

Obésité et rein
Dysfonction rénale
Données épidémiologiques
Donnes physiopathologiques

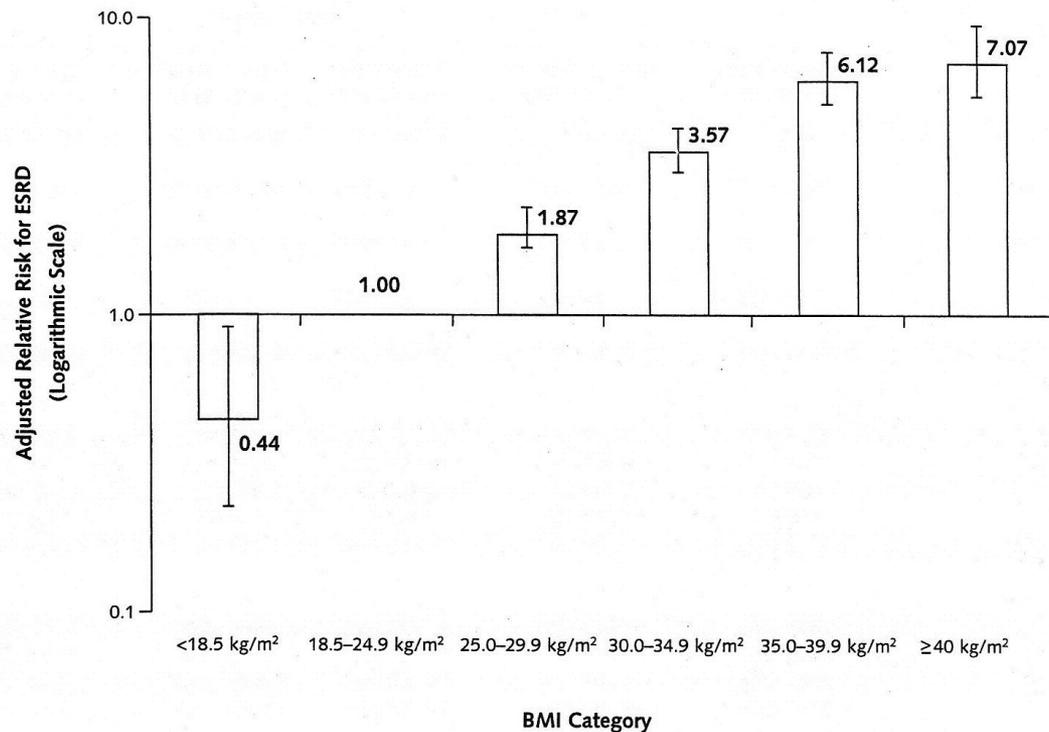
Académie nationale de Médecine - 09/03/2017

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Département de physiologie rénale
Hôpital Bichat

RISQUE RELATIF AJUSTÉ D'IRCT SELON L'IMC

POPULATION GENERALE

*Cohorte Kaiser Permanente (Californie du Nord), n = 320 252, Hsu CY. Ann Intern Med 2006
suivi de 15 à 35 ans*

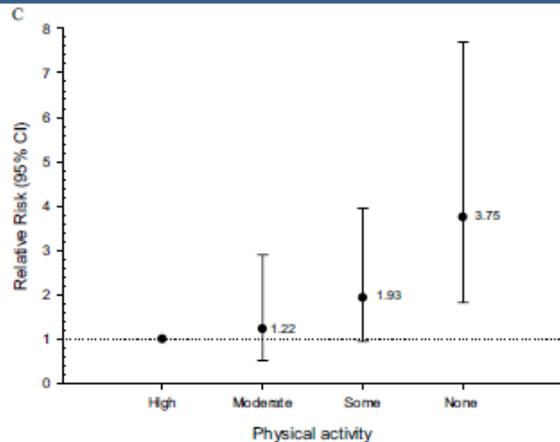
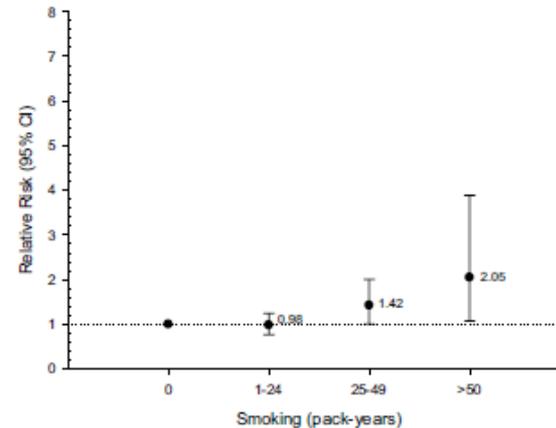
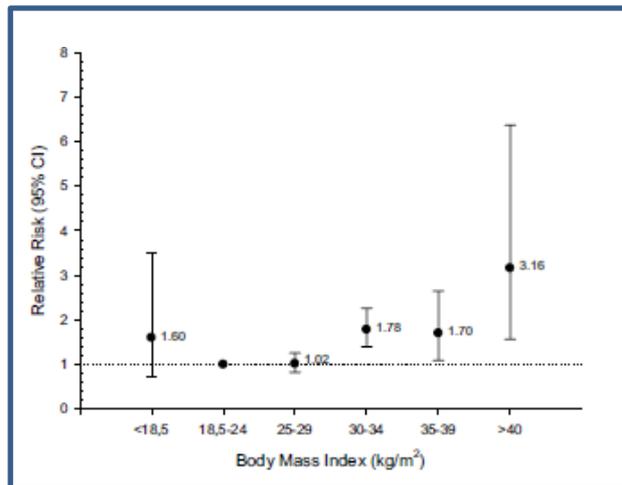


BMI >40kg/m²RR ESRD >7

indépendant HTA/Diabète/Tabac/Histoire IDM/ Cholestérol/ Pu/Hu/Niveau d'éducation

RISQUE RELATIF AJUSTÉ D'IRC stade 3 SELON L'IMC POPULATION GENERALE

Norway, Population-based, Cross-sectionnal, n = 65 193, Hallan SI. AJKD 2005



Critères d'ajustement : Age et sexe

1995
25,7 kg/m²

INITIATION DIALYSE



2005
27,5 kg/m²

1987
11,6%

OBESITE ATTENTE DE
TRANSPLANTATION



2001
25,1 %

Kramer JASN 2006
Friedman AmJKD 2003

POPULATION GENERALE

Healthy men, n = 11 104 Follow-up 14 ans , Gelber RP. AJKD 2005

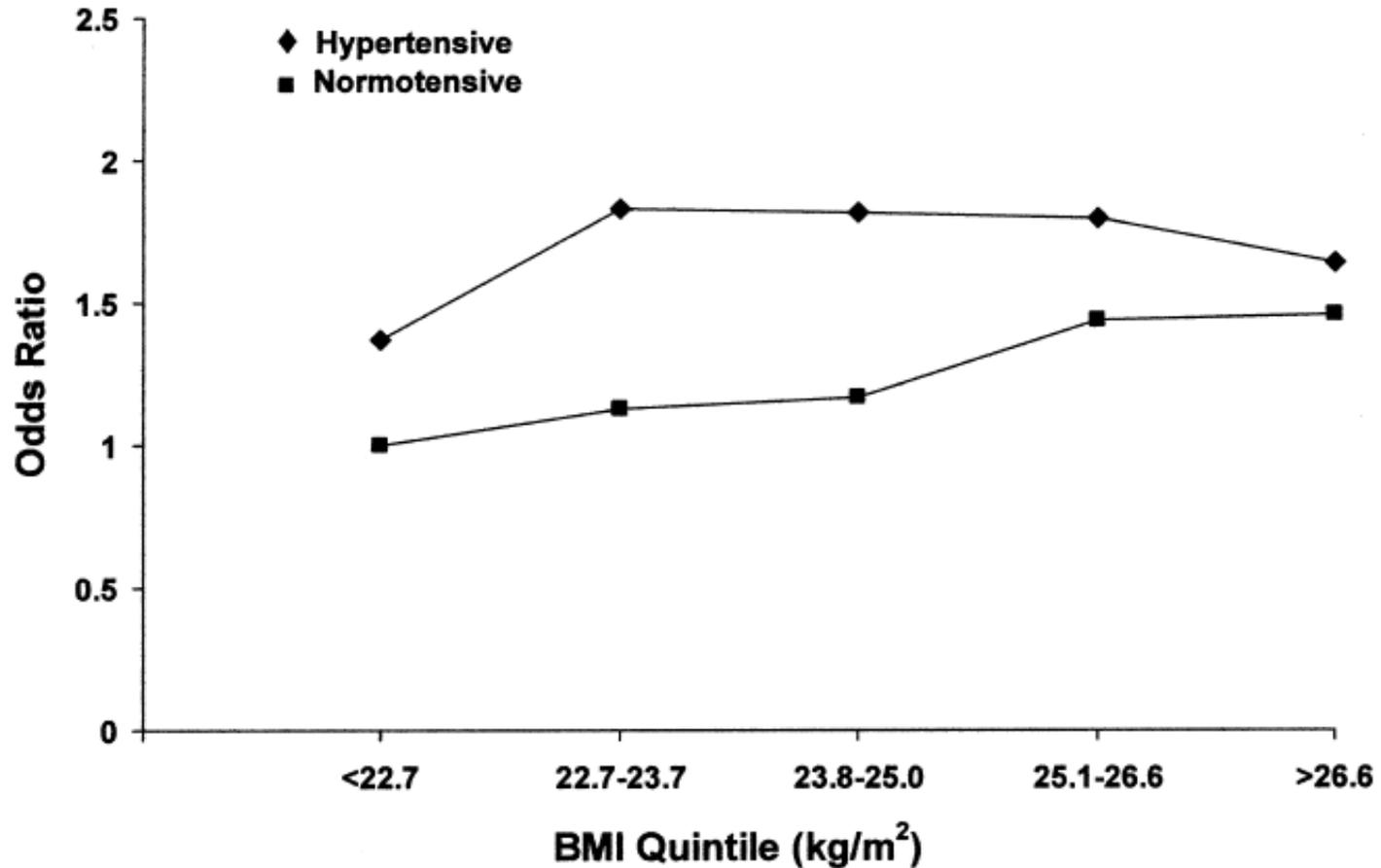


Fig 1. Age-adjusted ORs for decreased GFR (<60 mL/min/1.73 m² [<1.00 mL/s/1.73 m²]) at 14-year follow-up according to BMI quintile and hypertension status at baseline. Referent group (OR, 1.0): normotensive with BMI less than 22.7 kg/m² (*P* for trend: hypertensive, *P* = 0.70; normotensive, *P* < 0.001).

RISQUE RELATIF AJUSTÉ DE PROGRESSION DE LA MRC SELON L'IMC POPULATION GENERALE

Healthy men, n = 11 104 Follow-up 14 ans , Gelber RP. AJKD 2005

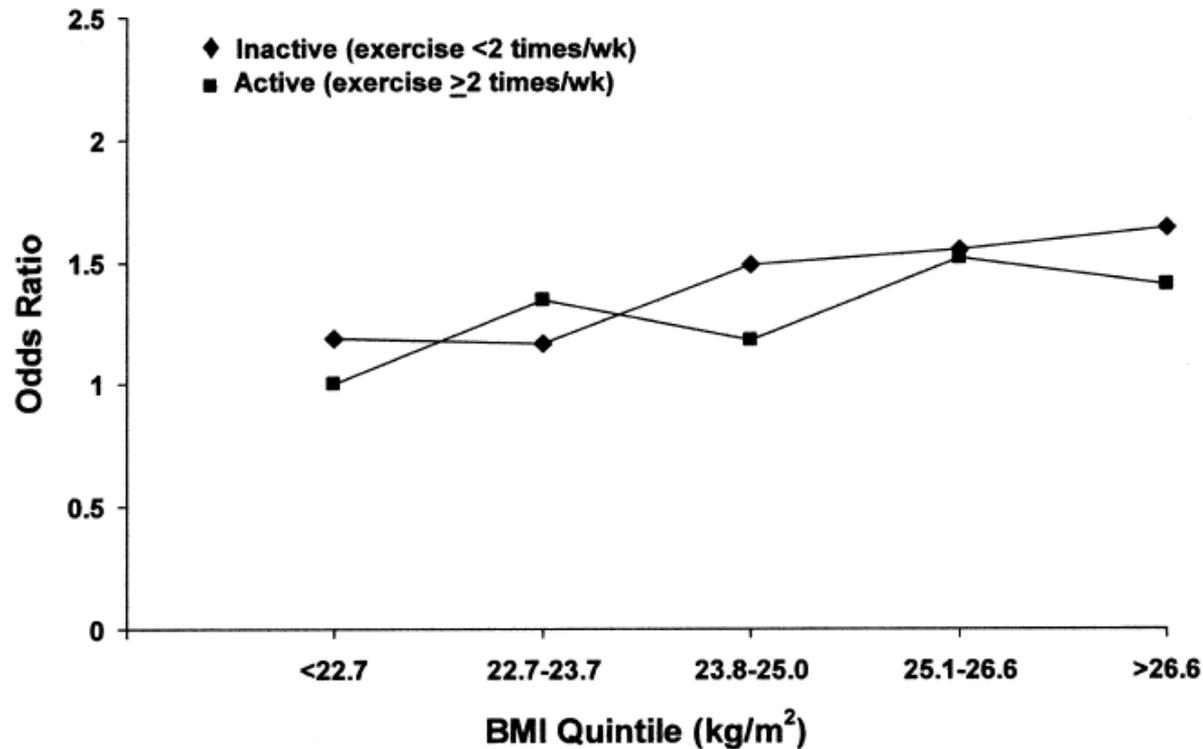
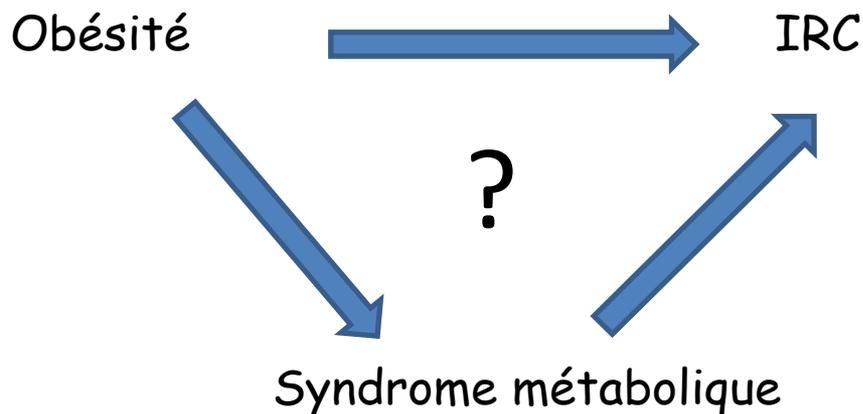


Fig 2. Age-adjusted ORs for decreased GFR (<60 mL/min/1.73 m² [<1.00 mL/s/1.73 m²]) at 14-year follow-up according to BMI quintile and physical activity level at baseline. Referent group (OR, 1.0): active with BMI less than 22.7 kg/m² (*P* for trend: inactive, *P* = 0.004; active, *P* = 0.007).



Facteurs de risque	Seuil retenu
Syndrome métabolique défini comme la présence d'au moins 3 des critères suivants:	
Tour de taille	>102 cm, homme >88 cm, femmes
Triglycérides	≥1,50 g/L
HDL cholestérol	<0,40 g/L, hommes <0,50 g/L, femmes
Pression artérielle	≥130/85 mm Hg
Glycémie à jeun	≥1,10 g/L

Risque relatif ajusté d'IRC (DFG < 60) selon le nombre de critères du syndrome métabolique

US, Population-based, Cross-sectionnal, n = 6 217, Chen J. Ann Int Med 2005

Variable	Odds Ratio of Chronic Kidney Disease (95% CI)					
	Crude	P Value	Multivariate-Adjusted†	P Value	Multivariate-Adjusted‡	P Value
Blood pressure ≥ 130/85 mm Hg	12.4 (7.66–20.2)	<0.001	2.66 (1.62–4.35)	<0.001	2.39 (1.43–4.01)	0.001
Serum HDL cholesterol level < 1.036 mmol/L (<40 mg/dL) in men or < 1.295 mmol/L (<50 mg/dL) in women	1.78 (1.21–2.63)	0.004	2.11 (1.37–3.27)	0.002	1.85 (1.16–2.95)	0.011
Serum triglyceride level ≥ 1.695 mmol/L (≥150 mg/dL)	2.55 (1.72–3.79)	<0.001	1.80 (1.20–2.69)	0.004	1.58 (1.04–2.40)	0.032
Plasma glucose level ≥ 6.10 mmol/L (≥110 mg/dL)	3.66 (2.61–5.12)	<0.001	1.40 (0.95–2.06)	0.092	1.16 (0.76–1.78)	>0.2
Waist circumference ≥ 102 cm in men and ≥ 88 cm in women	3.08 (2.14–4.42)	<0.001	2.07 (1.41–3.03)	<0.001	1.54 (0.94–2.53)	0.087
2 components§	4.86 (2.76–8.54)	<0.001	2.21 (1.16–4.24)	0.018	2.06 (1.10–3.86)	0.025
3 components§	8.52 (4.05–17.9)	<0.001	3.38 (1.48–7.69)	0.005	3.05 (1.31–7.07)	0.011
4 components§	12.2 (6.06–24.7)	<0.001	4.23 (2.06–8.63)	<0.001	3.67 (1.70–7.90)	0.001
5 components§	16.7 (9.55–29.1)	<0.001	5.85 (3.11–11.0)	<0.001	4.72 (2.31–9.64)	<0.001
Metabolic syndrome	5.34 (3.53–8.06)	<0.001	2.60 (1.68–4.03)	<0.001	2.21 (1.33–3.67)	0.003

* HDL = high-density lipoprotein.

† Adjusted for age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

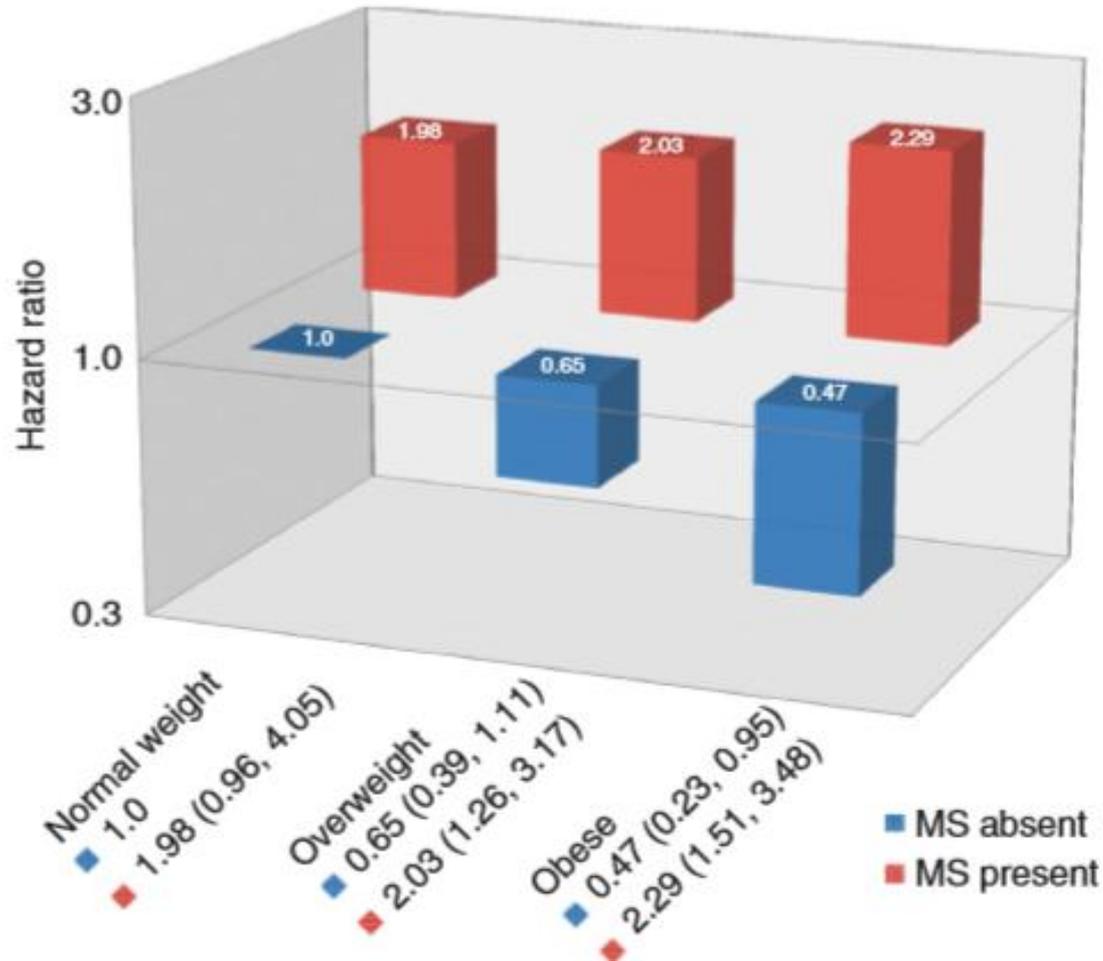
‡ Adjusted for body mass index in addition to age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

§ Compared with those with 0 or 1 component of the metabolic syndrome.

|| Compared with those with < 3 components of the metabolic syndrome.

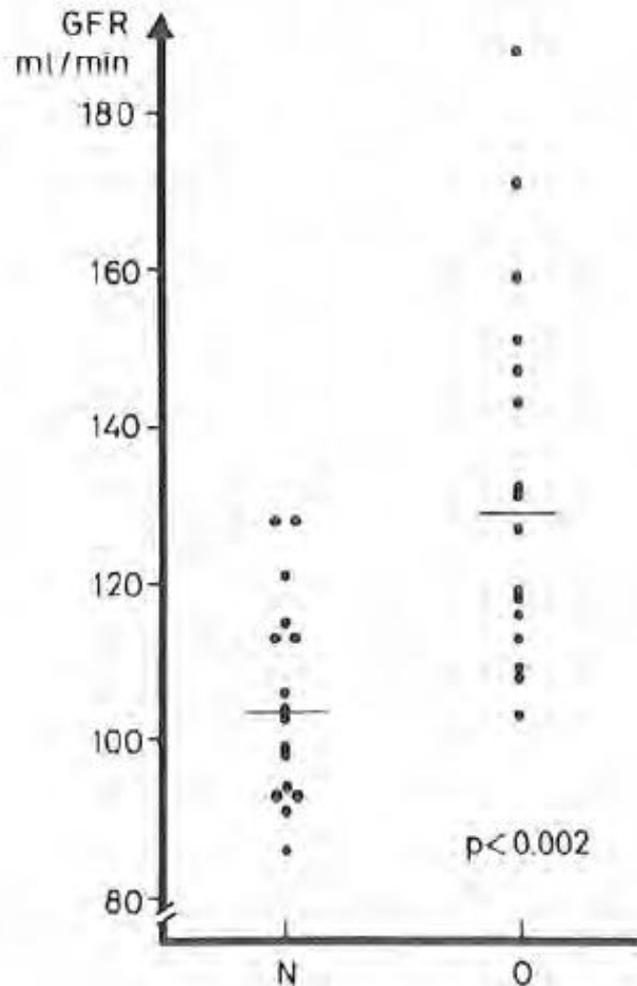
Risque relatif ajusté d'IRCT selon l'IMC et le syndrome métabolique

US, Population-based cohort (REGARDS), n = 21 840, Panwar B. KI 2015



Adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, history of coronary heart disease, and history of stroke

Hyperfiltration



*Clairance Cr-EDTA
Appariement âge et taille*

Fig. 1. GFR in 16 non-obese (N) and 16 obese (O) women. — indicates median value

Risque relatif ajusté de néphropathie selon l'IMC

Suède, Case-control, n = 926, Ejerblad E. JASN 2006



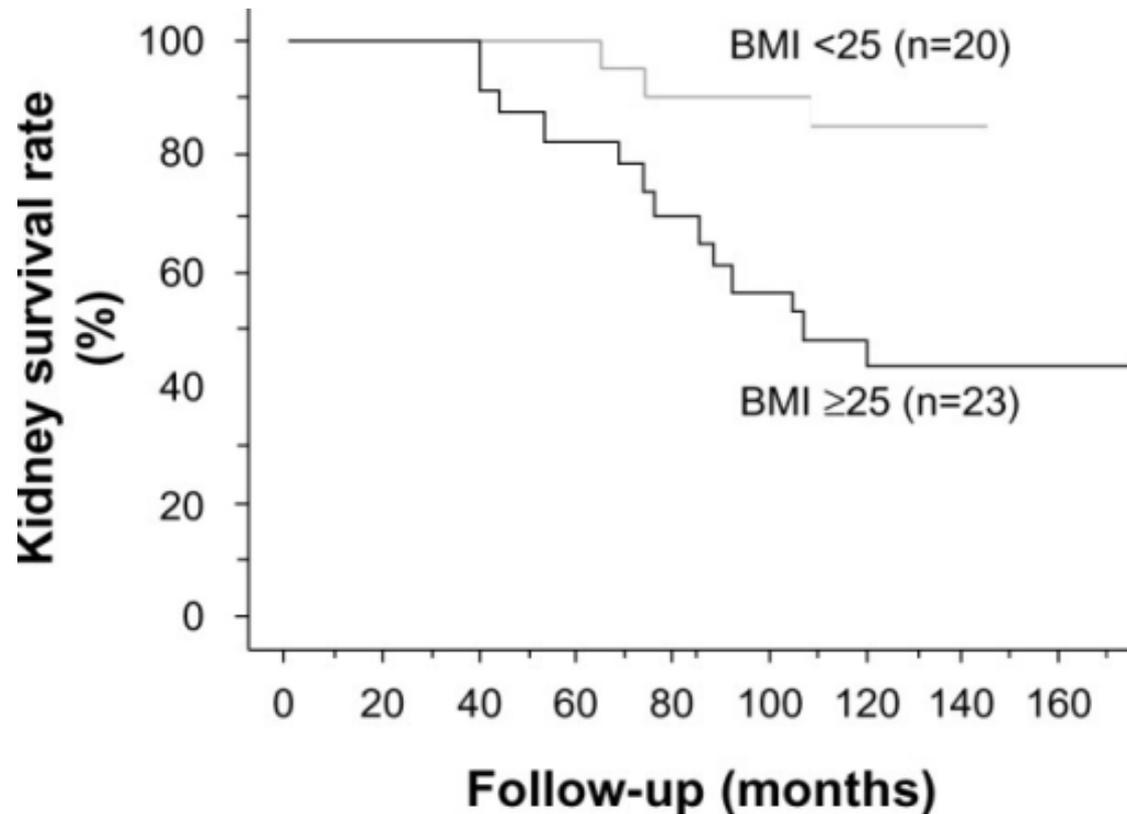
	No. of Control Subjects	Diabetic Nephropathy		Nephrosclerosis		Glomerulonephritis		Other	
		No. of Case Patients	OR ^a (95% CI)	No. of Case Patients	OR ^a (95% CI)	No. of Case Patients	OR ^a (95% CI)	No. of Case Patients	OR ^a (95% CI)
Highest BMI in lifetime (kg/m ²) ^b									
<25	349	59	1.0 (referent)	30	1.0 (referent)	58	1.0 (referent)	78	1.0 (referent)
25 to 29.9	456	90	1.2 (0.8 to 1.7)	61	1.4 (0.8 to 2.2)	99	1.3 (0.9 to 1.9)	130	1.3 (1.0 to 1.9)
30 to 34.9	125	65	2.8 (1.8 to 4.4)	32	2.4 (1.4 to 4.3)	43	2.0 (1.2 to 3.2)	39	1.5 (0.9 to 2.4)
≥35.0	35	56	7.4 (4.2 to 13.0)	12	2.8 (1.2 to 6.2)	14	2.0 (1.0 to 4.2)	22	2.0 (1.1 to 3.9)
BMI at age 20 (kg/m ²) ^c									
<25.00	780	149	1.0 (referent)	95	1.0 (referent)	154	1.0 (referent)	190	1.0 (referent)
≥25.00	53	49	5.2 (3.2 to 8.4)	18	3.0 (1.6 to 5.5)	30	3.0 (1.8 to 4.9)	25	2.1 (1.2 to 3.6)

^aAdjusted for age, gender, education, smoking, alcohol, and use of paracetamol and salicylates.

^bCut points in accordance with the WHO definition of overweight and obesity.

^cCut points in accordance with the WHO definition of overweight.

Risque évolutif néphropathie non lié à l'obésité IgA



Kataoka H, et al. Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. Clin Exp Nephrol. 2012;16(5):706–712.20

Albuminurie

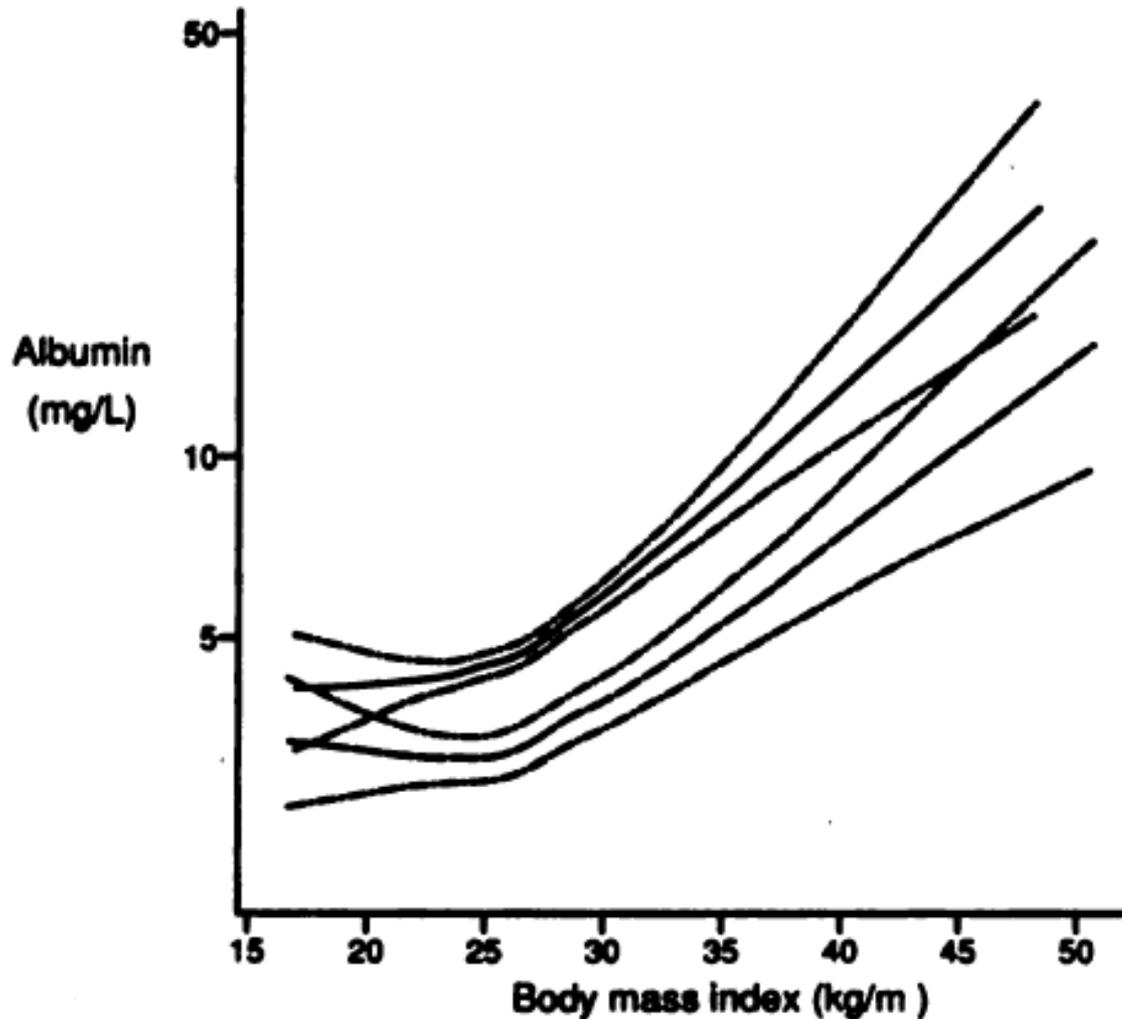


Fig. 3. Relationship between urinary albumin concentrations and body mass index in 4009 men (—) and 1416 women (---) who were Albustix negative and abacteriuric. Also shown are the 95% confidence intervals

Risque relatif ajusté d'albuminurie

Italie, Cross-sectionnal, n = 1 567, Cirillo M. Arch Int Med 1998

Table 5. Multiple Logistic Regression Analyses by Sex: Relationship of Other Variables to Prevalence of Microalbuminuria*

Variable	Difference	Difference in Relative Risk (95% Confidence Interval)			
		Urinary Albumin Excretion, ≥20 µg/min		Urinary Albumin Excretion, ≥25 µg/dL GFR†	
		Men	Women	Men	Women
Body mass index	4 kg/m ²	1.83 (1.23-2.72)‡	1.33 (0.91-1.93)	1.76 (1.16-2.67)‡	1.07 (0.74-1.55)
Systolic blood pressure	18 mm Hg	2.51 (1.80-2.98)§	1.62 (1.04-2.53)	1.82 (1.31-2.52)§	1.98 (1.40-2.82)§
Plasma cholesterol level	1.0 mmol/L (40 mg/dL)	2.25 (1.53-3.31)§	2.02 (1.25-3.26)‡	1.89 (1.27-2.81)‡	2.21 (1.47-3.31)§
Cigarette smoking	Yes vs no	1.99 (0.97-4.07)¶	1.91 (0.73-4.96)	2.53 (1.13-5.67)	2.32 (1.08-4.98)
Creatinine clearance†	20 mL/min	0.79 (0.55-1.40)	0.89 (0.53-1.47)	0.27 (0.16-0.43)§	0.29 (0.17-0.50)§

*Also in models: age; use of antihypertensive drugs; levels of plasma glucose, triglycerides, and uric acid; and logarithm-transformed alcohol intake, all these not significantly related to microalbuminuria.

†Described in the second footnote to Table 3.

‡P<.01.

§P<.001.

||P<.05.

¶P<.10.

Risque relatif mortalité en HD en fonction de l'IMC

Californie, n = 123 624, Doshi M. NDT 2016

PARADOXE APPARENT

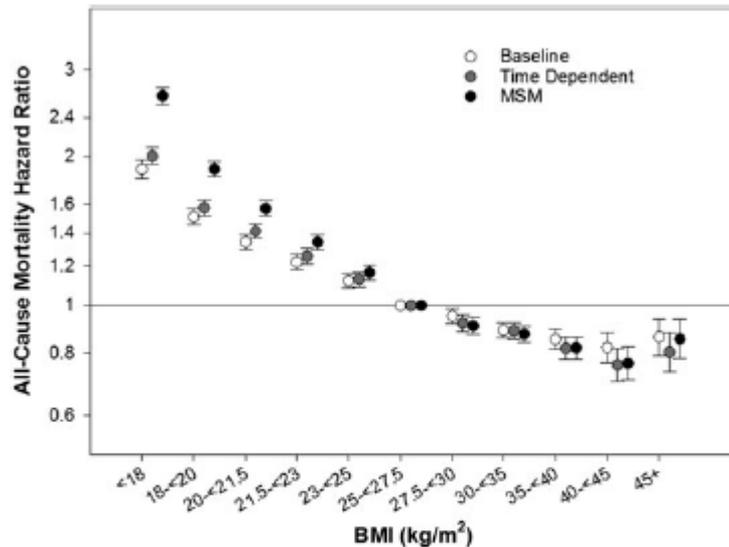


FIGURE 2: Hazard ratios (95% CI) for the associations between BMI categories (reference: 25 to <27.5 kg/m²) and all-cause mortality obtained from baseline, time-varying and MSM models. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

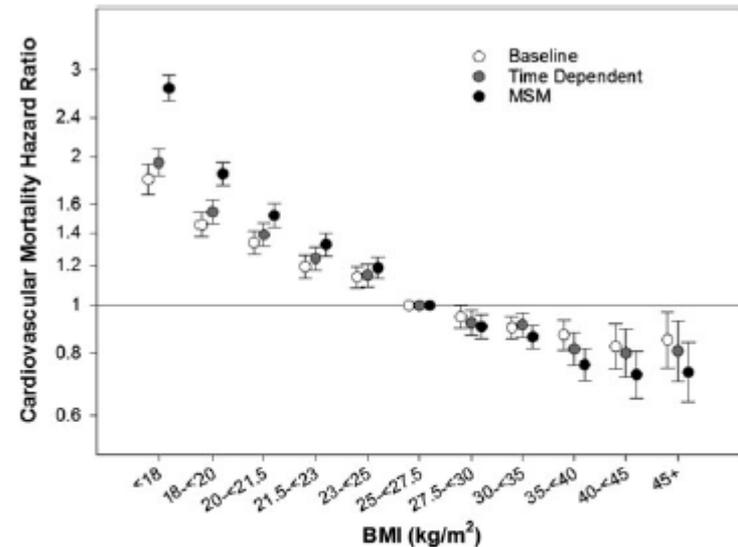


FIGURE 3: Hazard ratios (95% CI) for the associations between BMI categories (reference: 25 to <27.5 kg/m²) and cardiovascular mortality obtained from baseline, time-varying and MSM models. Models adjusted for case-mix covariates and markers of malnutrition and inflammation (see text for covariate list).

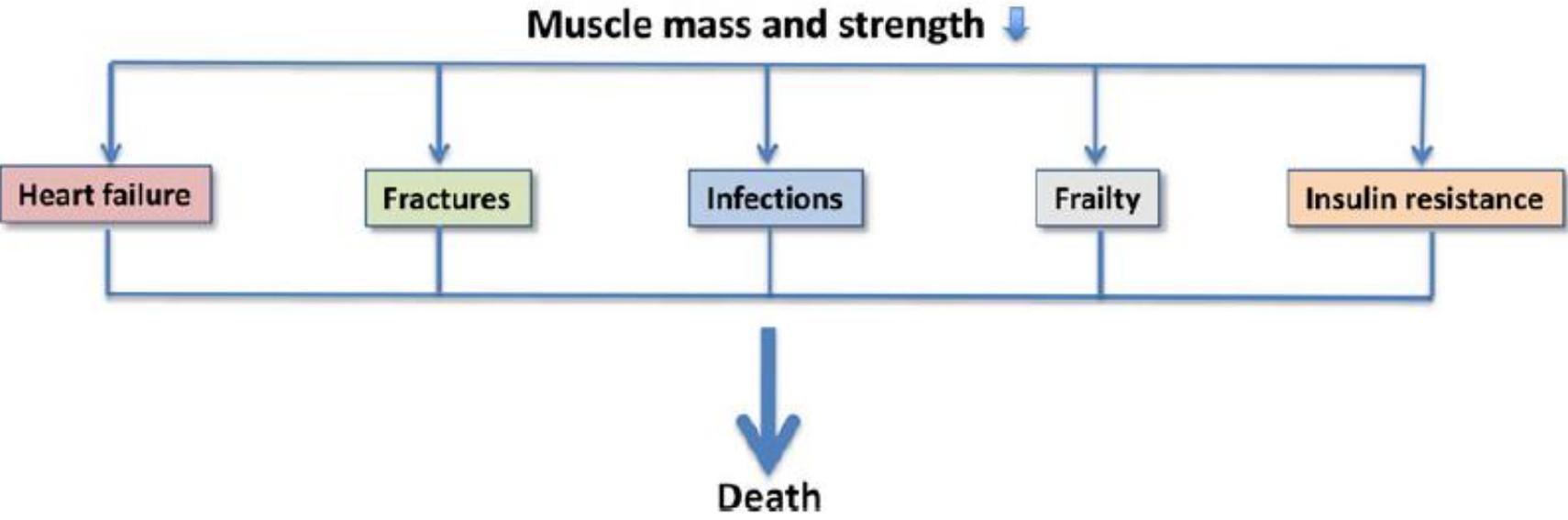


Figure 2: Loss of muscle mass and strength increase risk of various comorbid complications and premature death.



Hyperfiltration

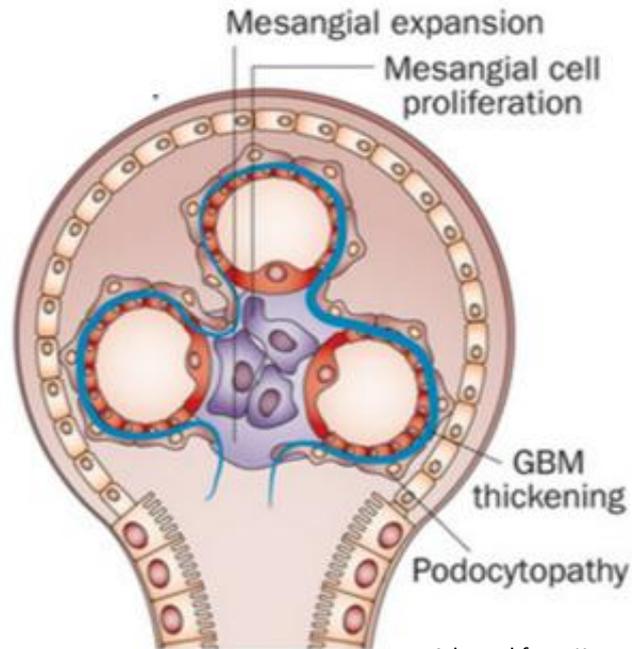
Albuminurie

HTA
Diabète
HSF
Progression autres néphropathies

IRC et ESRD

→ **Physiopathologie**

MODIFICATIONS ULTRASTRUCTURALES



Adapted from Kataoka H et al. Clin Exp Nephrol. 2012

**Réponse adaptative aux
modifications
hémodynamiques**



**Facteurs surajoutés
Hyperglycémie inflammation
SO Dyslipémie**

**Glomerulomégalie
Epaissement MBG
Expansion matrice mésangiale**

**Fibrose glomérulaire
prolifération mésangiale
Podocytopathie (HSF)**

EVENEMENTS FONCTIONNELS PRECOCES - HYPERTENSION GLOMERULAIRE - HYPERFILTRATION

→ Modification du comportement **tubulaire** rénal du Na

↑ Renal Na⁺
reabsorption



Macula
Densa
Feedback

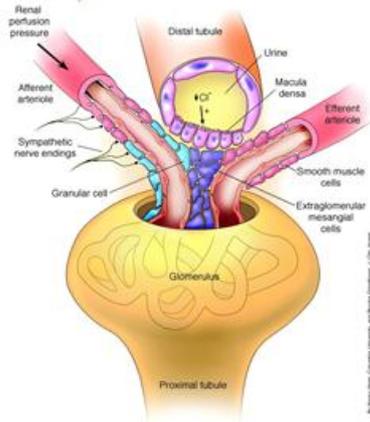
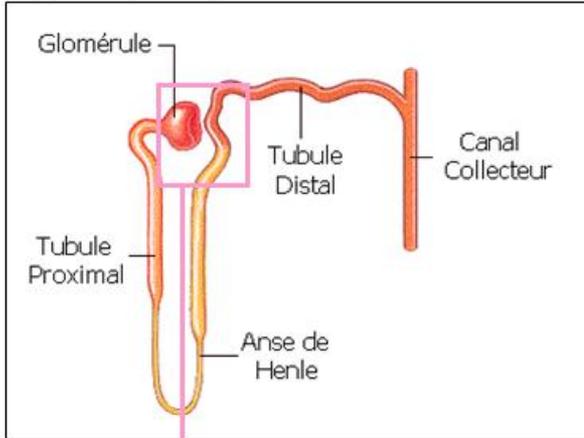


↓ Afferent
arteriolar
resistance

EVENEMENTS FONCTIONNELS PRECOCES - HYPERTENSION GLOMERULAIRE - HYPERFILTRATION

Modification du comportement **tubulaire** rénal du Na → Rétrocontrôle tubulo-glomérulaire

Appareil juxta-glomérulaire



François H. JCI 2004

↑ Renal Na⁺ reabsorption



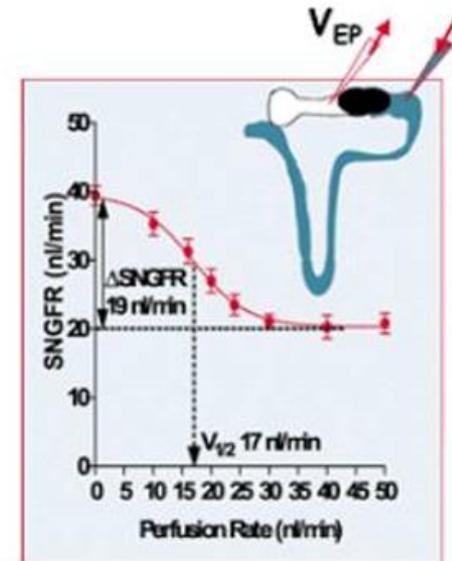
Macula Densa Feedback



↑ SRAA



↓ Afferent arteriolar resistance

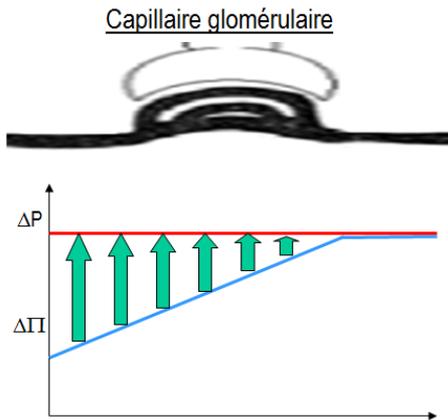


Schnermann J. JASN 2003

EVENEMENTS FONCTIONNELS PRECOCES - HYPERTENSION GLOMERULAIRE - HYPERFILTRATION

Pression dépendance du DFG

$$\text{DFG} = K_f \times \text{PUF} = K \times S \times (\Delta P - \Delta \pi)$$



↑ Vasodilatateurs
NO ANP Kinines PG

3

↑ Renal Na⁺
reabsorption

Macula
Densa
Feedback

1

↓ Afferent
arteriolar
resistance

SRAA

2

↑ Efferent
arteriolar
resistance

↑ PCap

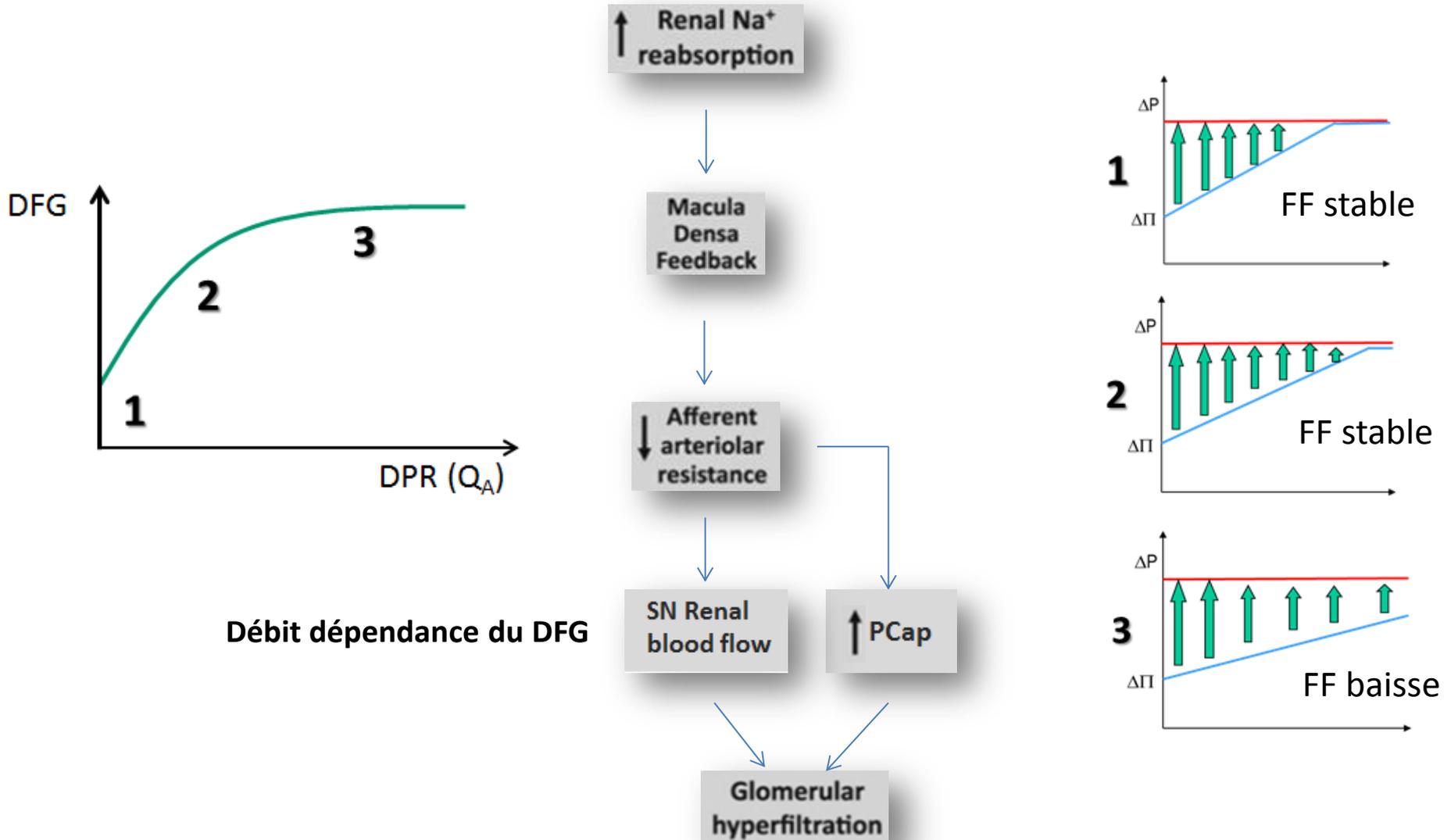
Pression dépendance du DFG

Glomerular
hyperfiltration

EVENEMENTS FONCTIONNELS PRECOCES - HYPERTENSION GLOMERULAIRE - HYPERFILTRATION

Débit dépendance du DFG
= Utilisation de la réserve de filtration

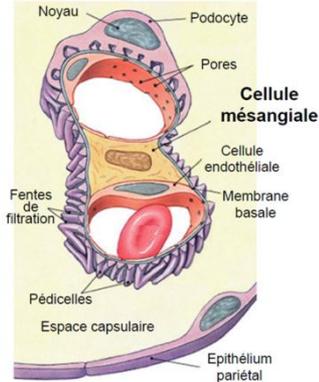
$$\text{DFG} = \text{DPR} \times \text{Fraction Filtration}$$



EVENEMENTS FONCTIONNELS PRECOCES - HYPERTENSION GLOMERULAIRE - HYPERFILTRATION

Modulation Kf = Augmentation de la débit dépendance

$$DFG = Kf \times PUF = K \times S \times (\Delta P - \Delta \pi)$$



↑ Renal Na⁺ reabsorption

Macula Densa Feedback

↓ Afferent arteriolar resistance

SN Renal blood flow

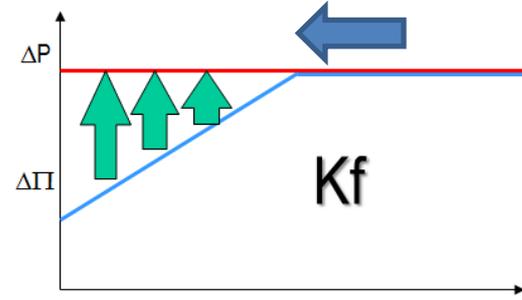
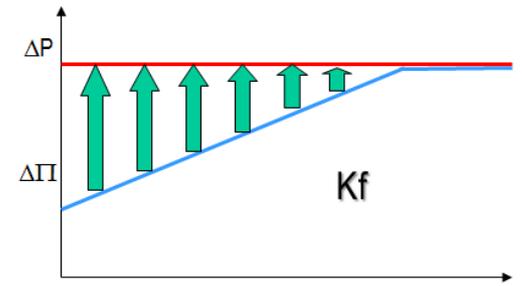
↑ PCap

↑ Vasodilatateurs
NO ANP Kinines PG

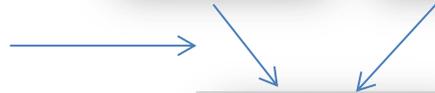
$$Kf = K \cdot S$$

↑ Débit dépendance du DFG

Glomerular hyperfiltration



Pression dépendance du DFG



DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

Obésité viscérale



?



↑ Renal Na⁺
reabsorption



Macula
Densa
Feedback

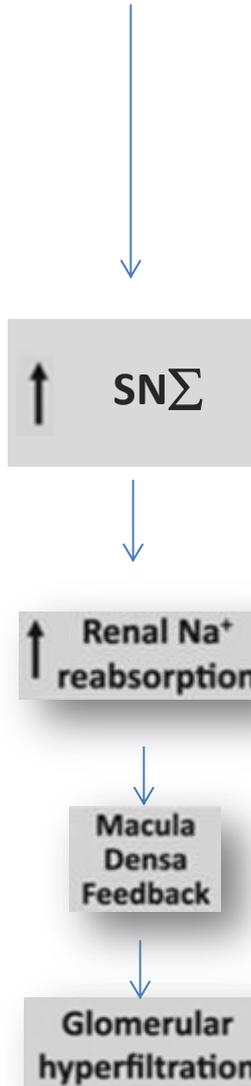


Glomerular
hyperfiltration

DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

1 ↑ de l'activité sympathique tissulaire rénale

Obésité viscérale

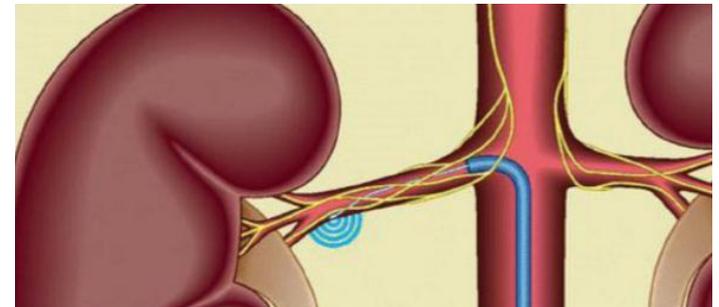


Efficacité des alpha et beta bloqueurs chez les patients obèses

Wofford MR Am J Hypertens. 2001

Dénervation rénale expérimentale diminue l'excrétion rénale et prévient le dvt HTA

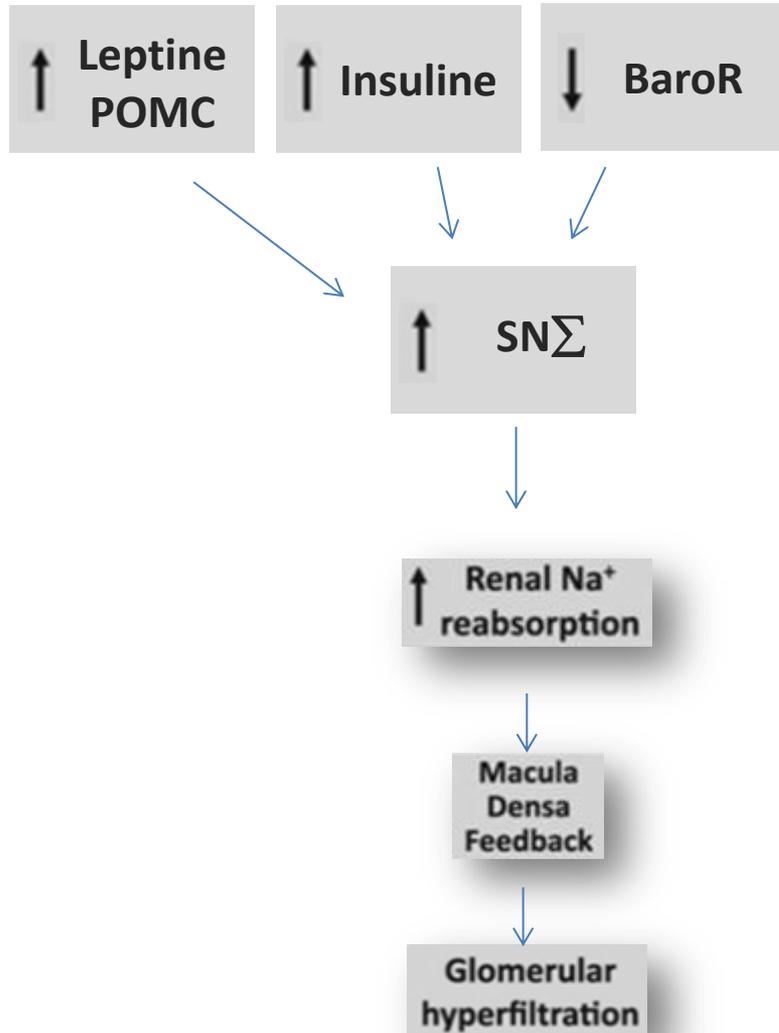
Kassab S Hypertension. 1995



DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

1 ↑ de l'activité sympathique tissulaire rénale

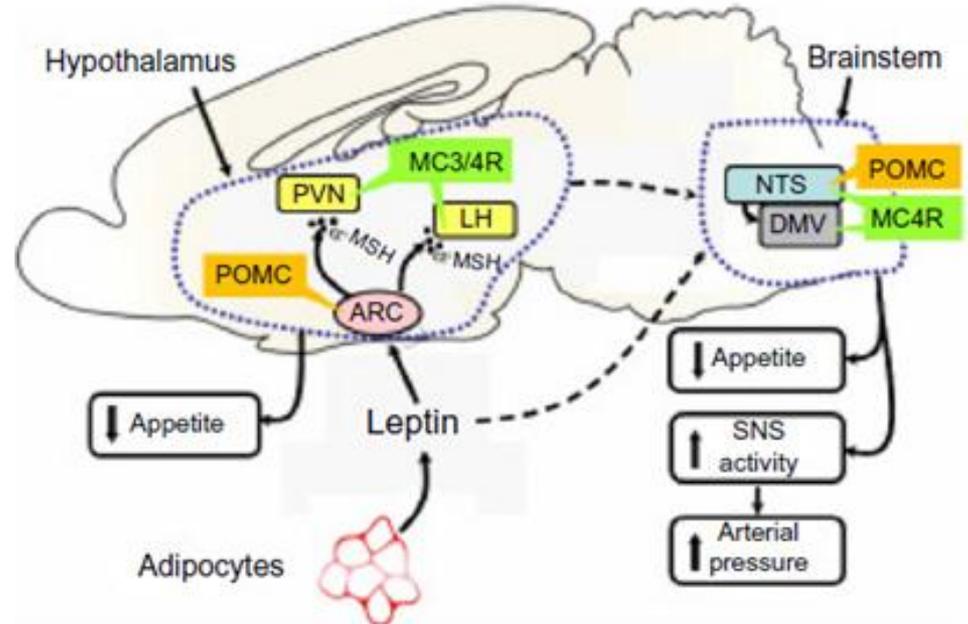
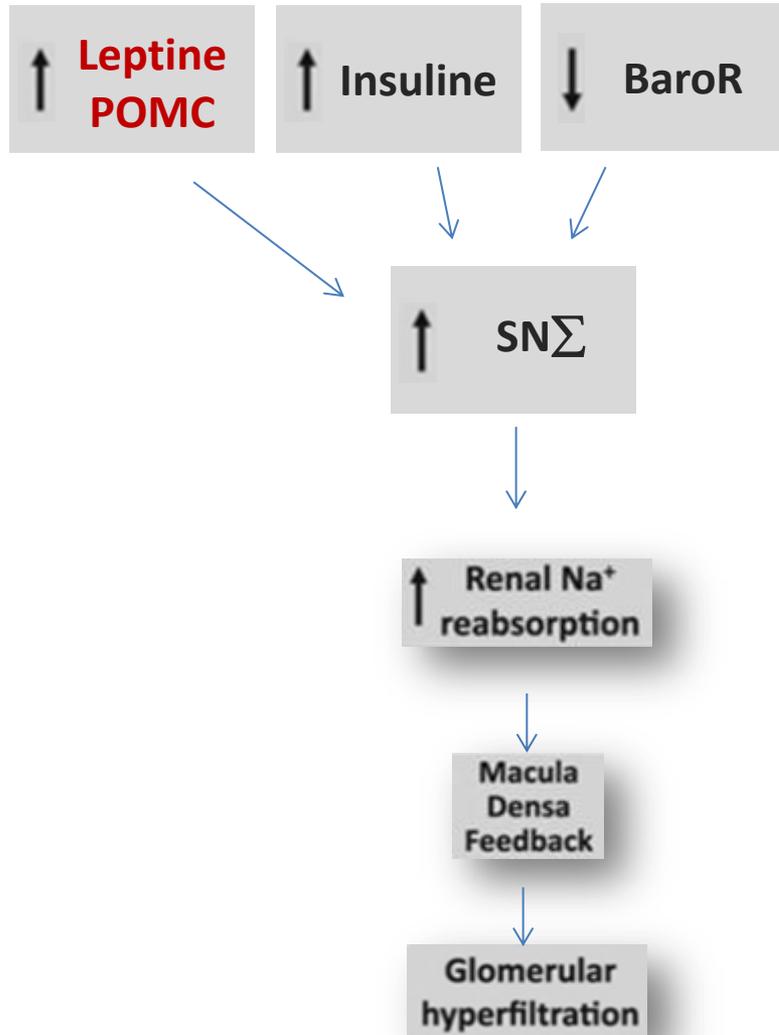
Obésité viscérale



DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

1 ↑ de l'activité sympathique tissulaire rénale

Obésité viscérale



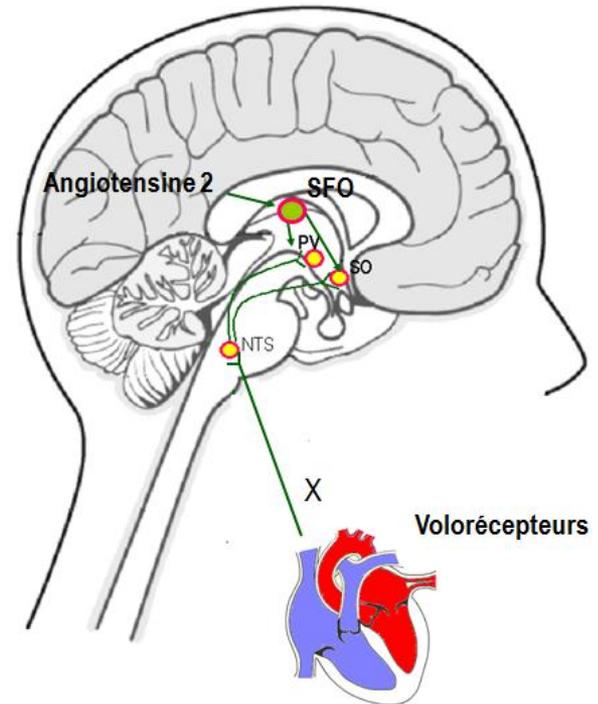
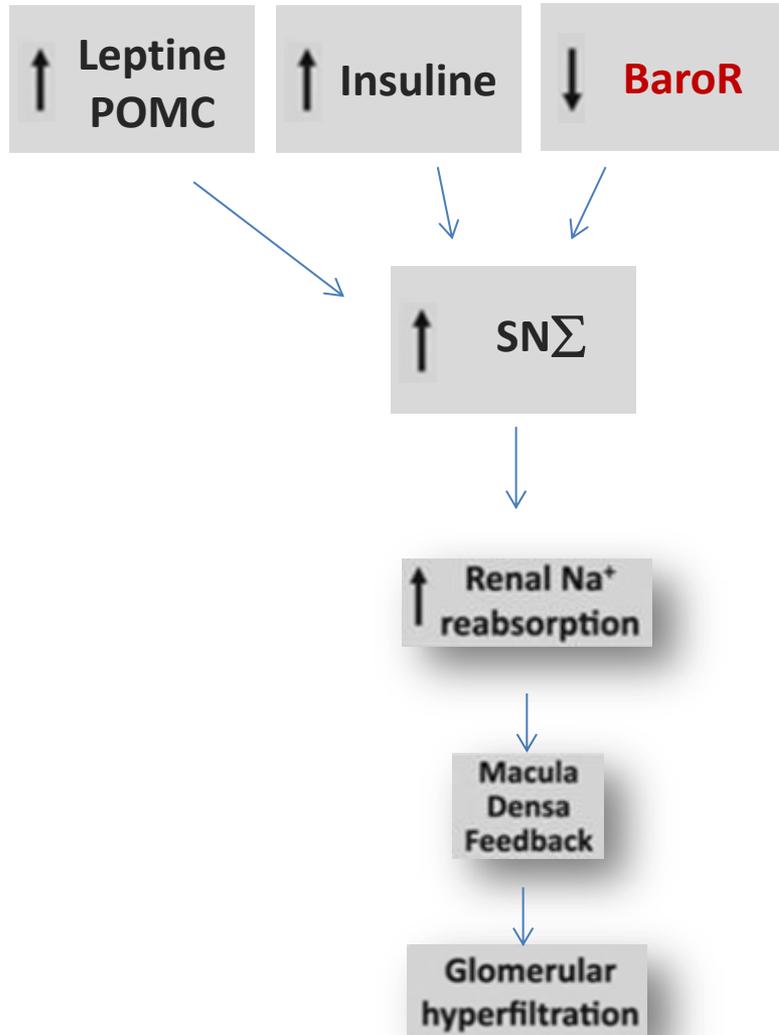
Leptine

- . Adipokine anorexigène
 - . Augmente l'activité Σ
 - . Voie de la POMC (Noyau arqué) – Melanocyte SH (Noyau PV)
 - . Agoniste M4CR
 - . Modification appétit - activité Σ (NTS)
- (ob/ob et db/db obèse sans HTA)

DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

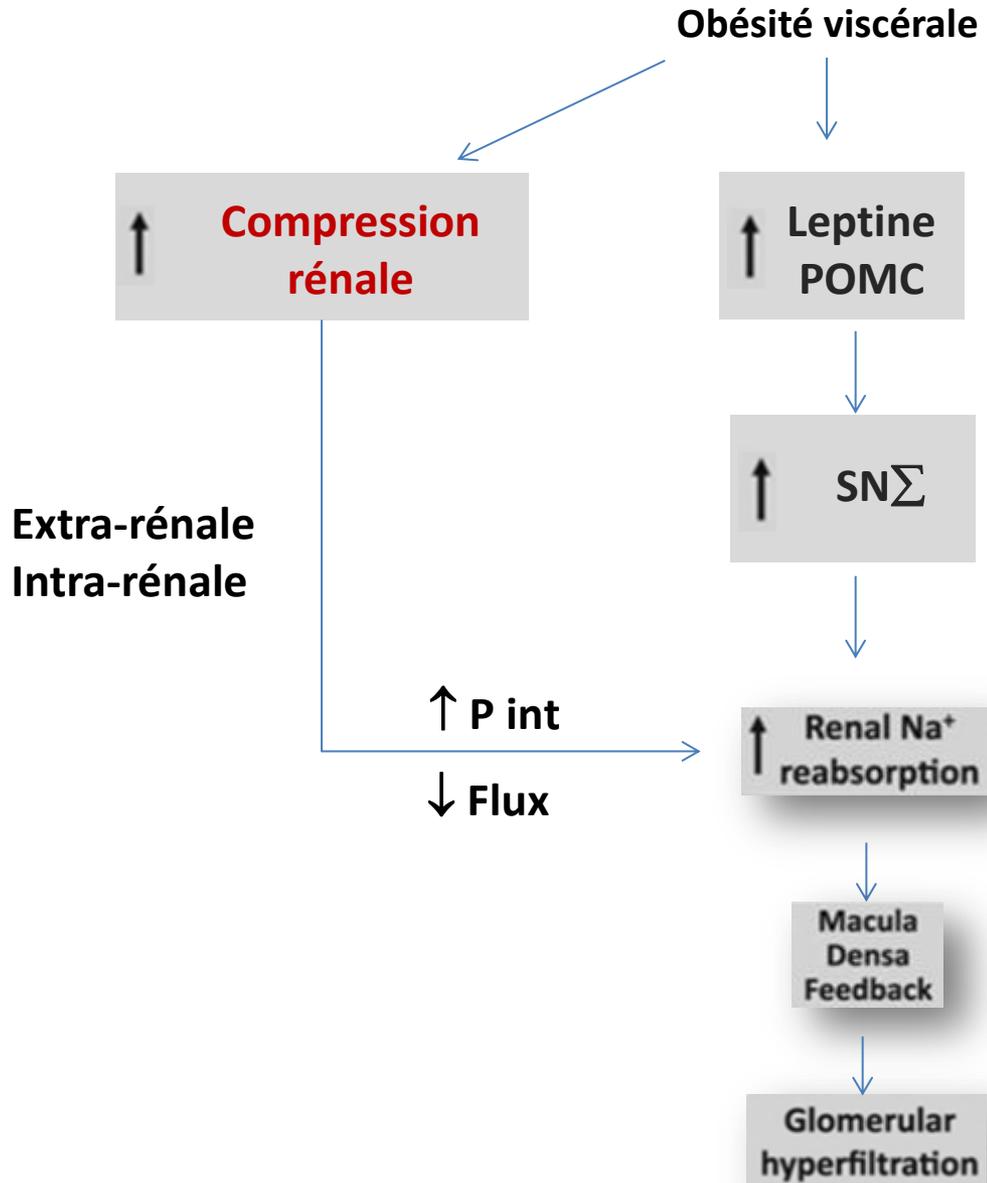
1 ↑ de l'activité sympathique tissulaire rénale

Obésité viscérale



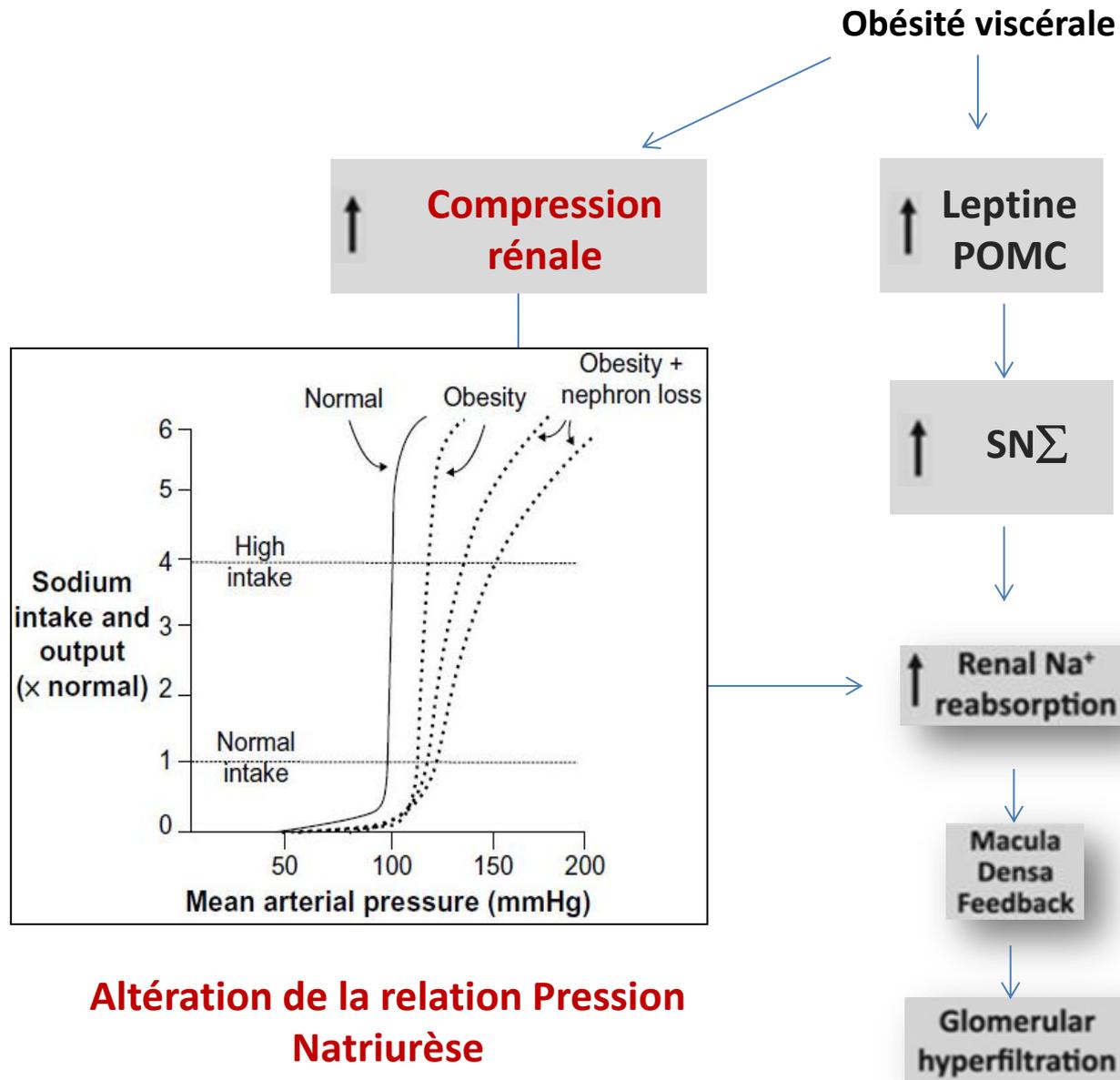
DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

2 Compression rénale



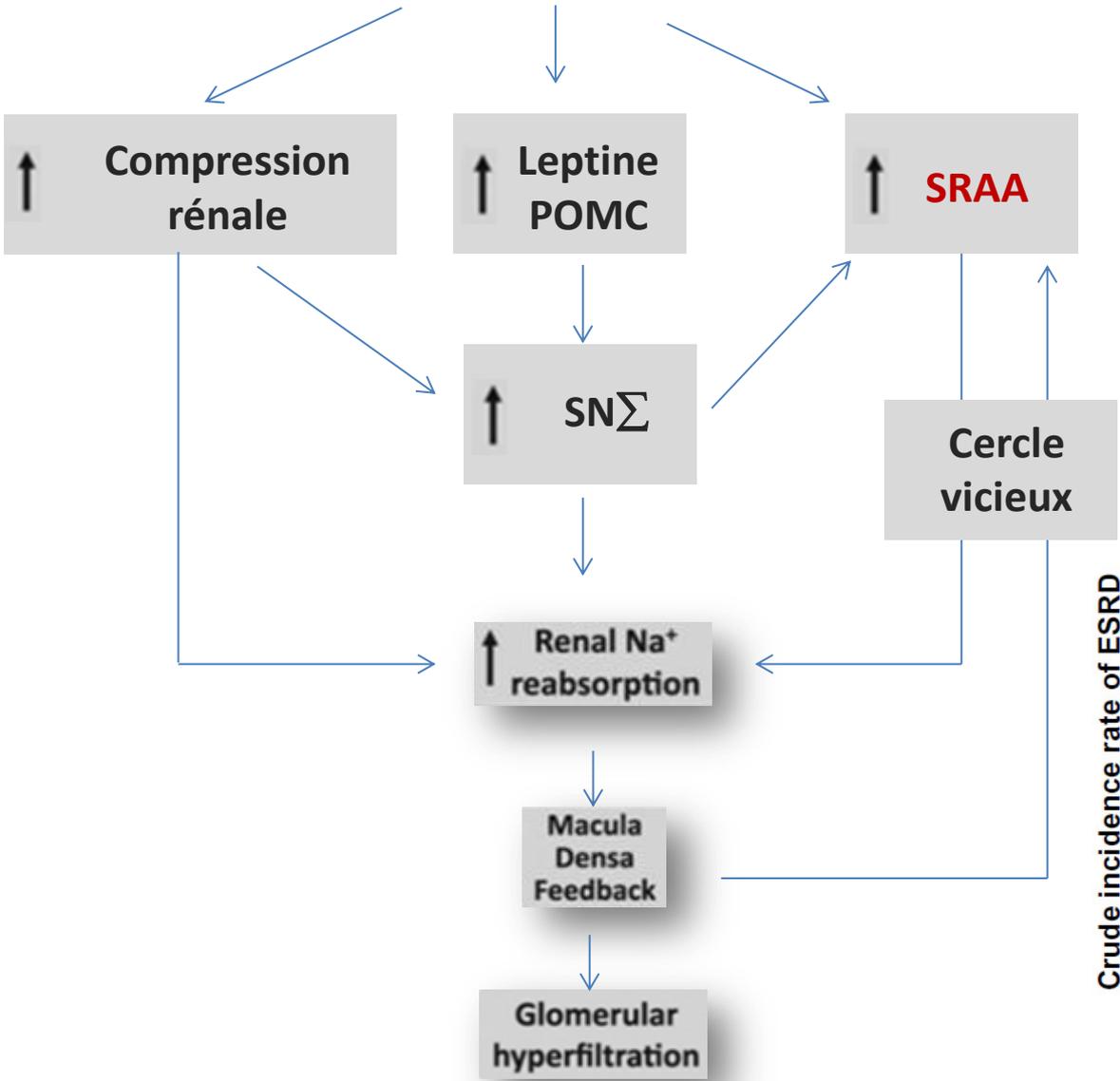
DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

2 Compression rénale

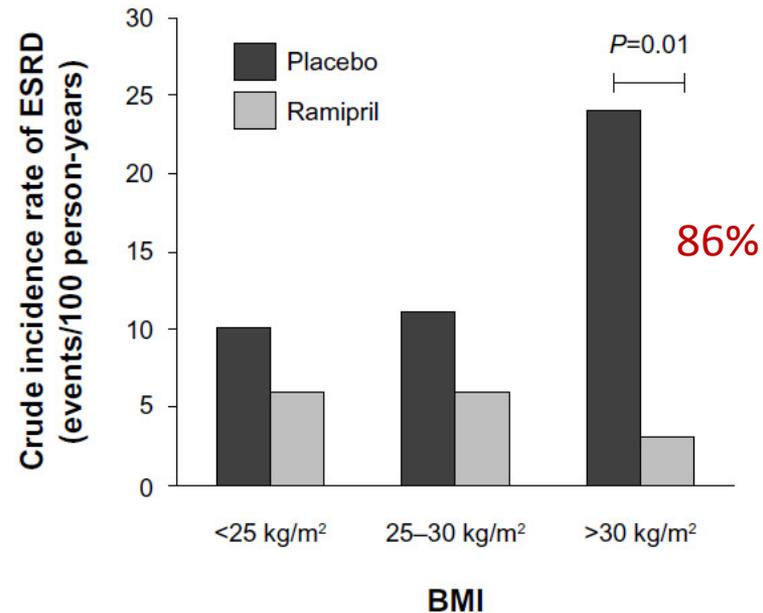


DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

Obésité viscérale



REIN Study group



DETERMINANTS DE LA DIMINUTION DE L'EXCRETION RENALE DE Na

Obésité viscérale

↑ Compression rénale

↑ Leptine
POMC

↑ SRAA

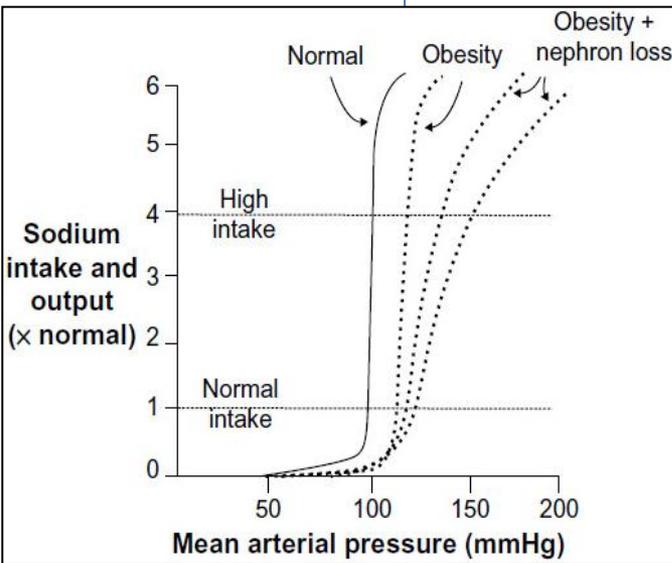
↑ $SN\Sigma$

↑ Renal Na^+ reabsorption

Macula Densa Feedback

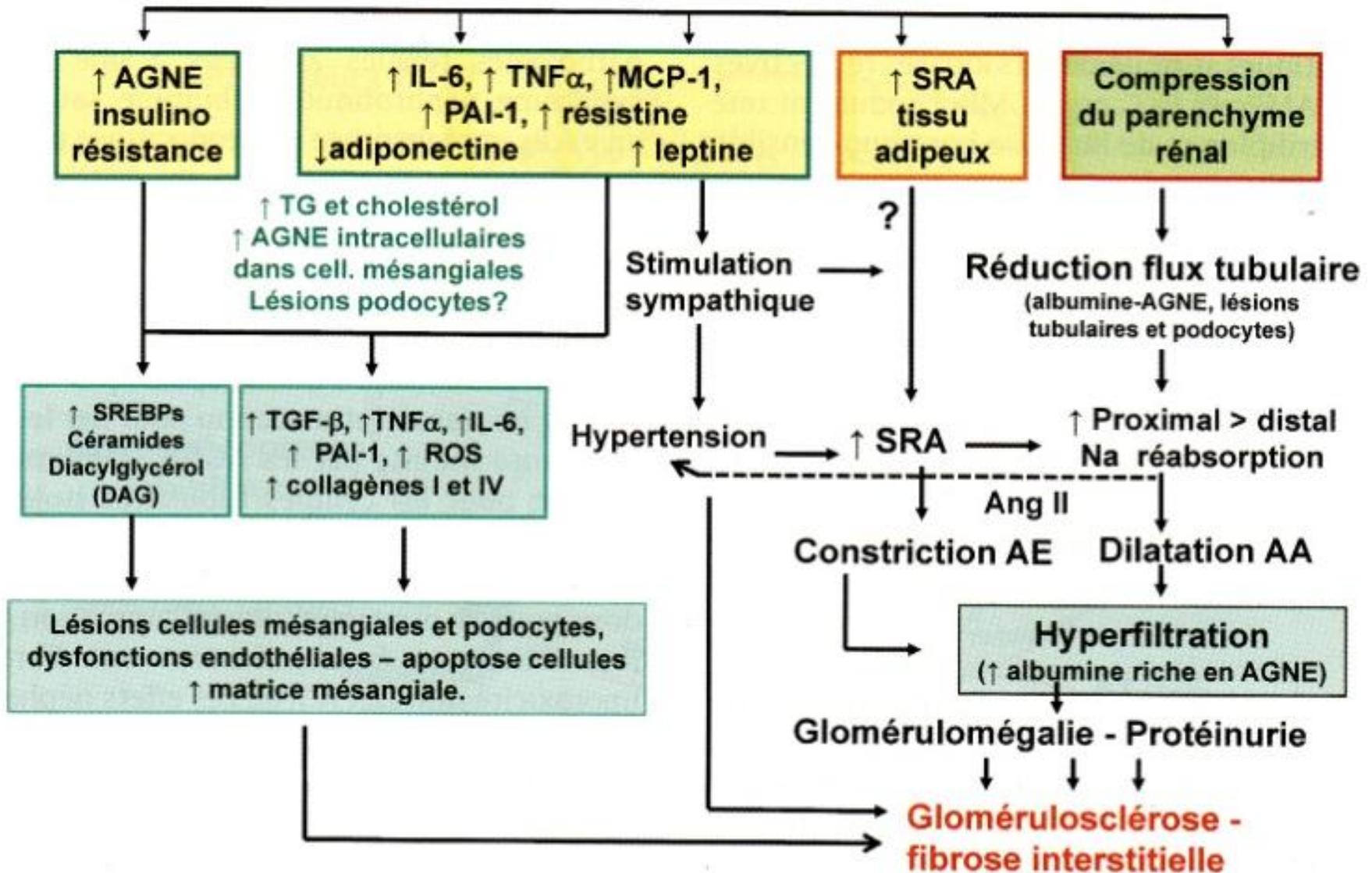
Glomerular hyperfiltration

HTA systémique

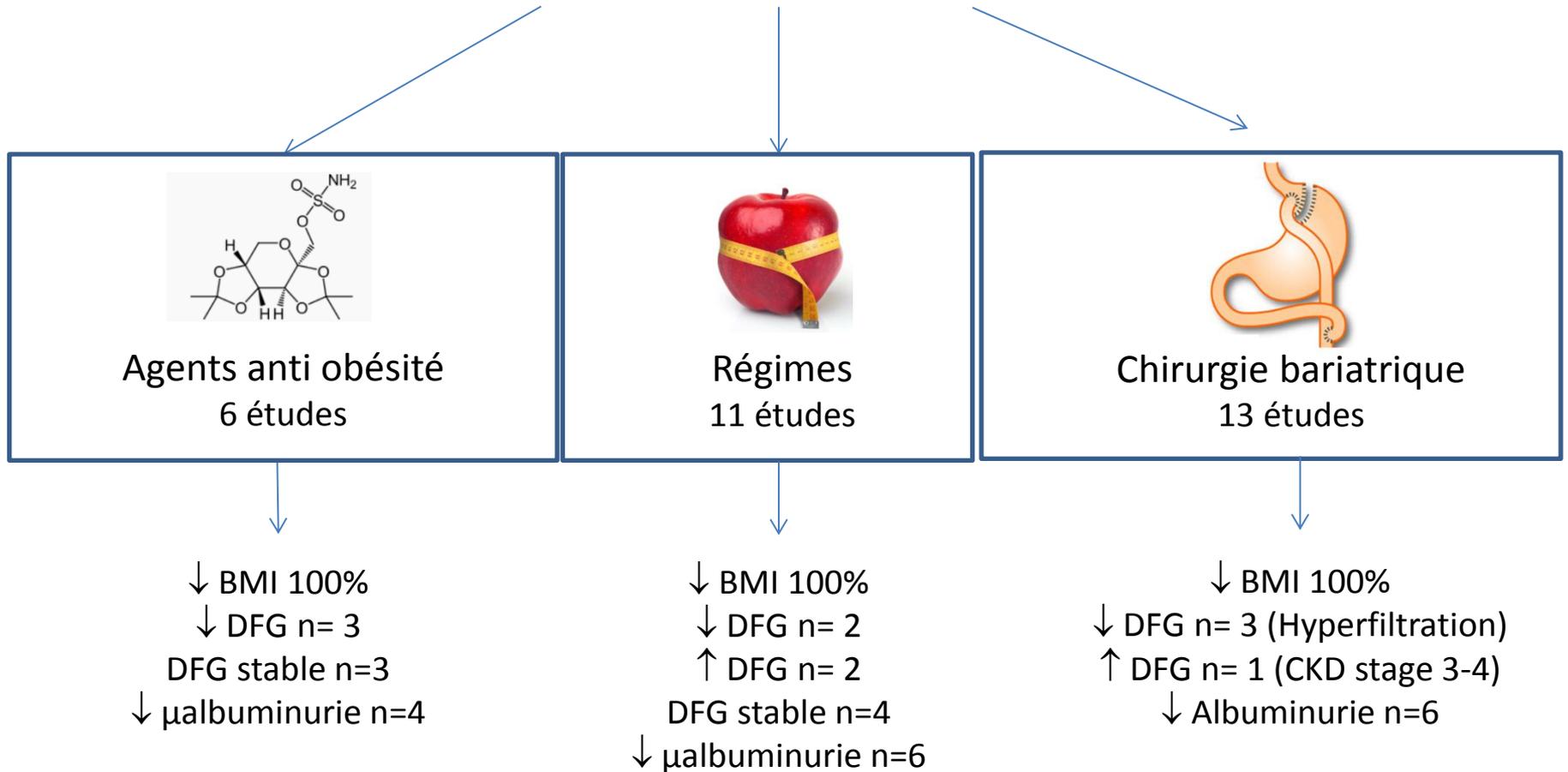


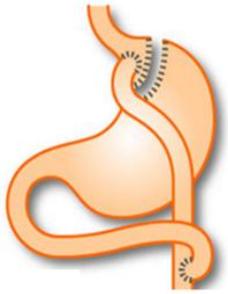
EVENEMENTS FONCTIONNELS SECONDAIRES

Expansion du tissu adipeux – obésité – syndrome métabolique



EFFET PERTE DE POIDS SUR L'EVOLUTION DE LA FONCTION RENALE

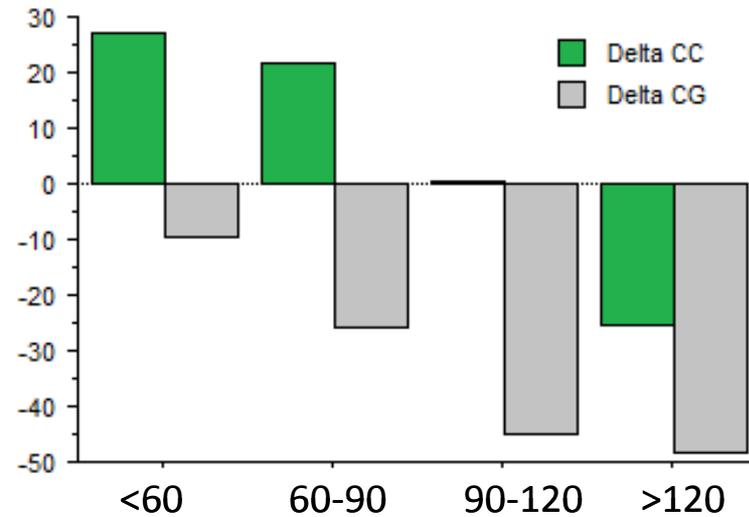




Chirurgie bariatrique 13 études

	n	Méthode	Evolution
Brochner 1980	25	mDFG (CrEDTA)	↓ DFG
Chagnac 2003	8	mDFG (Inuline)	↓ DFG
Navarro diaz 2006	61	Creat P (eDFG)	↓ DFG
Agrawal 2008	94	Creat P	Stable
Serpa 2009	140	Creat P	↓ DFG
Wesley 2009	9	Creat P	Stable
Navaneethan 2009	25	Creat P (eDFG)	↑ DFG
Schuster 2011	56 CKD	Creat P	↑ DFG
Mac Laughlin 2012	9	Creat P	↓ DFG
Hou 2013	233	Creat P (eDFG)	Variable

Evolution du DFG = f (DFG initial)



Initial GFR (ml/min)	N	Mean GFR before surgery	Mean GFR after Surgery	% with increase/decrease
GFR < 60	13	50.1 ± 5.5	77.3 ± 41.7**	85/15
60 < GFR < 90	49	76.8 ± 8.7	98.4 ± 35**	67/33
90 < GFR < 120	73	105.6 ± 9.1	106.9 ± 38.3	45/55
GFR >120	190	162.5 ± 36.7	137.0 ± 49.6***	22/78

Values are mean ± SD, ** p < 0.01 *** p < 0.001

ANOVA 2 facteurs

Effet Classe p<0.0001

Effet Méthode p<0.0001

Interaction p<0.01

. Effets opposés chirurgie bariatrique sur l'évolution de la fonction rénale en fonction du DFG initial

Baisse du DFG aux valeurs initiales élevées

Augmentation du DFG aux valeurs initiales basses

. Formule d'estimation (Cockcroft) surestime la baisse du DFG après chirurgie

Perte de poids proportionnellement supérieure à la perte de masse musculaire

CONCLUSION

- Lien Obésité / dysfonction rénale bien établie épidémiologiquement
- Lésions spécifiques avec histoire naturelle passant par un phénomène d'hypertension glomérulaire en partie indépendante de l'HTA systémique
- Facteur d'aggravation des autres néphropathies et associant aux lésions rénales associées au diabète et à l'HTA
- Physiopathologie complexe phénotype mais reposant sur l'interaction tubule/glomérule
- Réversibilité probable = Cible de néphroprotection...