
32 DT1
Définition DPN
NDS ≥ 2 + ↘ MNCV SPE et/ou SNCV sural et ↗cheville VPT
et/ou chaleur TPT et/ou froid TPT dos du pied

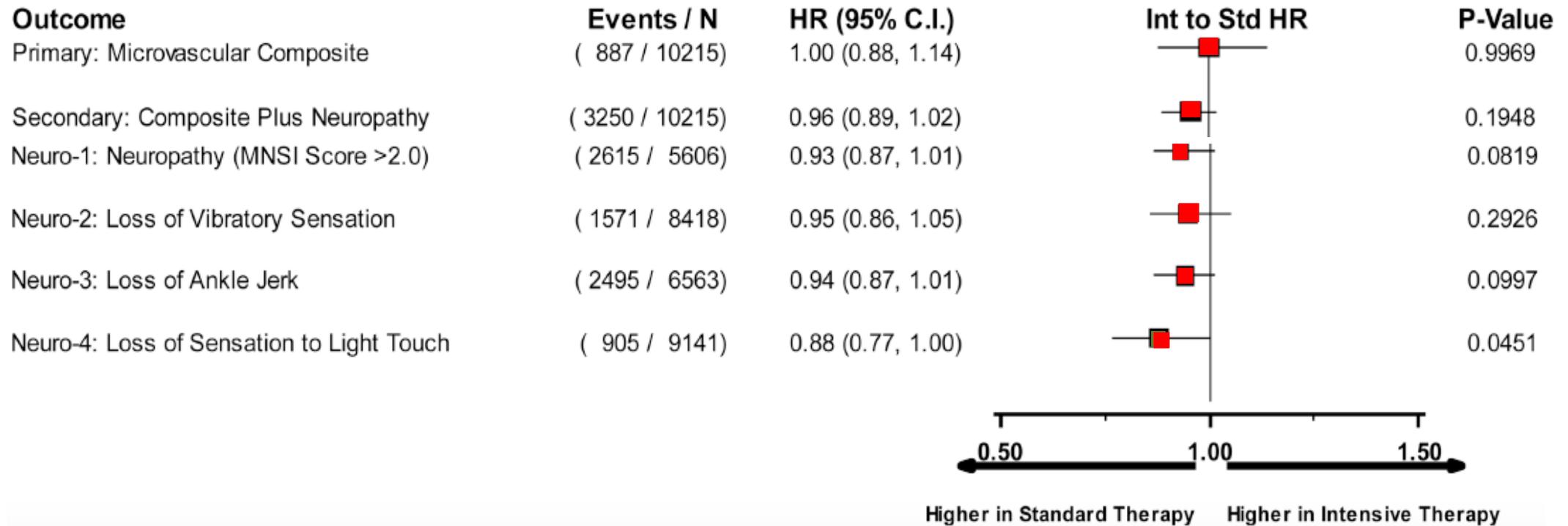
Excès de mortalité pour HbA1c < 6.9%



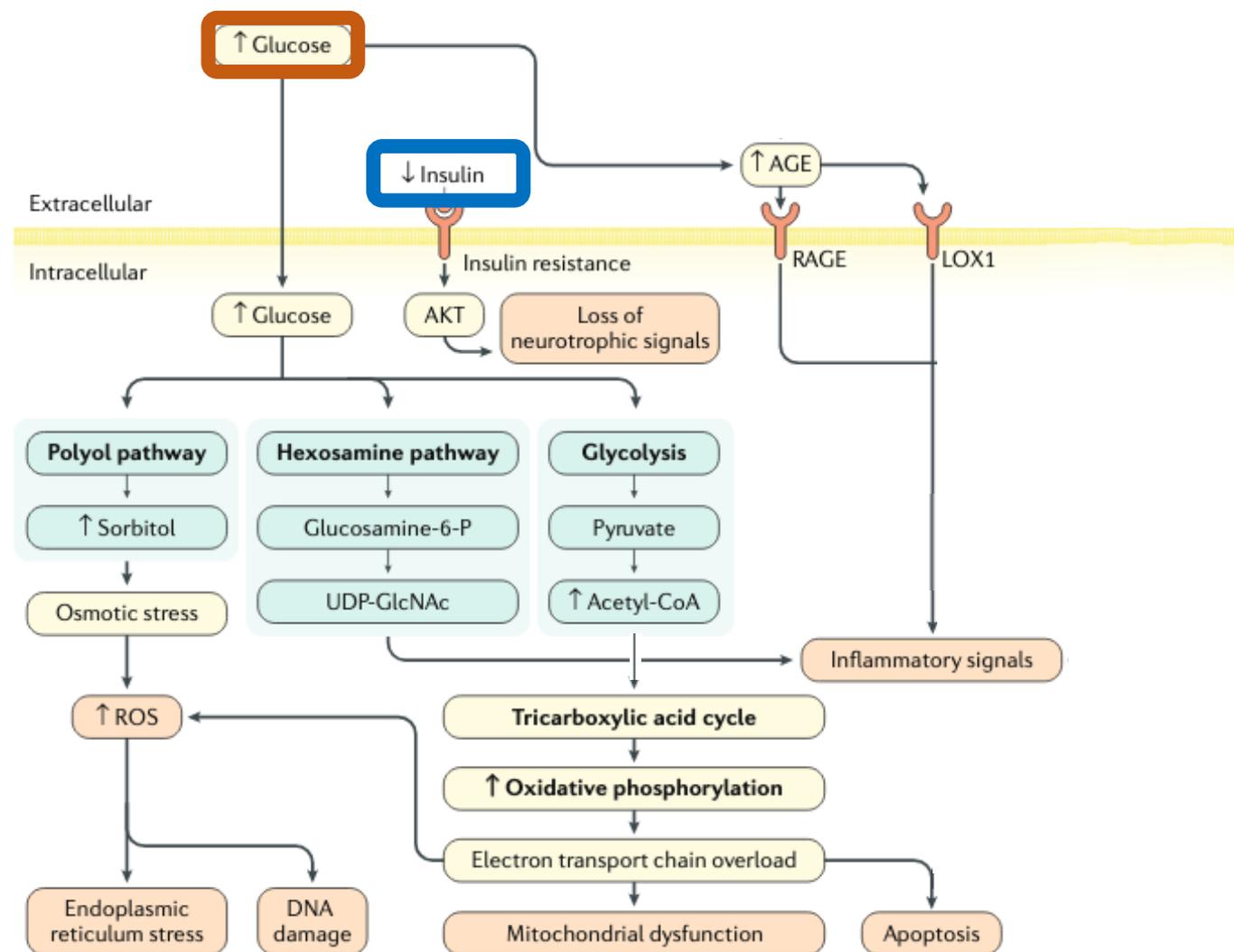
Lind, NEJM 2014

Correction de la glycémie: DT2

ACCORD

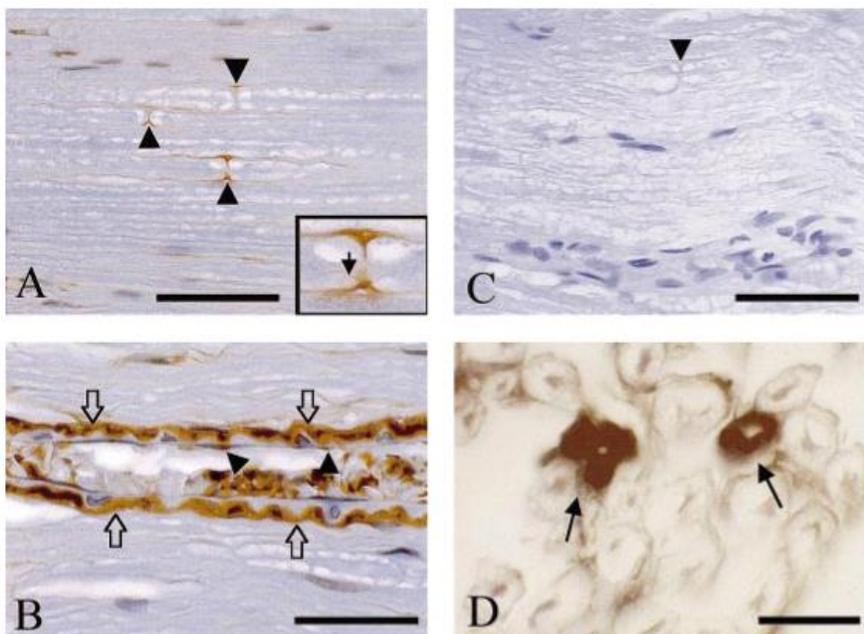


Physiopathologie



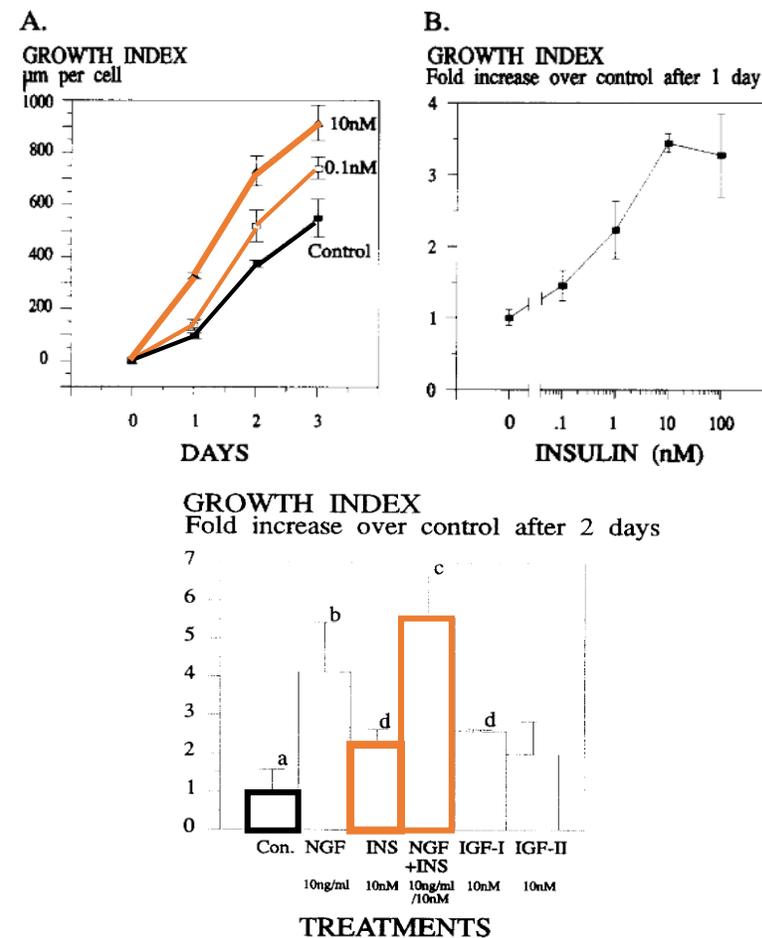
Insuline

Récepteurs à l'insuline



Nœuds de Ranvier, cell endoneuriales, Cell Schwann

Favorise la régénération des neurones sensitifs en culture



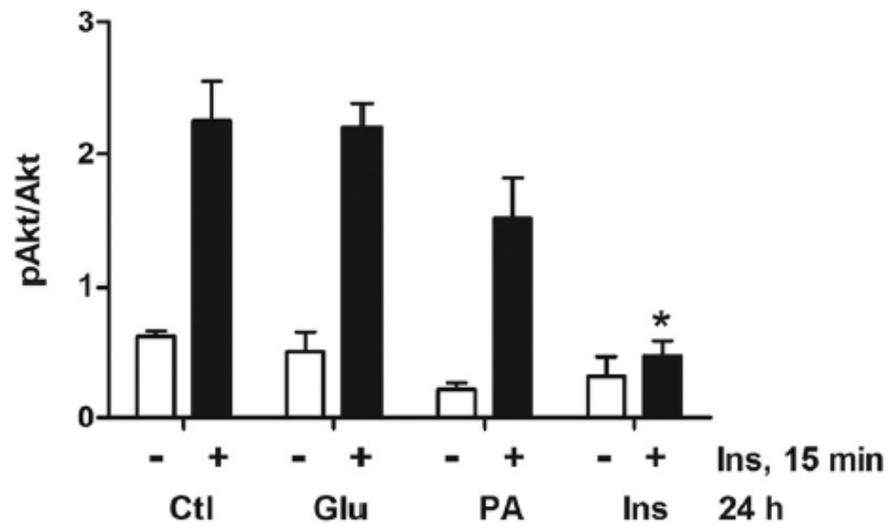
Résistance à l'insuline

Foie, muscle, tissu adipeux et.... neurones

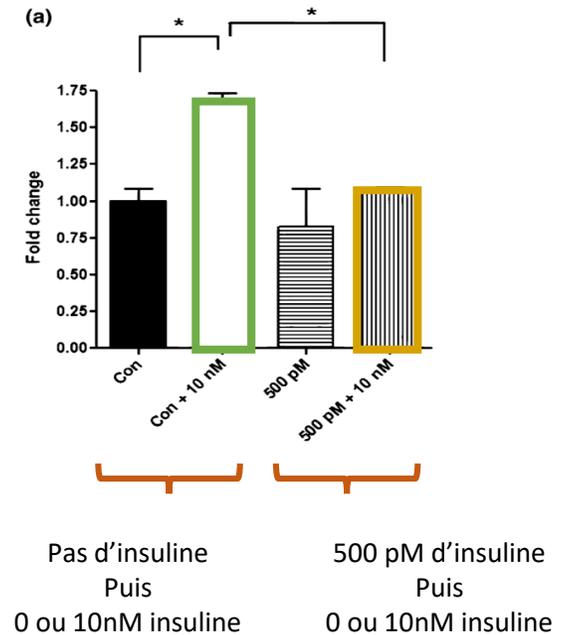
L'insuline active le métabolisme cellulaire des **DRG**

Sauf

Chez les animaux recevant un traitement chronique par insuline



L'insuline favorise la croissance des **prolongements neurones sensitifs**



Cette croissance est inhibée par l'exposition chronique à l'insuline

Variation glycémique

36.152 DT2 sans NP (suivi moyen 7,23 ans)

7.219 cas de neuropathie 27.62/1,000 personnes/an (25,8 : hommes et 29.3 : femmes)

Examen annuel: piqure, T°, diapason monofilament 10g, ROT achilléens

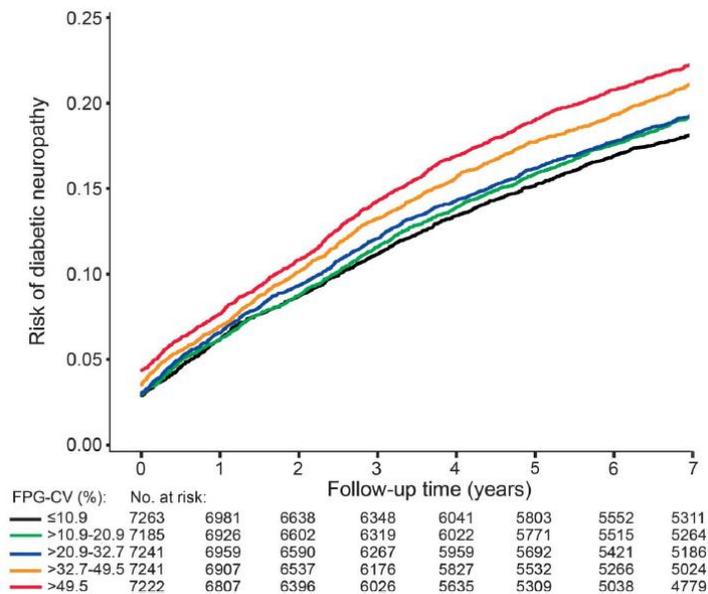
Transversale

312 DT2 (mai 2011-juin 2014)

HbA1c <7%

PDN: : symptômes ou signes + anomalies ENMG

Variation glycémique évaluation annuelle



Variation glycémique 3 jours consécutifs

Variable	Univariate analysis OR; 95% CI)	p	Multivariate analysis OR; 95% CI)	p
SDBG (mmol/L)	2.95 (1.55-5.61)	0.001	-	
MODD (mmol/L)	4.38 (1.48-12.93)	0.008	-	
<u>MAGE</u> (mmol/L)	2.18 (1.47-3.24)	<0.001	2.05 (1.36-3.09)	0.001

SDBG: standard deviation of blood glucose

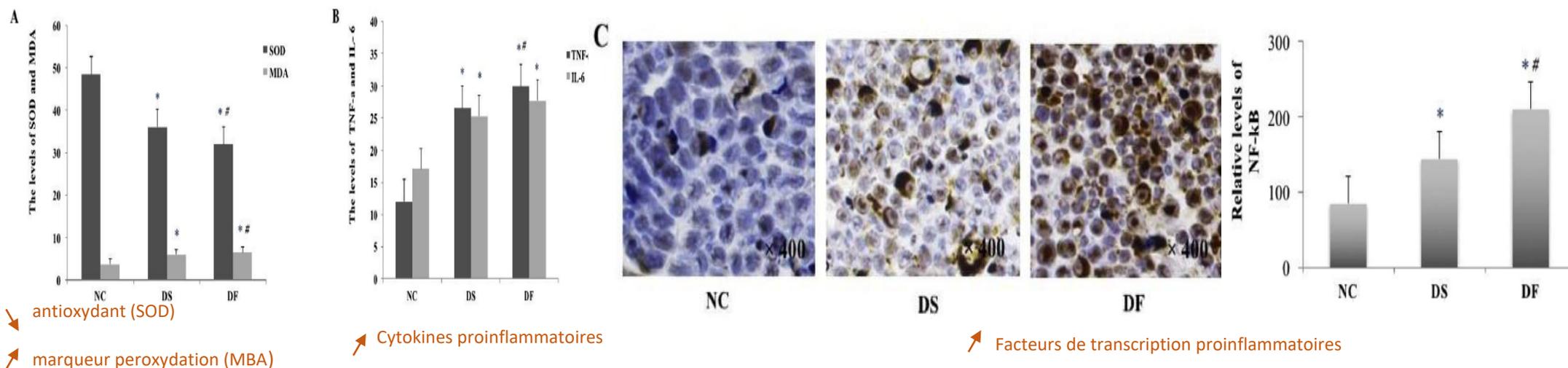
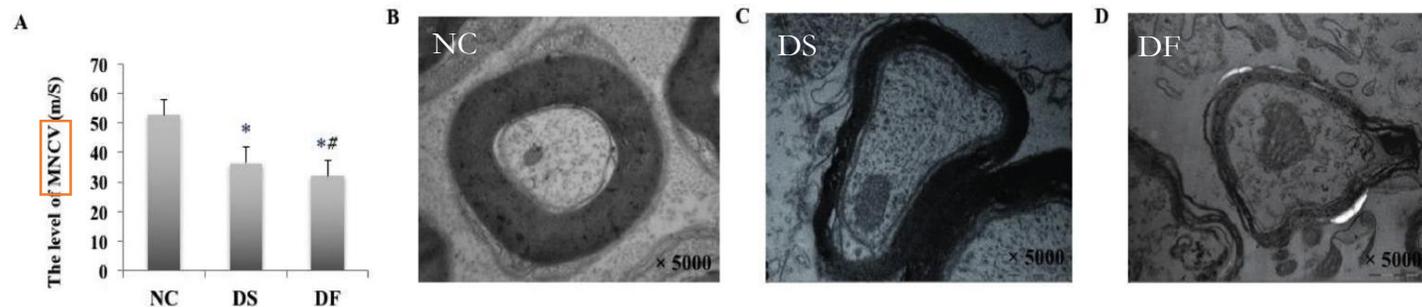
MODD: mean of daily differences

MAGE: mean amplitude of glycemic excursions

Variation glycémique

Altérations structure / fonction du nerf

Rats males SD
 Streptozotocin 60 mg/kg).
 NC et DS: injections Serum Phy
 DF: injections répétées de glucose et insuline



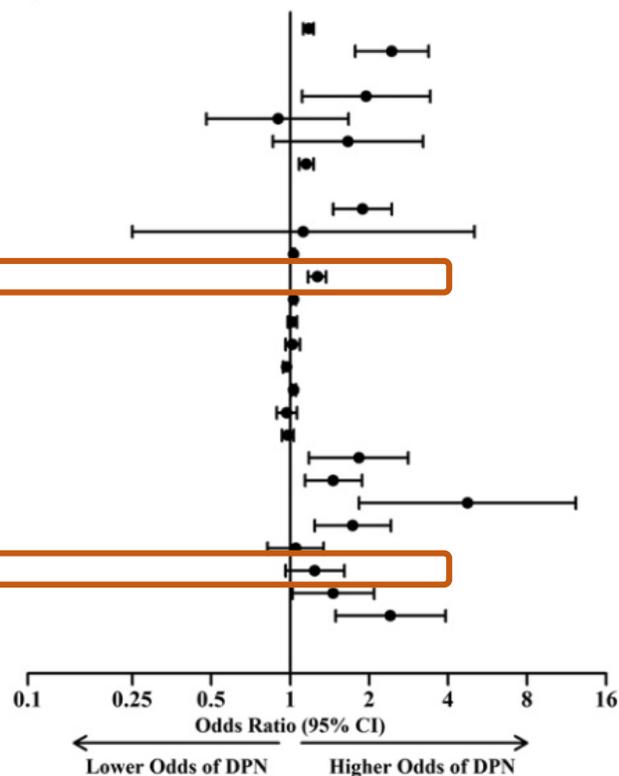
Contrôle glycémique continu

N = 81 + 24
68 ans
Diabète 20 ans

DT1

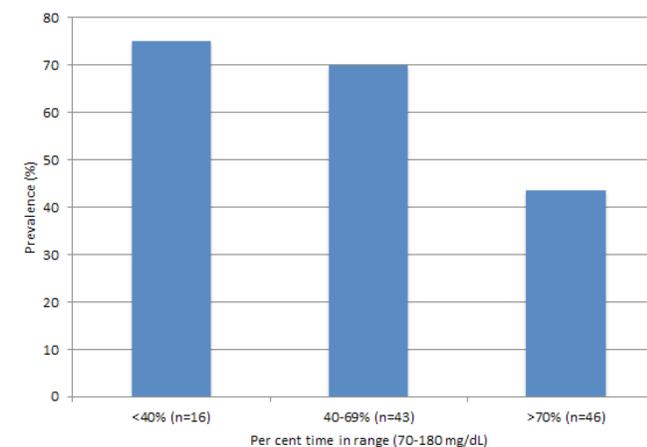
Facteurs associés à la neuropathie

Characteristic	Odds Ratio (95% CI)
Age (per 5 yr increase)	1.18 (1.12, 1.23)
Gender (F vs. M)	2.44 (1.77, 3.37)
Race/Ethnicity	
Black vs. White	1.95 (1.11, 3.42)
Hispanic vs. White	0.90 (0.48, 1.67)
Other vs. White	1.66 (0.86, 3.21)
Education Level (Lower vs. Higher)	1.15 (1.08, 1.23)
Insurance Status	
Other vs. Private	1.89 (1.46, 2.44)
None vs. Private	1.12 (0.25, 5.04)
T1D Duration (per 1 yr increase)	1.03 (1.02, 1.04)
HbA1c (per 1.0% mmol/L increase)	1.27 (1.17, 1.37)
BMI (per 1.0 kg/m ² increase)	1.05 (1.01, 1.05)
Systolic BP (per 5 mmHg increase)	1.02 (0.98, 1.06)
Diastolic BP (per 5 mmHg increase)	1.02 (0.96, 1.09)
eGFR (per 5 mL·min ⁻¹ /1.73m ² increase)	0.97 (0.94, 1.00)
Triglycerides (per 10 mg/dL increase)	1.03 (1.01, 1.05)
HDL (per 10 mg/dL increase)	0.97 (0.89, 1.06)
LDL (per 10 mg/dL increase)	0.98 (0.93, 1.03)
Smoker vs. Non-Smoker	1.83 (1.18, 2.82)
Retinopathy vs. No Retinopathy	1.46 (1.14, 1.88)
Charcot vs. No Charcot	4.75 (1.83, 12.28)
CVD vs. No CVD	1.73 (1.24, 2.42)
Insulin Pump User vs. No Use	1.05 (0.82, 1.34)
CGM User vs. No Use	1.24 (0.96, 1.61)
≥ 1 SH Event vs. No SH Events	1.46 (1.02, 2.09)
≥ 1 DKA Event vs. No DKA Events	2.41 (1.49, 3.91)



DT2

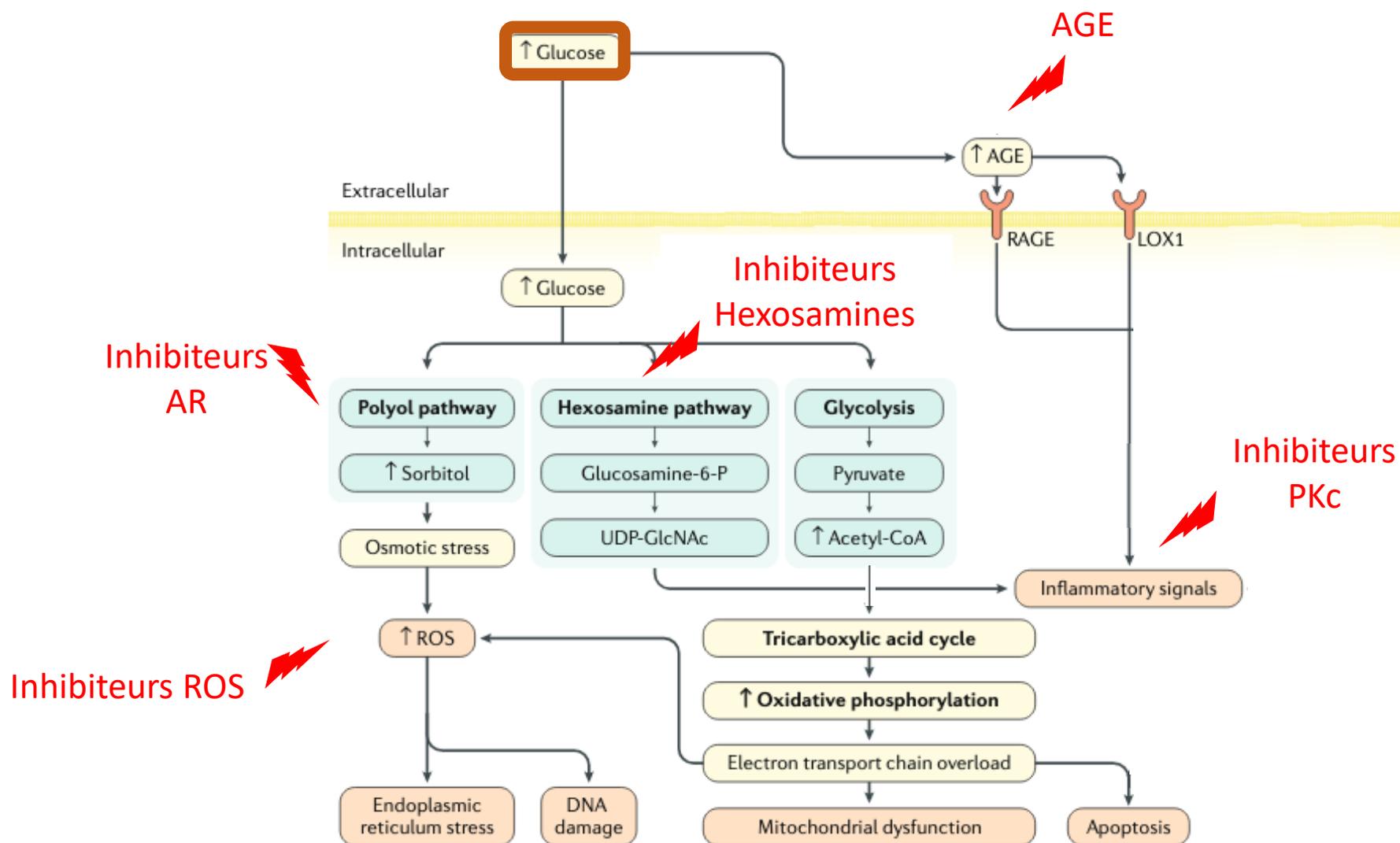
Prévalence de la neuropathie en fonction TIR



Exposure	Unadjusted		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Time in range (70–180 mg/dL) (per 10% lower)*	1.26 (1.04 to 1.53)	0.021	1.25 (1.02 to 1.52)	0.031	1.23 (0.99 to 1.52)	0.060
Time above range (>180 mg/dL) (per 10% higher)*	1.24 (1.03 to 1.50)	0.024	1.23 (1.02 to 1.50)	0.035	1.22 (0.99 to 1.50)	0.061
% coefficient of variations (per 6% higher (1 SD))	1.25 (0.83 to 1.86)	0.283	1.24 (0.82 to 1.88)	0.312	1.19 (0.75 to 1.90)	0.457
GMI (per 1% higher)	1.82 (1.08 to 3.07)	0.024	1.79 (1.05 to 3.04)	0.033	1.81 (1.02 to 3.20)	0.042
HbA1c (per 1% or 11 mmol/mol higher)	1.29 (0.97 to 1.70)	0.08	1.25 (0.93 to 1.69)	0.139	1.29 (0.93 to 1.79)	0.129
Duration of diabetes (per 10 years longer)	1.15 (0.77 to 1.71)	0.51	1.19 (0.77 to 1.82)	0.433	1.13 (0.73 to 1.75)	0.575

Sixty-two of 105 participants with a total MNSI questionnaire score ≥ 2 were defined as having distal peripheral neuropathy in this analysis. Model 1 is adjusted for age, gender, race. Model 2 additionally adjusts for BMI, eGFR, use of insulin and use of sulfonylureas. In model 2, all outcomes except duration of diabetes additionally adjust for duration of diabetes.

Traitements mécanistiques



Les autres facteurs

Eurodiab study : DT1

Prospective
N= 1172 DT1
Suivi: 7.3 ± 0.6 ans

Variable	(95% CI)	P Value
Total cholesterol (mmol/liter)	1.26 (1.10–1.45)	0.001
Low-density lipoprotein cholesterol (mmol/liter)	1.22 (1.03–1.45)	0.02
Triglycerides (mmol/liter)	1.35 (1.16–1.57)	<0.001
von Willebrand factor (U/ml)†	1.20 (1.02–1.42)	0.03
Weight (kg)	1.34 (1.17–1.54)	<0.001
Body-mass index	1.40 (1.22–1.61)	<0.001
Waist-to-hip ratio	1.06 (0.93–1.22)	0.4
Estimated glucose disposal rate (mg/kg/min)	1.37 (1.08–1.73)	0.01
Albumin excretion rate (µg/min)†	1.25 (1.10–1.43)	0.001
Insulin dose per kg of body weight (IU)	1.09 (0.95–1.26)	0.2
History of smoking	1.55 (1.17–2.04)	<0.001
Hypertension	1.92 (1.30–2.82)	<0.001
Macroalbuminuria	2.08 (1.11–3.90)	0.02
Microalbuminuria or macroalbuminuria	1.48 (1.07–2.04)	0.02
Proliferative retinopathy	1.54 (0.79–2.98)	0.2
Any retinopathy	1.70 (1.19–2.43)	0.003
Cardiovascular disease	2.74 (1.68–4.49)	<0.001

Tesfaye, NEJM 2005

ADDITION-Denmark: DT2

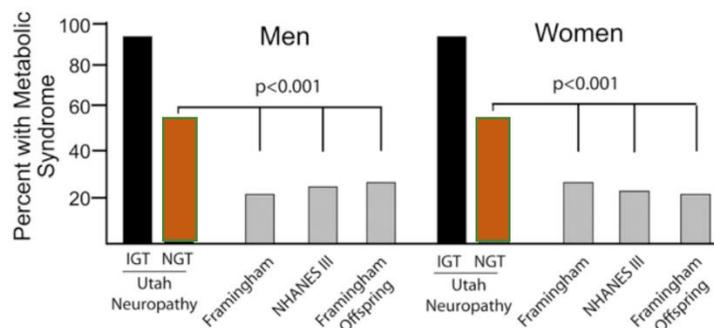
Prospective
1,256 sans DPN
13 ans

10% d'incidence cumulée de neuropathie à 13 ans

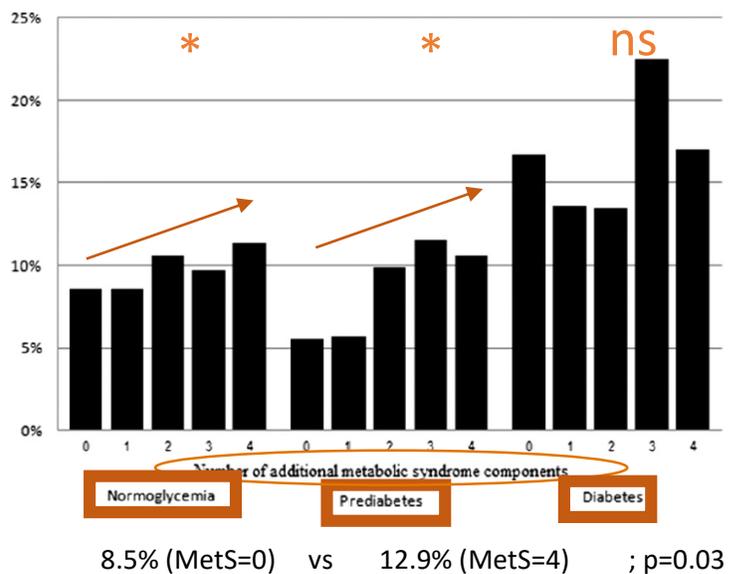
	HR of incident DPN (95% CI)†
HbA _{1c} (unit = 1%)	0.93 (0.75; 1.15)
HbA _{1c} (unit = 10 mmol/mol)	0.94 (0.77; 1.14)
SBP (unit = 10 mmHg)	1.02 (0.90; 1.16)
DBP (unit = 5 mmHg)	0.96 (0.83; 1.12)
Height (unit = 5 cm)	0.97 (0.83; 1.13)
Weight (unit = 5 kg)	1.09 (1.03; 1.16)*
Waist circumference (unit = 5 cm)	1.14 (1.05; 1.24)*
BMI (unit = 2 kg/m ²)	1.14 (1.06; 1.23)*
Total cholesterol (unit = 0.5 mmol/L)	0.90 (0.80; 1.01)
LDL cholesterol (unit = 0.25 mmol/L)	0.92 (0.86; 0.98)*
HDL cholesterol (unit = 0.25 mmol/L)	0.82 (0.69; 0.99)*
Triglycerides (unit = 0.5 mmol/L)	1.04 (0.98; 1.09)
Log ₂ methylglyoxal (unit = doubling)	1.45 (1.12; 1.89)*

Andersen, Diab Care 2018

Syndrome métabolique et diabète



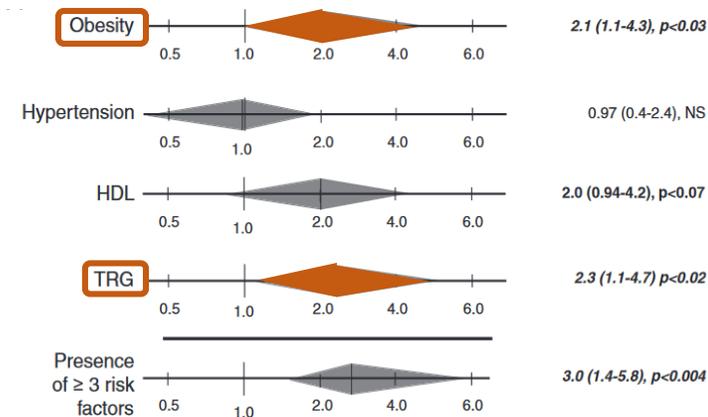
Smith, J Neurol Sci 2008



Utah Diabetic Neuropathy Study (UDNS)

Prospective

N=218 DT2 sans NP (15%) ou NP <5 ans (moyenne 16±32 mois)



L'obésité et hyperlipidémie sont des facteurs de risque de neuropathie diabétique précoce

Smith, J Diab Complic 2013

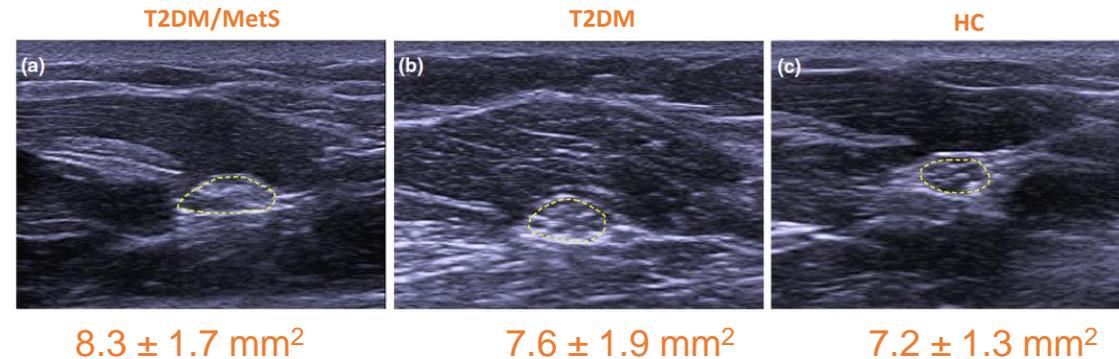
Syndrome métabolique et diabète

Etude de cohorte monocentrique
148 DT2 consécutifs
60 contrôles « appariés » âge et sexe

	CNFL	CNFD	CNBD	CNFrD	IWL	IWFrD
Waist circumference	-0.400**	-0.330*	-0.439**	-0.371**	-0.468***	-0.403**
Triglycerides	-0.488*	-0.383*	-0.383*	-0.519**	-0.617***	-0.682***

Petites
fibres

$r = 0.504, p < 0.01$

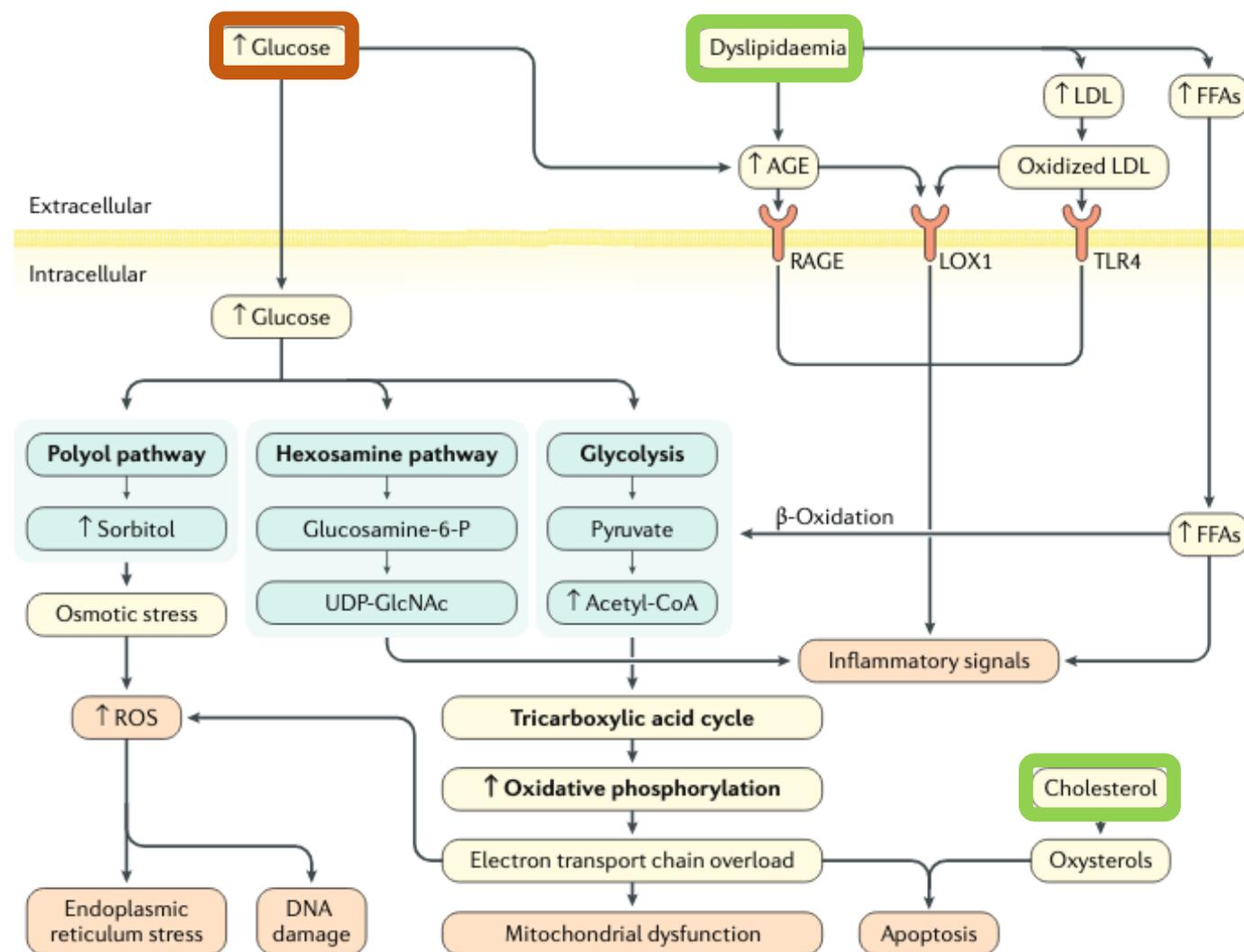


morphologie

	T2DM/MetS, n = 89	T2DM, n = 59	Control, n = 60	T2DM/MetS vs. T2DM	T2DM/MetS vs. control	T2DM vs. control
Residuelle Na ⁺ conductance Ranvier						
SDTC, μ s	0.47 \pm 0.01	0.45 \pm 0.02	0.45 \pm 0.01	0.450	0.239	0.676
Rheobase, mA	3.7 \pm 0.2	3.7 \pm 0.2	2.8 \pm 0.2	0.905	<0.001	0.002
TEd, peak, %	63.8 \pm 0.7	64.2 \pm 0.8	68.8 \pm 0.7	0.729	<0.001	<0.001
TEd, S2, %	20.3 \pm 0.4	20.7 \pm 0.6	23.3 \pm 0.5	0.471	<0.001	0.001
Accommodation half-time, ms	40.4 \pm 0.5	42.5 \pm 0.6	41.7 \pm 0.8	0.013	0.145	0.381
Conductance nœuds / internœuds						
TEd, 40-60 ms, %	49.6 \pm 0.5	51.3 \pm 0.7	52.7 \pm 0.6	0.036	<0.001	0.140
TEd, 90-100 ms, %	43.6 \pm 0.5	43.4 \pm 0.6	45.5 \pm 0.6	0.886	0.021	0.024
TEh, 10-20 ms, %	-72.1 \pm 0.8	-71.1 \pm 0.9	-73.5 \pm 0.9	0.396	0.239	0.066
TEh, 20-40 ms, %	-88.2 \pm 1.2	-87.8 \pm 1.4	-91.4 \pm 1.3	0.822	0.096	0.083
TEh, 90-100 ms, %	-110.3 \pm 2.4	-111.4 \pm 2.6	-116.5 \pm 2.3	0.751	0.085	0.189
Conductance internœuds						
Resting I/V slope	0.67 \pm 0.02	0.64 \pm 0.02	0.60 \pm 0.01	0.128	0.006	0.203
RRP, ms	3.3 \pm 0.1	3.3 \pm 0.1	3.2 \pm 0.1	0.753	0.219	0.383
Activité canaux Na ⁺ et K ⁺ nœuds						
Superexcitability, %	-18.3 \pm 0.8	-20.6 \pm 0.6	-24.7 \pm 0.7	0.031	<0.001	0.001
Subexcitability, %	11.4 \pm 0.4	11.2 \pm 0.5	15.0 \pm 0.5	0.785	<0.001	0.001

Excitabilité

Physiopathologie



Fibres nerveuses

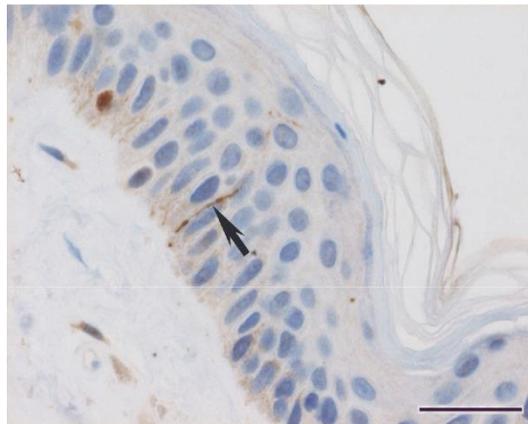
Perte axonale

Grosses fibres



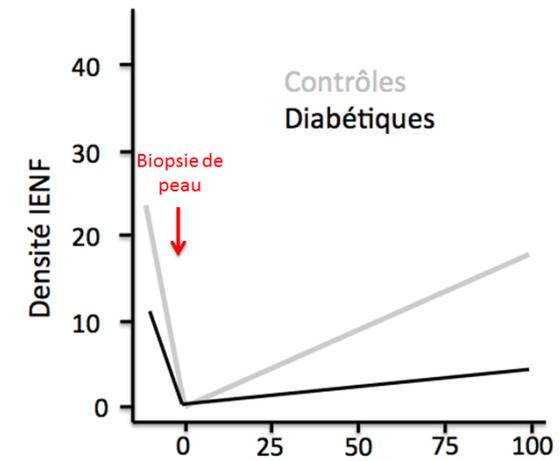
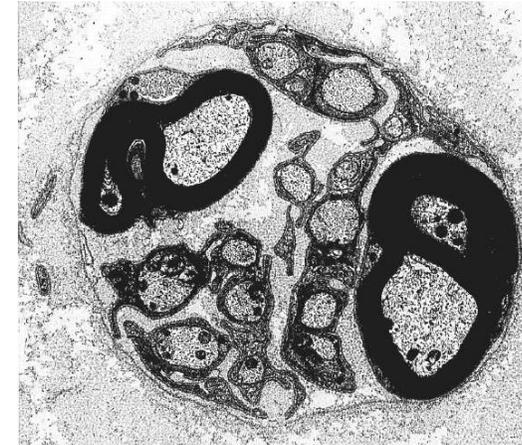
Bleu toluidine

Petites fibres



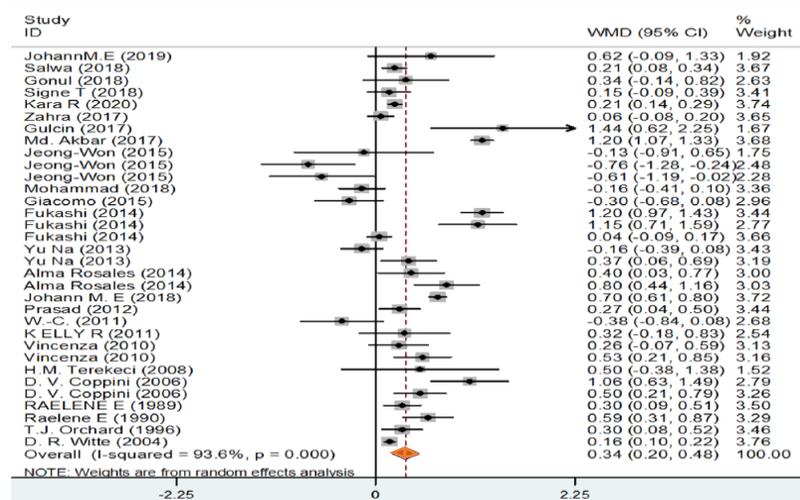
PGP 9.5

Défaut de régénération

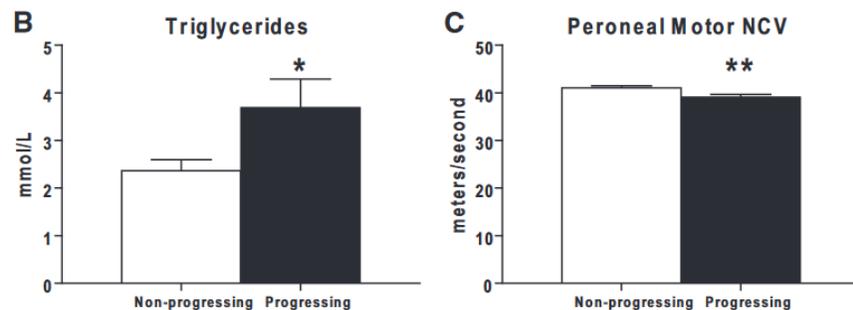


Diabète et dyslipidémie

Augmentation TG PDN chez DT1 et DT2



Cai, Sci Rep 2021



Augmentation TG dans la neuropathie progressive

Wiggin, Diabetes 2009

Fibrates / Statines

N=1237 DT2

Prevalent neuropathy	Odds ratio (95% CI)	p value
Age (increase of 10 years)	2.28 (1.93–2.69)	<0.001
Height (increase of 1 cm)	1.04 (1.03–1.06)	<0.001
Diabetes duration (increase of 5 years)	1.18 (1.07–1.31)	0.001
Log _e (urinary albumin:creatinine) ^a (mg/mmol)	1.18 (1.07–1.30)	0.001
Fasting serum glucose (increase of 1 mmol/l)	1.08 (1.03–1.12)	0.001
Systolic blood pressure (increase of 10 mmHg)	0.93 (0.87–0.99)	0.020
On fibrate therapy	0.30 (0.10–0.86)	0.025
Aboriginal background	3.70 (1.17–11.70)	0.026
Overweight/obese (by waist circumference)	1.58 (1.05–2.39)	0.029

N=395 DT2 initialement sans neuropathie

Incident neuropathy	HR (95% CI)	p value
Age (increase of 10 years)	1.86 (1.60–2.15)	<0.001
Other European ethnicity	1.77 (1.15–2.72)	0.010
Asian ethnicity	0.20 (0.05–0.84)	0.028
Retinopathy (any)	1.61 (1.10–2.37)	0.015
Married/de facto relationship	0.75 (0.57–0.98)	0.038
Time-dependent fibrate use	0.51 (0.27–0.97)	0.040
Time-dependent statin use	0.70 (0.49–0.997)	0.048

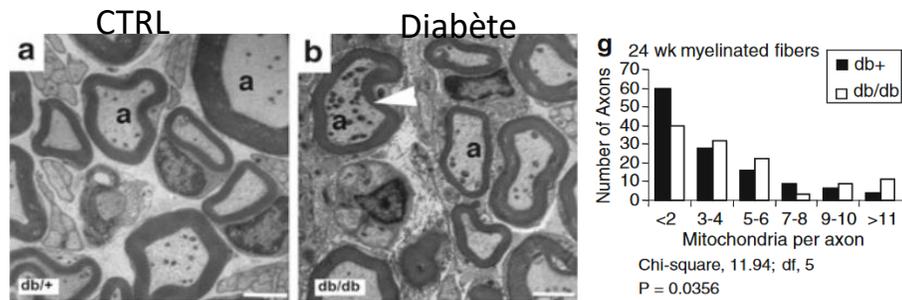
Durée de traitement par fibrates et statines associée à un moindre risque de développer une DPN

Davis, Diabetologia 2008

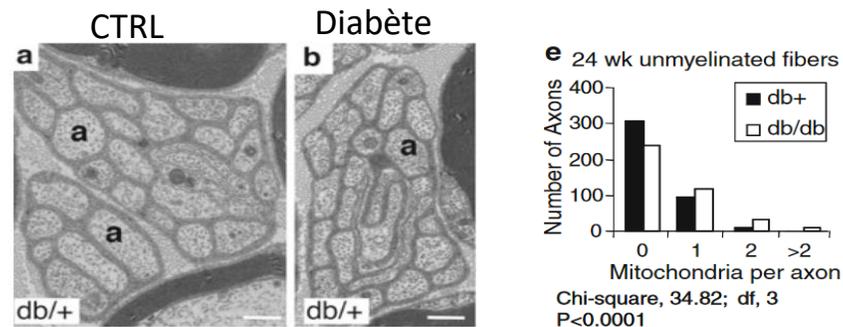
Mitochondries

Souris db/db
de 24 sem

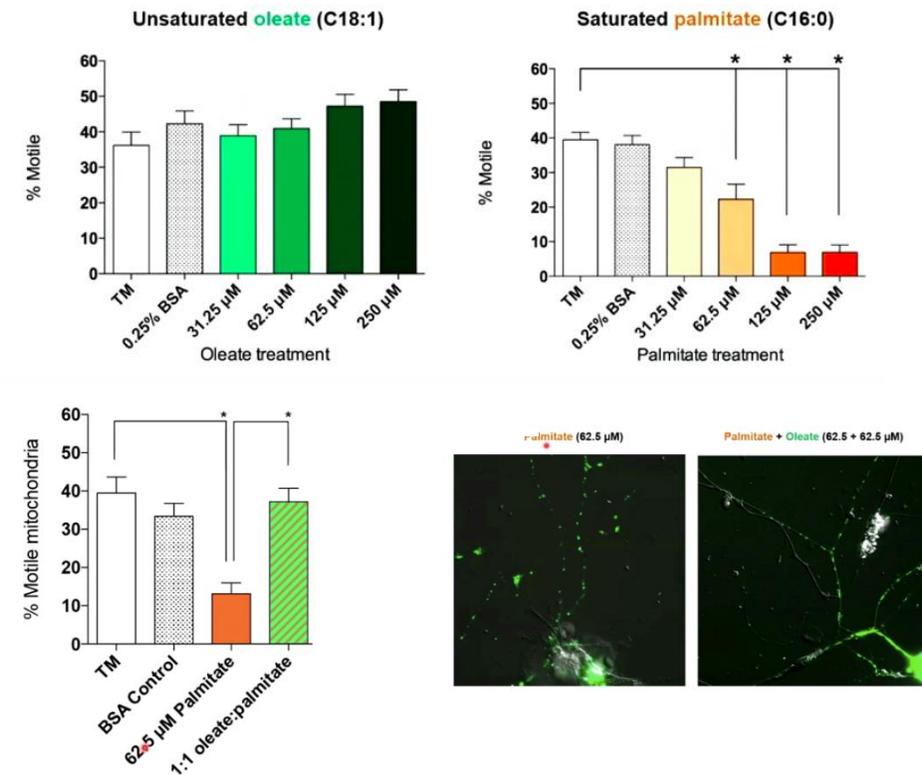
Mitochondries et diabète



Augmentation des mitochondries des axones myélinisés et non myélinisés provenant des DRG



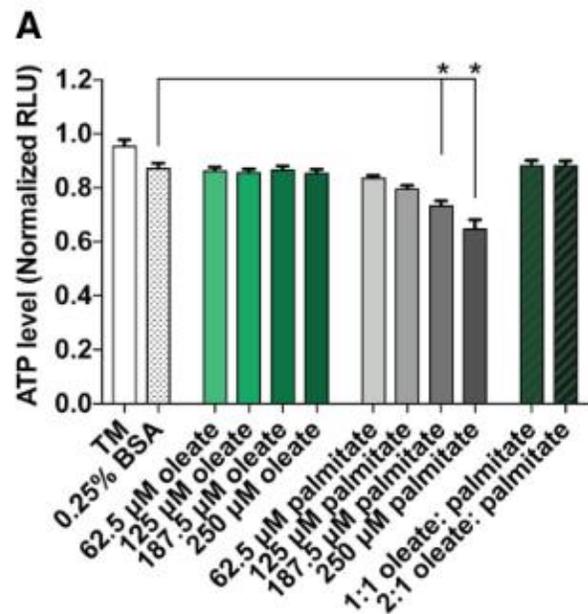
Trafic mitochondrial et oléate vs palmitate



Palmitate affecte le trafic mitochondrial
L'oléate prévient l'altération induite par le palmitate

Effets de l'hypertriglycéridémie

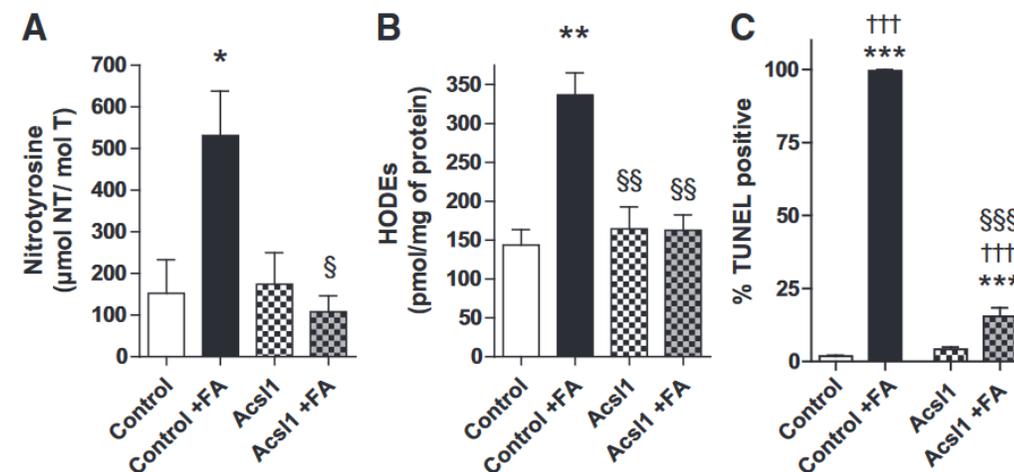
Production d'ATP



MUPA

↘ production ATP

Stress oxydant et cellules de Schwann

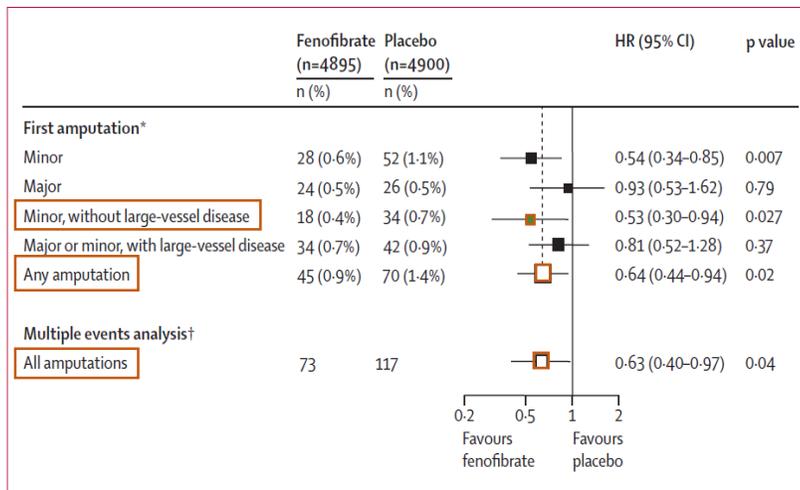


Surexpression de Acs11 et un prétraitement par antioxidant sont protecteurs du stress oxydant induit par les LCFA

Neuropathie diabétique et dyslipidémie

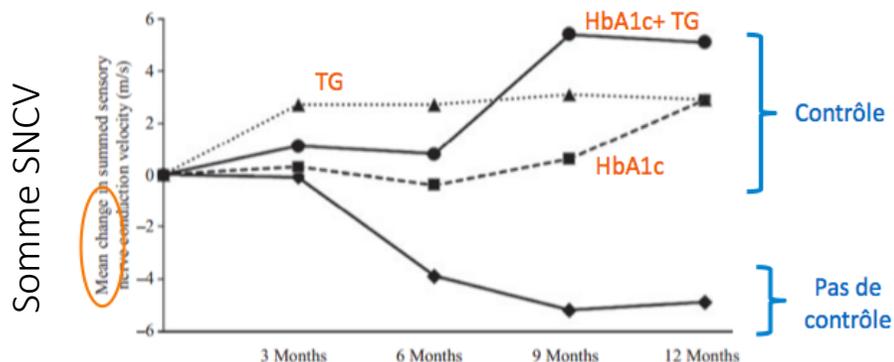
Moins d'amputation sous fibrates

Etude Field



Rajamani, Lancet 2009

Amélioration SNCV quand on contrôle TG et HbA1c



Supplémentation acides gras Omega-3

RCDB vs P

Deux capsules par jours pdt 6 mois

1,080 mg/j EPA (acide eicosapentaenoique) et 720 mg/j DHA (acide docosahexaenoique)

Placébo: huile d'olive n-9 MUFA 600 mg/j (acide oléique)

N=21 + 22

	n-3 PUFAs			Placebo			n-3 PUFAs vs. placebo	P*
	Baseline (n = 21)	Day 180 (n = 21)	Change from baseline (n = 21)	Baseline (n = 22)	Day 180 (n = 19)	Change from baseline (n = 19)		
Primary outcome: CNFL (mm/mm ²)	11.49 (3.34)	13.55 (3.58)	2.06 (1.73)	12.38 (3.21)	11.41 (3.66)	-0.72 (1.68)	2.70 (1.64, 3.75)	<0.001
Key secondary outcomes								
CNFD (nerves/mm ²)	19.93 (7.72)	23.41 (8.08)	3.48 (4.15)	20.27 (7.36)	18.45 (7.57)	-1.57 (4.02)	4.98 (2.51, 7.44)	0.004
CNBD (branches/mm ²)	19.69 (10.76)	27.06 (13.59)	7.37 (6.34)	23.48 (10.27)	19.54 (12.64)	-3.68 (7.35)	11.23 (7.01, 15.45)	0.002
Central corneal sensitivity threshold (mbar)								
Room-temperature stimulus†	0.47 (0.38-0.75)	0.38 (0.25-0.60)	-0.12 (-0.20 to -0.00)	0.30 (0.28-0.45)	0.30 (0.22-0.62)	0.12 (-0.03 to 0.20)	0.84 (0.60, 1.16)††	0.39†
Cooled stimulus†	0.43 (0.30-0.70)	0.35 (0.22-0.60)	-0.07 (-0.20 to 0.03)	0.32 (0.15-0.47)	0.40 (0.20-0.52)	0.05 (-0.00 to 0.20)	0.81 (0.54, 1.20)†§	0.29§

Britten-Jones, Diabetes 2021

Diabète et règles hygiéno-diététiques

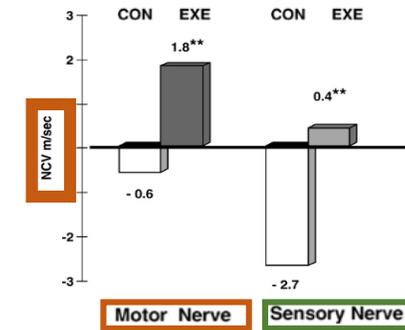
Amélioration VPT

	CON		EXE	
	Baseline	4 years	Baseline	4 years
<i>n</i>	47	47	31	31
<i>VPT</i>				
VPT Malleolus (mV)	18.6±8.5	21.4±9.60	17.9±6.20	17.9±6.90
VPT Hallux (mV)	14.2±6.7	16.7±9.23	14.1±4.00	13.6±7.00*
Patients with VPT altered	0 (0%)	10 (21.2%)	0 (0.0%)	4 (12.9%)*

Randomisée prospective
Exercice physique supervisé
Evaluation à 4 ans

Balducci, J Diab Complic 2006

Amélioration VCN



Amélioration force mais pas de IENFD

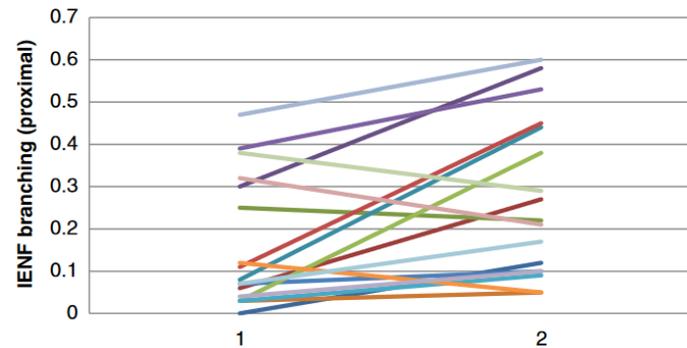
Variable	Healthy control group		<i>p</i> value	Individuals without DPN		<i>p</i> value	Individuals with DPN		<i>p</i> value	Between group effect <i>p</i> value ^a
	Non-PRT (<i>n</i> = 16)	PRT (<i>n</i> = 14)		Non-PRT (<i>n</i> = 17)	PRT (<i>n</i> = 13)		Non-PRT (<i>n</i> = 15)	PRT (<i>n</i> = 15)		
Muscle strength										
Ankle dorsal, plantar flexion, Nm	-0.7 ± 9.7 (-5.9, 4.5)	-2.2 ± 4 (-4.6, 0.7)	0.58	1.2 ± 13.1 (-5.5, 8.0)	2.6 ± 4.2 (0.1, 5.2)	0.7	-0.3 ± 6.8 (-4.0, 3.5)	4.8 ± 10.2 (-0.9, 11)	0.12	0.36
Knee-extension, knee flexion, Nm	-0.4 ± 8.4 (-4.5, 4)	6.3 ± 9.0 (1.1, 12)	0.04*	0.6 ± 8.8 (-4.0, 5.0)	7.5 ± 5.8 (4.0, 11)	0.02*	-0.4 ± 8.2 (-5.0, 4.1)	10.3 ± 9.6 (5.0, 15.7)	0.002*	0.56
Motor function										
6MWT, m	-19.6 ± 79.7 (-63.7, 24.5)	-6.14 ± 44 (-31, 19)	0.58	9.2 ± 38.1 (-10.4, 28.8)	9.4 ± 24.4 (-5.3, 24.2)	0.44	2.7 ± 19.6 (-15, 9)	34.6 ± 40.9 (11.9, 57.2)	0.001*	0.2
FTSST, s	-0.6 ± 0.9 (-1, -0.04)	-0.9 ± 1.2 (-1.7, 0.1)	0.4	-0.7 ± 1.4 (-1.4, 0.1)	-1.5 ± 0.9 (-2.1, -0.9)	0.08	1.5 ± 4.6 (-1.2, 4.2)	-1.5 ± 2.2 (-2.8, -0.3)	0.02*	0.06
Postural instability index										
ST in neutral positions	1.2 ± 2.5 (-0.1, 2.5)	-0.9 ± 2.9 (-2.6, 0.7)	0.03*	-1.0 ± 3.5 (-2.8, 0.8)	-0.5 ± 3.2 (-2.5, 1.5)	0.7	-0.9 ± 4.8 (-3.6, 1.8)	0.7 ± 5.5 (-2.6, 4.2)	0.40	0.2
ST in tilt/turn positions	-0.3 ± 5.3 (-3.1, 2.5)	-0.3 ± 4.2 (-2.8, 2.1)	0.9	1.3 ± 4.5 (-1.2, 3.8)	-2 ± 4.6 (-4.7, 0.8)	0.07	1.0 ± 8.5 (-3.7, 5.7)	-3.6 ± 14.2 (-12, 5)	0.3	0.5
Clinical neuropathy score										
TCNS	-1.3 ± 2.5 (-2.7, 0.0)	0.0 ± 1.4 (-0.9, 0.7)	0.1	1 ± 3 (-1.0, 2.1)	-1.3 ± 3.2 (-3.0, 0.2)	0.05	-0.1 ± 2.7 (-2.0, 1.4)	-1 ± 2.7 (-2.5, 0.5)	0.3	0.05
Diabetes and clinical profile										
BMI, kg/m ²	-0.4 ± 1.0 (-0.7, 0.6)	-0.1 ± 1.1 (-0.1, 0.6)	0.42	0.2 ± 1.8 (-0.6, 1.0)	0.3 ± 0.5 (0.1, 0.6)	0.77	-0.4 ± 1.0 (-0.9, 0.1)	-0.1 ± 1.1 (-0.6, 0.4)	0.42	0.95
Waist circumference in men, cm	-0.4 ± 2.5 (-2.6, 1.7)	-1.1 ± 2.9 (-3.1, 0.1)	0.6	-1.8 ± 5.2 (-7.3, 3.7)	0.5 ± 1.2 (-1.4, 2.5)	0.4	-0.9 ± 3.2 (-3.2, 1.4)	-1.1 ± 3.6 (-4.5, 0.7)	0.5	0.42
Waist circumference in women, cm	-3.5 ± 4.8 (-8.1, 0.9)	-7.8 ± 6.0 (-17, 1.9)	0.2	-2.1 ± 3.0 (-4.2, 0.1)	-2.9 ± 4.5 (-6.4, 0.6)	0.6	1.6 ± 3.5 (-2.7, 6.0)	2.9 ± 1.6 (0.9, 5.0)	0.5	0.32
HbA _{1c} , mmol/mol	0.5 ± 1.2 (-0.1, 1.1)	-0.1 ± 1.1 (-0.6, 0.5)	0.18	2.5 ± 4.0 (0.5, 4.4)	-0.2 ± 3.5 (-2.2, 1.7)	0.07	-0.9 ± 5.5 (-3.7, 1.9)	-3.0 ± 5.2 (-5.6, -0.4)	0.30	0.55
HbA _{1c} , %	0.1 ± 0.1 (-0.0, 0.1)	-0.1 ± 0.1 (-0.1, 0.1)	0.18	0.2 ± 0.4 (0.0, 0.4)	-0.0 ± 0.3 (-0.2, 0.2)	0.07	-0.1 ± 0.5 (-0.4, 0.2)	-0.3 ± 0.5 (-0.5, -0.1)	0.30	0.55

SBRC
3 mois d'exercice
N =102
42 DPN + sans 35
DPN + 35 HC

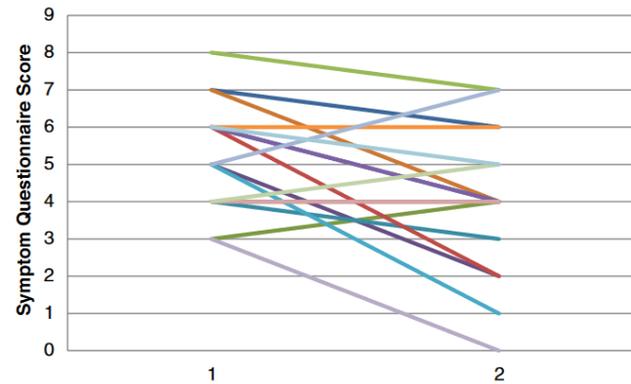
Diabète et règles hygiéno-diététiques

19 DT2 HbA1C 7.8% durée 12.4 ± 12.2 ans
10 sem exercice 50 -> 70% VO2max, 30 -> 50 min /j

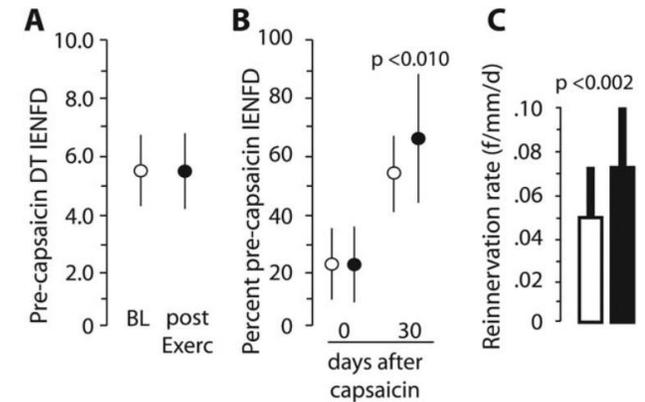
↗ Branchements IENF



↘ Douleurs



↗ capacités de régénération après exercice



Chez les patients avec amélioration du syndrome métabolique

Traitement pluri factoriel

Etude Steno-2

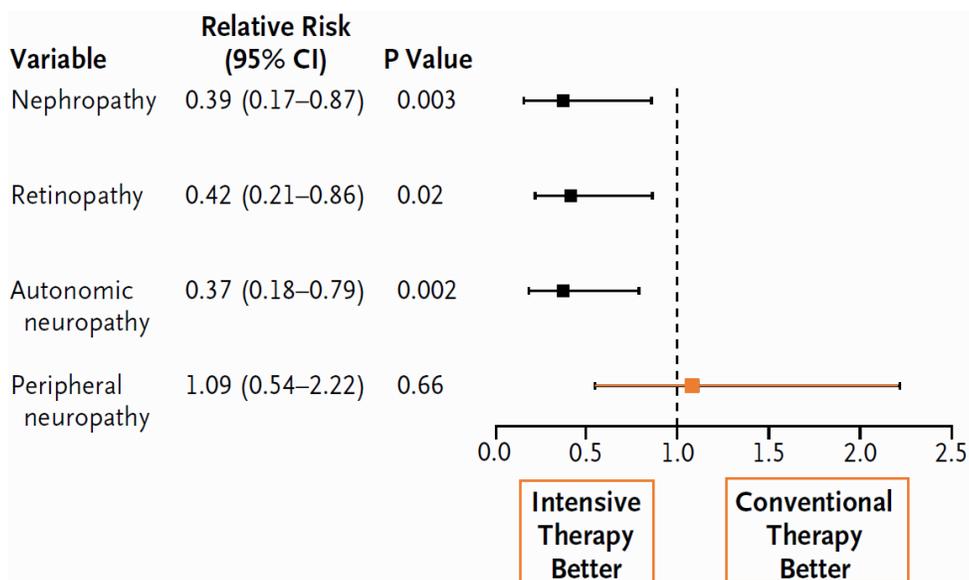
- 160 patients DT2
- Traitement médicamenteux
 - hyperglycémie, HTA, dyslipidémie et microalbuminurie

Look AHEAD

Etude prospective randomisée multicentrique (16) simple aveugle 2001-2012; DT2; surcharge pondérale ou obésité; 45-76 ans
 -ILI (intensive life style modification): perte de poids et éducation physique
 -DES (diabetes support and education)

Traitement HbA1c, Chol tot, PAS, LDL chol, PAD, TG

Hygiène de vie

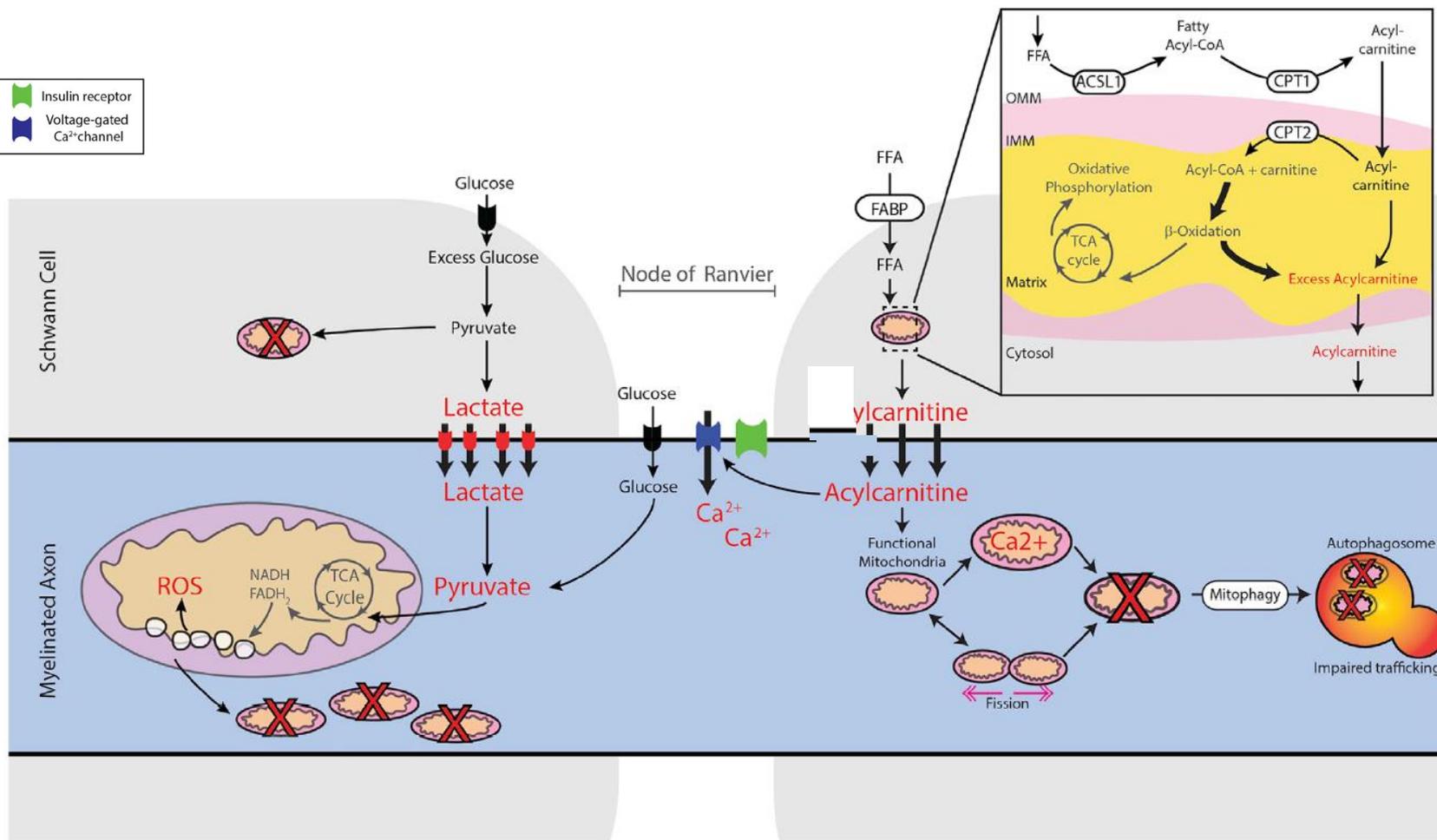
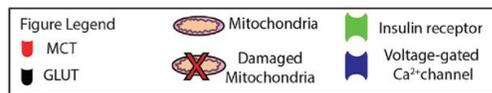


Test result	All participants (n = 3775)	DSE group (n = 1870)	ILI group (n = 1905)	p value for ILI vs DSE
<u>MNSI physical examination score^a</u>				
MNSI score <2.5	1224 (32.42)	603 (32.25)	621 (32.60)	0.82
MNSI score ≥2.5	2551 (67.58)	1267 (67.75)	1284 (67.40)	
<u>Monofilament testing of light touch perception^b</u>				
Left big toe 8–10	2790 (74.08)	1355 (72.58)	1435 (75.57)	0.11
Left big toe 1–7	793 (21.06)	414 (22.17)	379 (19.96)	
Left big toe 0	183 (4.86)	98 (5.25)	85 (4.48)	
Right big toe 8–10	2752 (73.06)	1338 (71.70)	1414 (74.38)	0.18
Right big toe 1–7	831 (22.06)	433 (23.20)	398 (20.94)	
Right big toe 0	184 (4.88)	95 (5.09)	89 (4.68)	
Either big toe <8	1222 (32.44)	644 (34.49)	578 (30.42)	0.008

Développement ou progression de la neuropathie pendant traitement

Amélioration tact gros orteil

Rôle de la cellule de Schwann



Ralentissement de la conduction nerveuse

associé à un plus grande gravité clinique

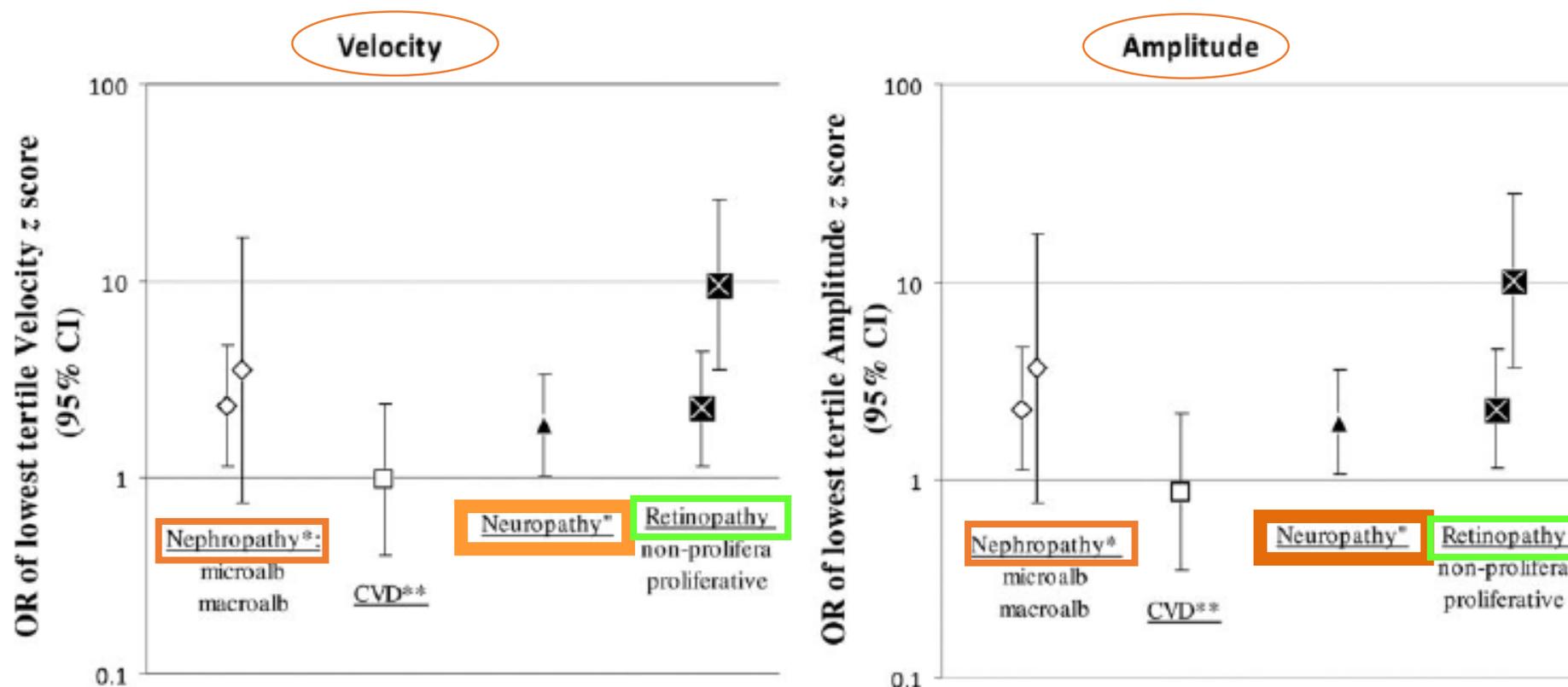
111 DT2

Longitudinale: Nov 2008 – dec 2012

PDN: 1 sural ou Fib + 1 signe ou spt

	Axonal	Conduction slowing	Combined	ANOVA P for trend
<i>n</i>	51	29	31	
Age (years)*	61.9 ± 10.7	61.5 ± 11.8	68.9 ± 8.7	0.007
Male, <i>n</i> (%)	37 (73)	24 (86)	23 (77)	0.39
BMI (kg/m ²)	30.6 ± 6.1	31.5 ± 4.4	31.2 ± 7.0	0.86
Duration of DM (years)	14.9 ± 7.9	15.2 ± 10.6	16.4 ± 10.3	0.78
Duration of PNP (years)	7.1 ± 4.1	5.4 ± 4.8	10.6 ± 6.0	0.03
Systolic blood pressure (mmHg)	132.2 ± 13.8	140.8 ± 17.7	151.6 ± 21.4	0.02
Diastolic blood pressure (mmHg)	75.8 ± 7.2	77.1 ± 10.5	79.9 ± 8.1	0.43
VPT, upper right	5.2 ± 2.1	5.9 ± 2.5	7.3 ± 2.5	0.002
VPT, upper left	5.3 ± 2.1	6.0 ± 2.5	7.3 ± 2.3	0.001
VPT, lower right	18.4 ± 9.4	29.1 ± 14.0	33.4 ± 12.0	<0.0001
VPT, lower left	18.2 ± 9.0	28.5 ± 13.0	33.5 ± 11.7	<0.0001
TCNS, median (IQR)	9 (7–11.5)	11 (8–14)	12 (10.8–15)	0.003
DTR, median (IQR)†	2 (1.5–6)	4 (2–6)	6 (3.5–6)	0.004
Retinopathy, <i>n</i> (%)	7 (15)	4 (14)	5 (19)	0.89
Nephropathy, <i>n</i> (%)	10 (21)	5 (18)	6 (23)	0.89
Hypertension, <i>n</i> (%)	29 (69)	17 (71)	18 (75)	0.87
HbA _{1c} , % (mmol/mol)‡	7.9 ± 1.6 (63.0 ± 17.5)	8.1 ± 2.0 (65.0 ± 21.9)	7.2 ± 1.1 (55.0 ± 31.6)	0.18
Nerve conduction parameters				
Sural nerve amplitude potential (μV)	4.08 ± 2.1 (0–11.1)§	2.18 ± 1.6 (0–5.0)	0.22 ± 0.6 (0–1.8)	<0.0001
Sural nerve distal latency (ms)	3.33 ± 0.3 (2.6–3.8)	3.75 ± 0.4 (3.0–4.6)	3.63 ± 0.2 (3.4–3.9)	<0.0001
Sural nerve conduction velocity (m/s)	42.0 ± 3.9 (36.4–51.9)	37.6 ± 4.0 (30.4–46.7)	33.7 ± 2.2 (35.9–41.2)	0.0001
Peroneal nerve amplitude potential, ankle (mV)	3.45 ± 1.5 (0.2–7.8)	2.32 ± 1.6 (0–7.3)	0.26 ± 0.3 (0–0.8)	<0.0001
Peroneal nerve amplitude potential, knee (mV)	3.29 ± 1.9 (0.2–13.1)	2.0 ± 1.3 (0–5.4)	0.2 ± 0.2 (0–0.7)	<0.0001
Peroneal nerve distal latency (ms)	4.52 ± 0.5 (3.4–6.0)	5.01 ± 0.7 (3.9–6.2)	6.11 ± 1.5 (4.1–9.3)	<0.0001
Peroneal nerve conduction velocity, fibular head (m/s)	40.0 ± 2.1 (35.5–45.2)	35.5 ± 2.5 (29.8–39.0)	32.0 ± 5.1 (22.0–39.2)	<0.0001
Peroneal nerve conduction velocity, popliteal fossa (m/s)	41.8 ± 2.8 (36.4–47.2)	37.2 ± 2.7 (30.8–40.9)	34.7 ± 5.3 (22.3–41.2)	<0.0001
Peroneal nerve F-wave (ms)	55.8 ± 6.2 (28.2–65.5)	62.4 ± 3.7 (56.3–70.0)	NR (NR–NR)	0.0004
Conduction block (%)	4.5 ± 36.8	10.7 ± 13.3	19.8 ± 26.7	0.15

Association atteinte microvasculaire



Corrélation entre atteinte EMG et atteinte microvasculaire

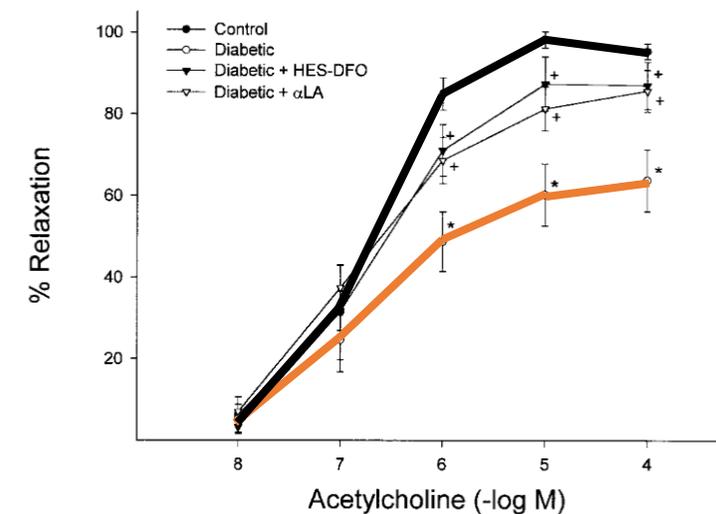
Capillaires

Densité capillaire

	Diabetes	IGT	NGT	P
<i>n</i>	12	7	6	—
Capillary morphology				
Endoneurial capillary density (number/mm ²)	86.0 (24.3)*	56.1 (22.8)	54.9 (17.1)	0.0380
Luminal area (μm ²)	14.0 (5.2)	13.3 (14.5)	20.8 (4.9)	0.0787
Basement membrane area (μm ²)	80.7 (42.8)	98.4 (26.7)	146.0 (58.4)	0.3065
Endothelial/pericyte nuclear ratio	2.4 (2.1)	2.5 (1.9)	2.0 (0.4)	0.1631
Nerve fiber morphology				
Light microscopy: MNFD (number/mm ²)	5,090 (914)	5,134 (1,400)	4,358 (1,276)	0.5425
Electron microscopy: MNFD (number/mm ²)	4,847 (763)	4,999 (1,530)	3,997 (1,428)	0.4329
Neurophysiology (sural nerve) at follow-up study				
SNAP (μv)	4.0 (7.5)	7.5 (4.0)	6.5 (2.0)	0.6276
SNCV (m/s)	44.5 (8.0)	48.5 (5.0)	48.0 (7.0)	0.0904

Augmentée chez les diabétiques

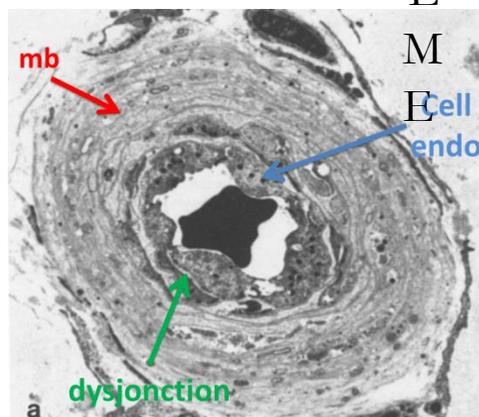
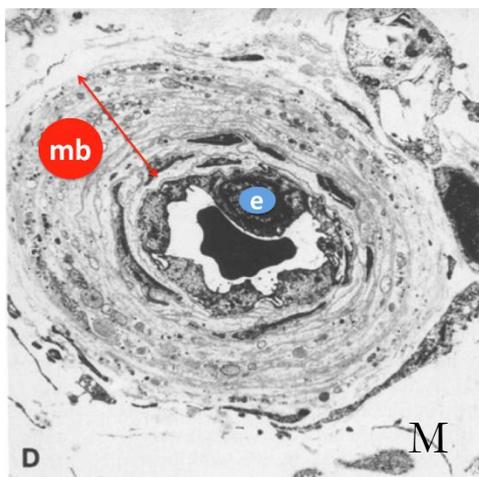
Vasoréactivité



Diminuée chez les diabétiques

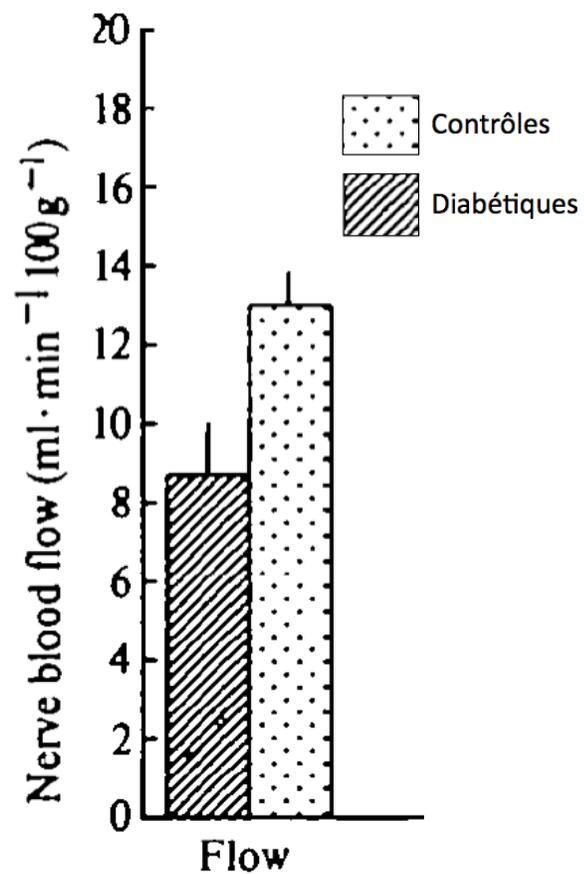
Microangiopathie

Modifications morphologiques



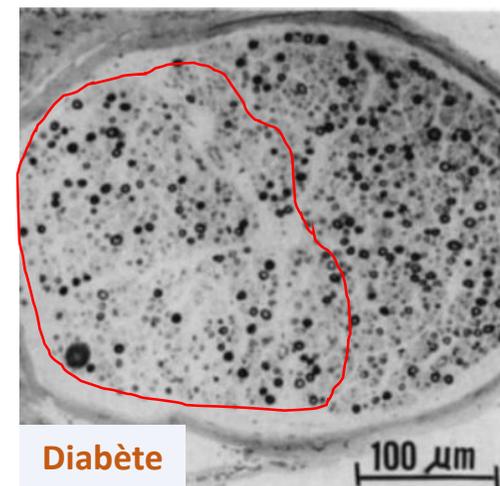
Malik, Diabetologia 1989

Diminution flux endoneural



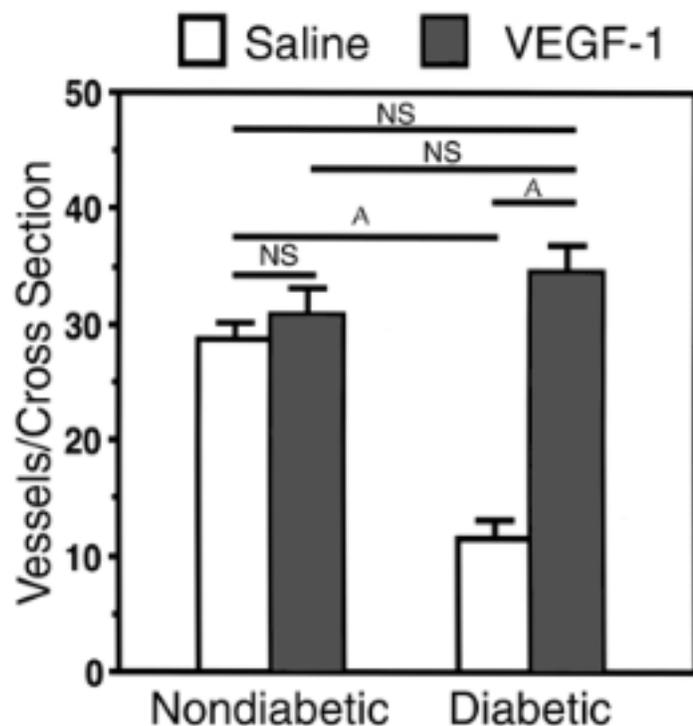
Tuck, Brain 1984

Perte en fibre centrofasciculaire

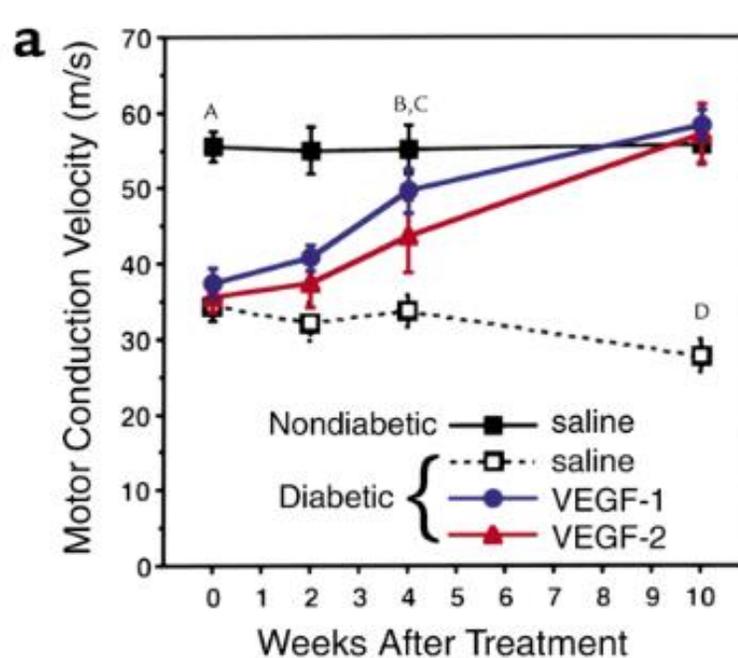


VEGF

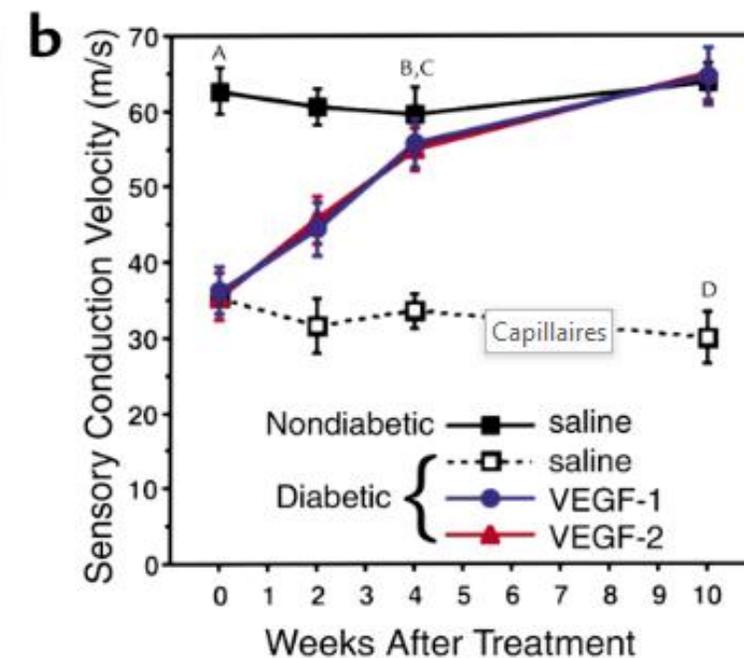
VEGF gene transfer
Female Sprague-Dawley rats



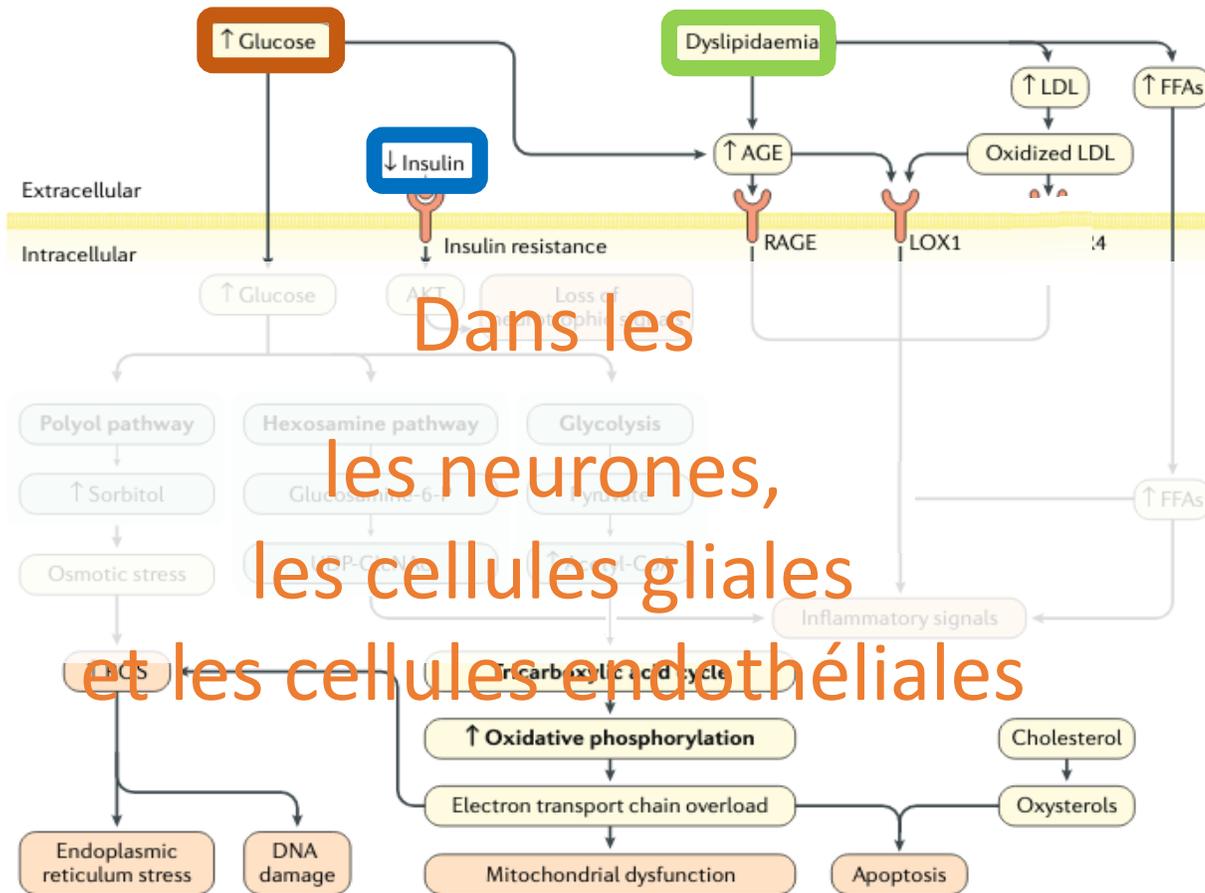
Augmente la densité de vasa nervorum



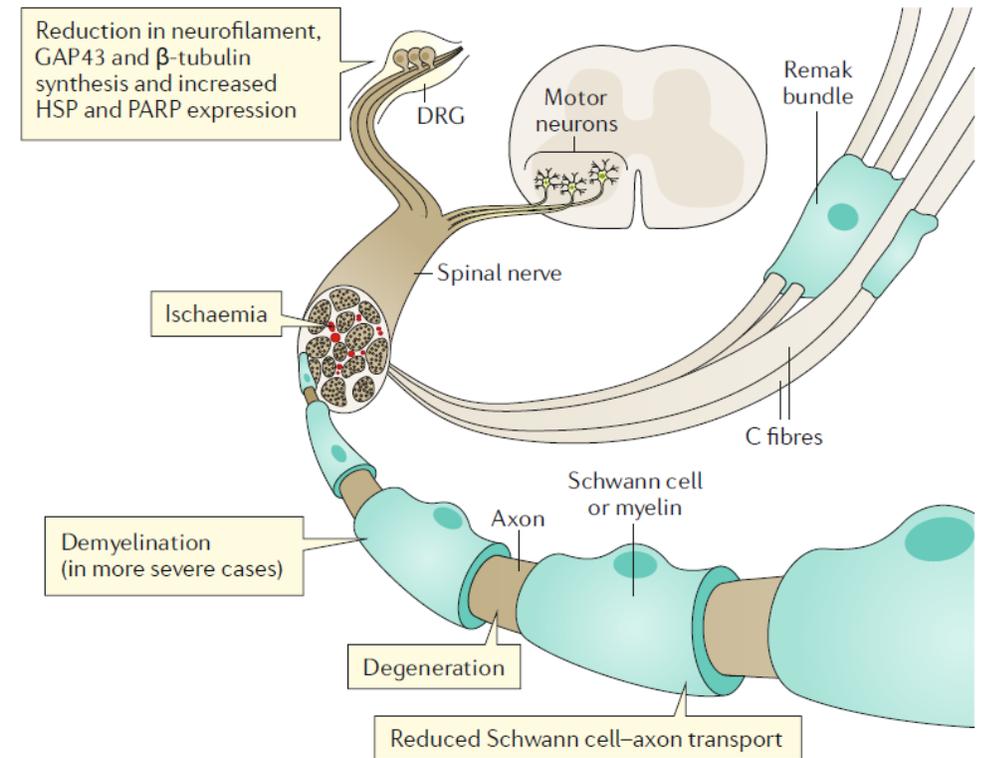
Corrige les vitesses de conduction nerveuse



Synthèse



Dans les
les neurones,
les cellules gliales
et les cellules endothéliales



Merci de votre attention

« Certains hommes parlent durant leur sommeil. Il n'y a guère que les conférenciers pour parler pendant le sommeil des autres ».

Alfred Capus (1858-1922)

« L'incompétent se présente toujours comme expert, le cruel comme pitoyable, le pécheur comme dévot, l'usurier comme bienfaiteur, l'arrogant comme humble, le vulgaire comme distingué et l'abruti comme intellectuel. »

Carlos Ruiz Zafón (1964-2020)