



The 18th Budapest Nephrology School (Nephrology, Hypertension, Dialysis, Transplantation)

26-31 August 2011



Metabolic Syndrome, Obesity, Hypertension and Chronic Kidney Disease

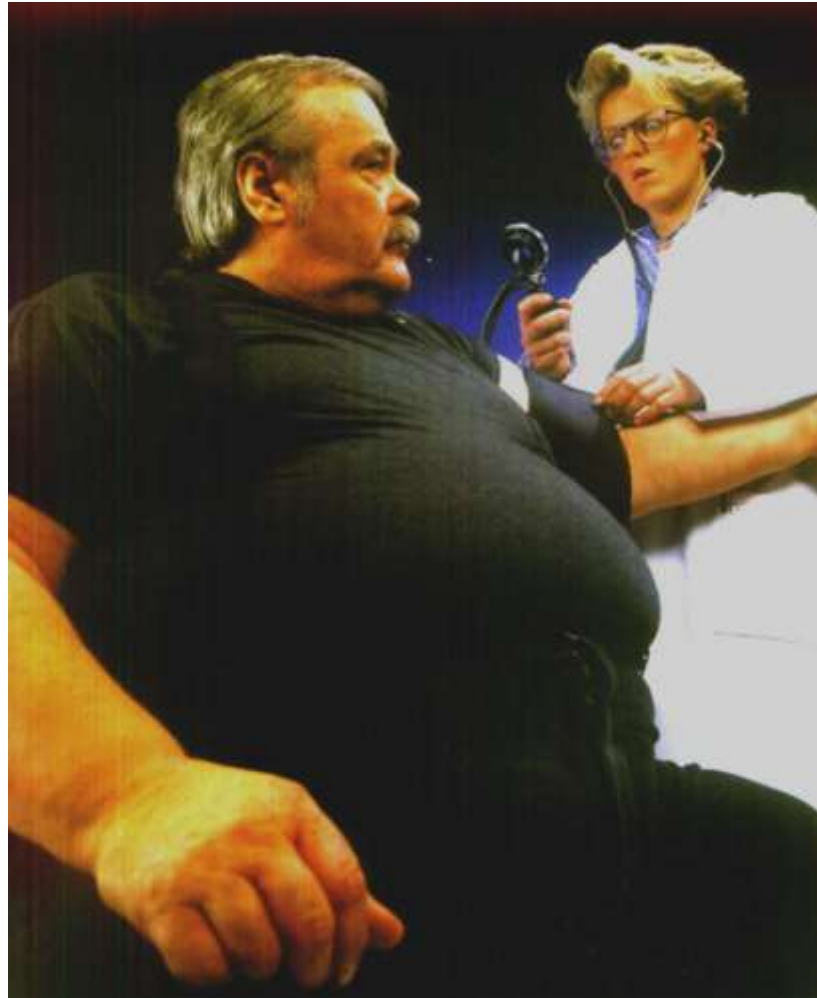
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Obesity- the public health problem not only in a Western Countries



Prevalence of obesity

❖ In USA:

- the age-adjusted prevalence of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was 33.8% overall, 32.2% among men, and 35.5% among women
- the corresponding prevalence estimates for overweight and obesity combined ($\text{BMI} \geq 25$) were 68.0%, 72.3% and 64.1%

Flegal K et al. JAMA. 2010; 303: 235-241

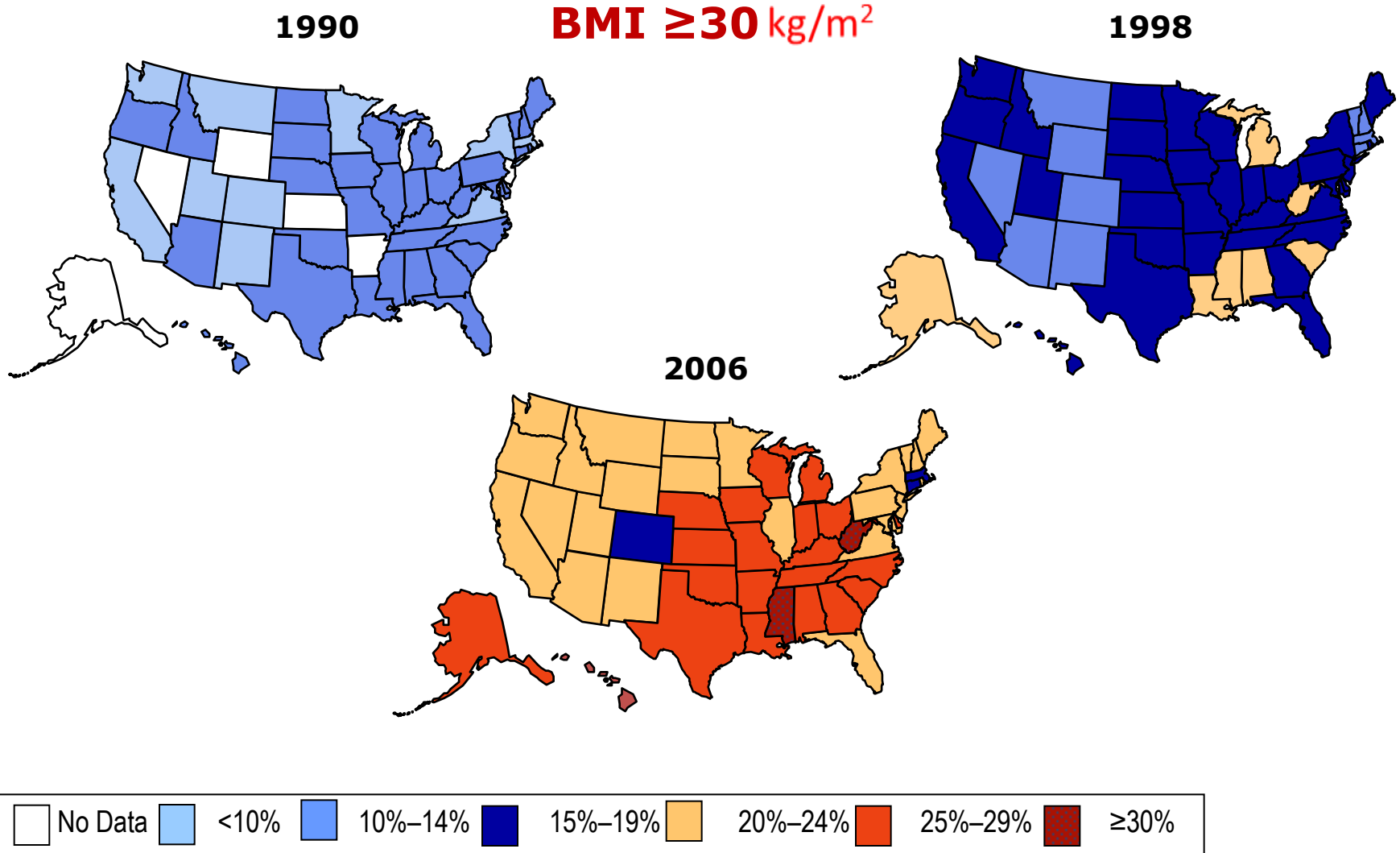
❖ In Europe:

- the prevalence of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) in men ranged from 4.0% to 28.3% and in women from 6.2% to 36.5%

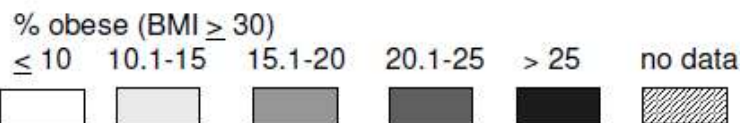
Berghöfer A et al. BMC Public Health. 2008; 8: 200

Obesity Trends Among U.S. Adults

Behavioral Risk Factors Surveillance System (BRFSS), 1990, 1998, 2006

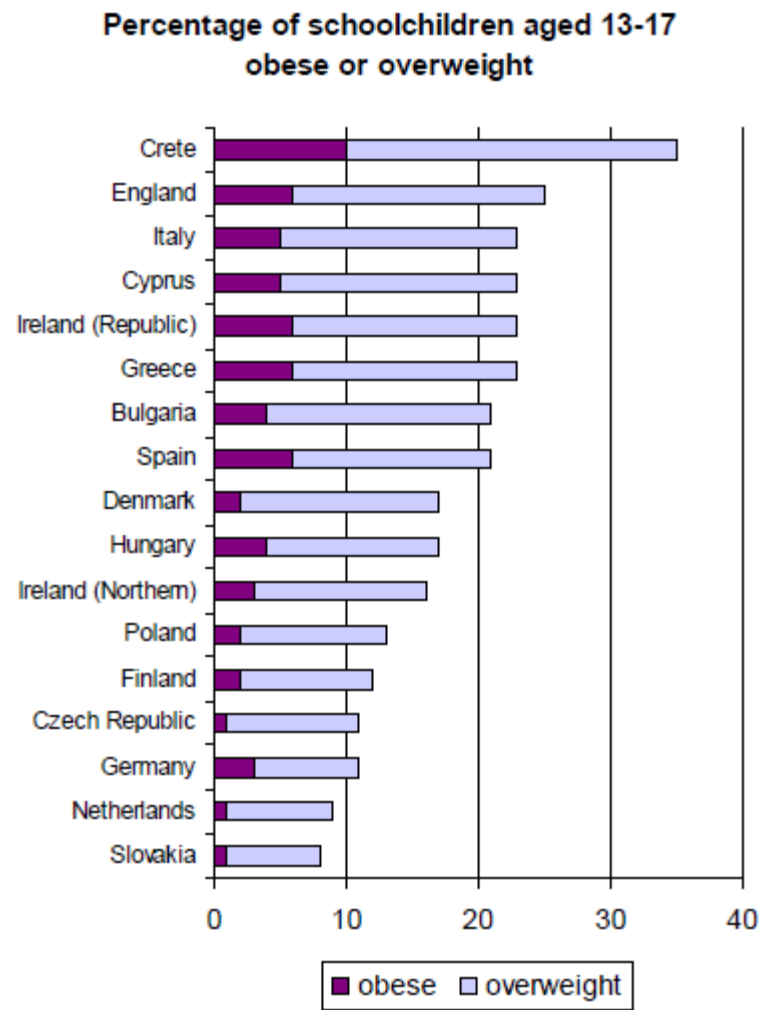
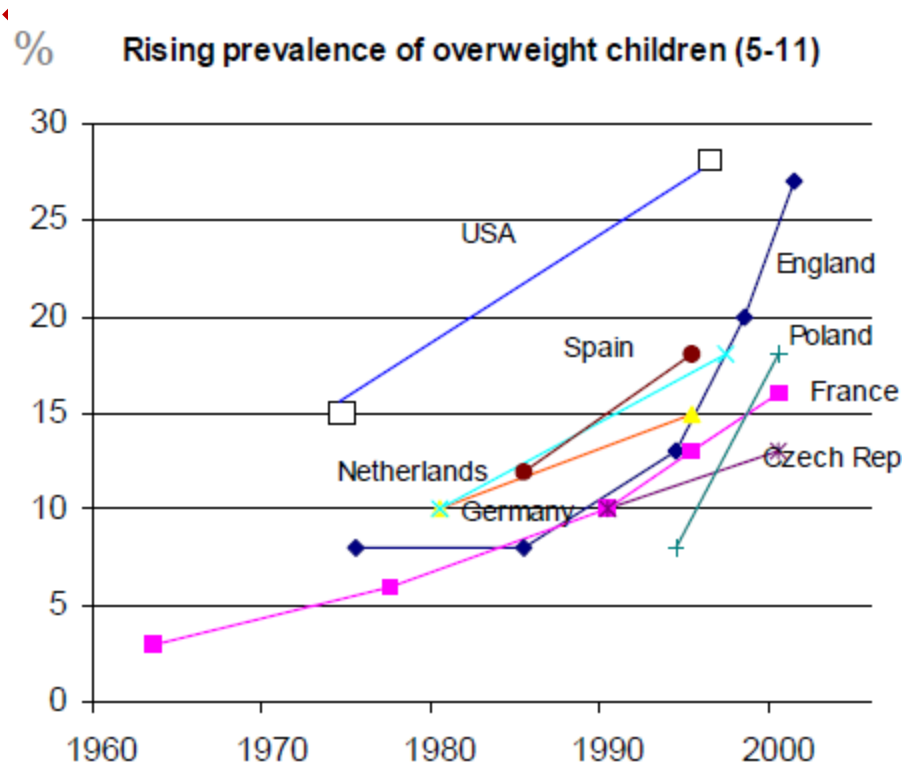


Regional variation in prevalence of obesity (BMI ≥ 30 kg/m²) in Europe





Prevalence of overweight and obesity in children

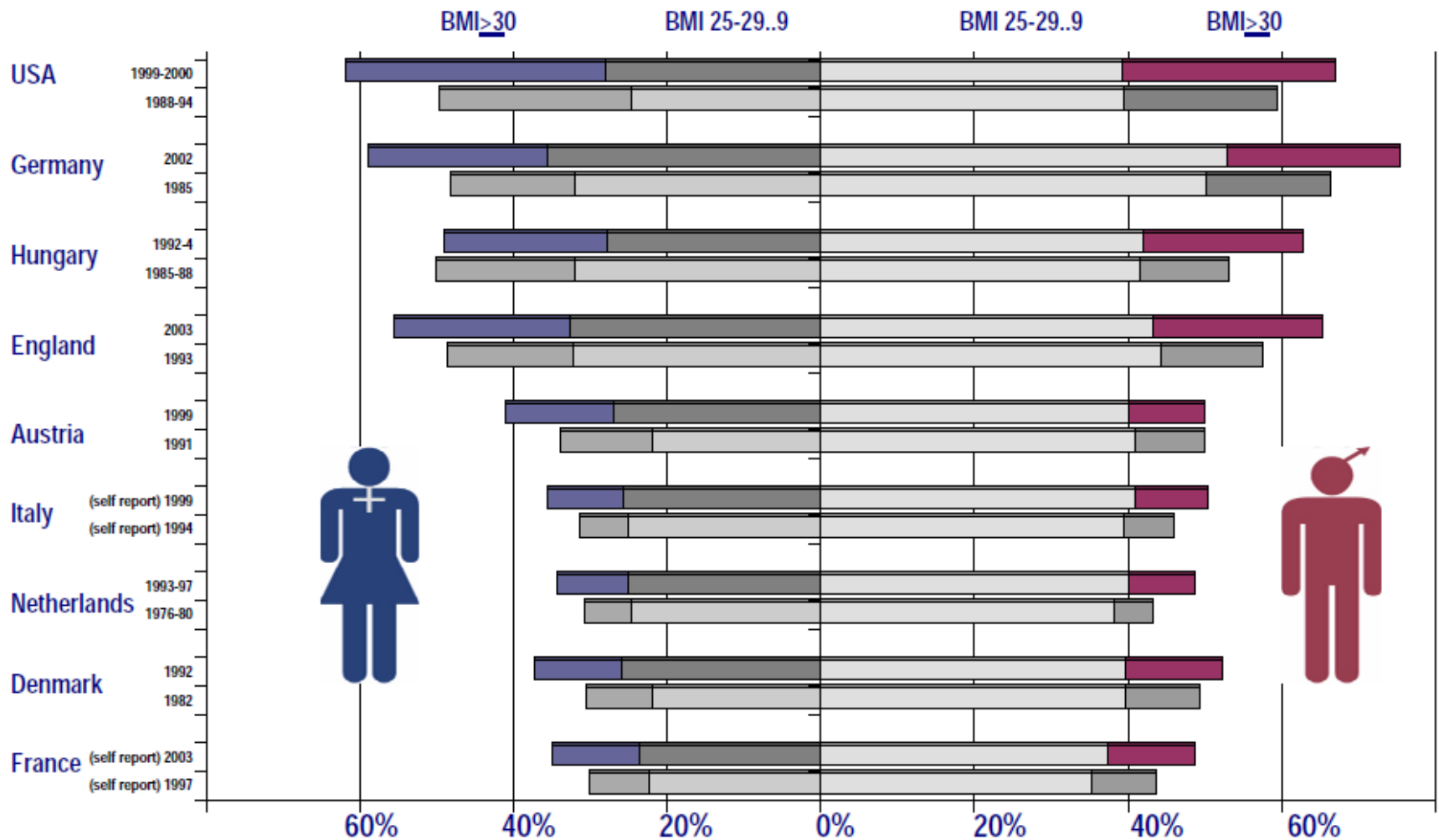


Lobstein T et al. International Obesity Task Force , EU Platform Briefing Paper

prepared in collaboration with the European Association for the Study of Obesity, Brussels 2005



Changes in prevalence of overweight and obesity in adults

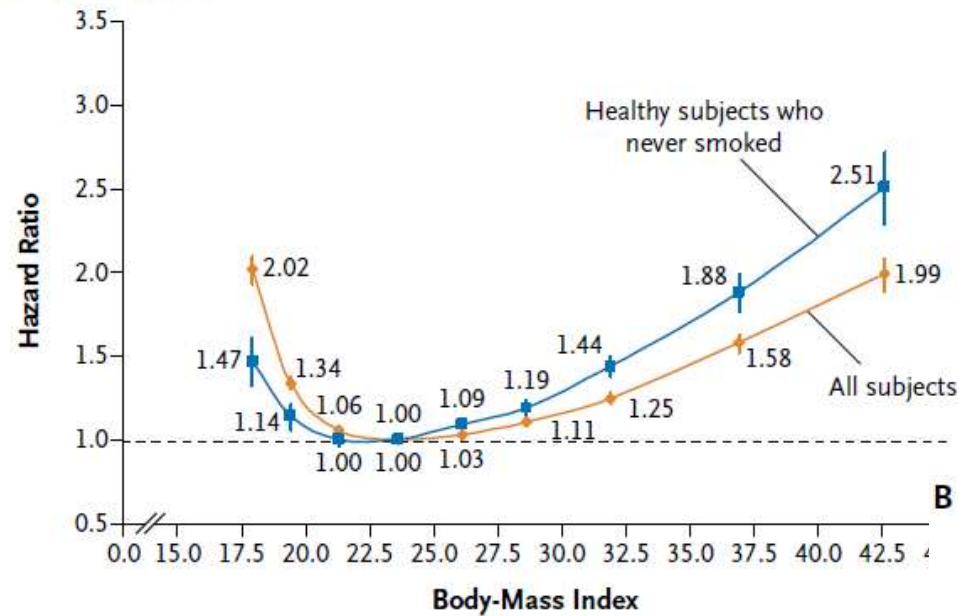


Lobstein T et al. International Obesity Task Force , EU Platform Briefing Paper

prepared in collaboration with the European Association for the Study of Obesity, Brussels 2005

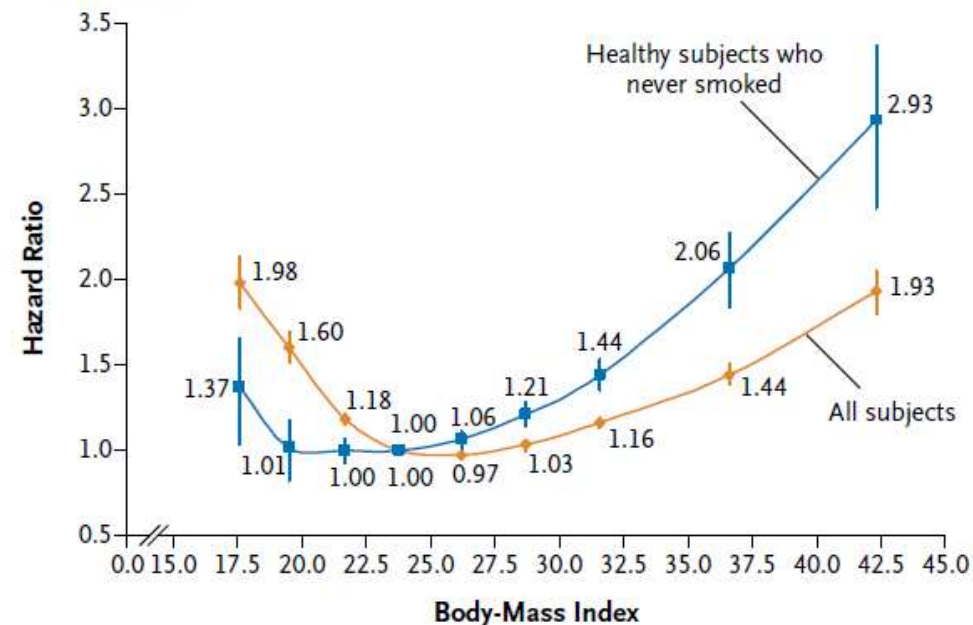
Body-Mass Index and mortality among 1.46 million white adults

A White Women



Estimated Hazard Ratio for death from any cause according to BMI for all study participants and for healthy subjects who never smoked

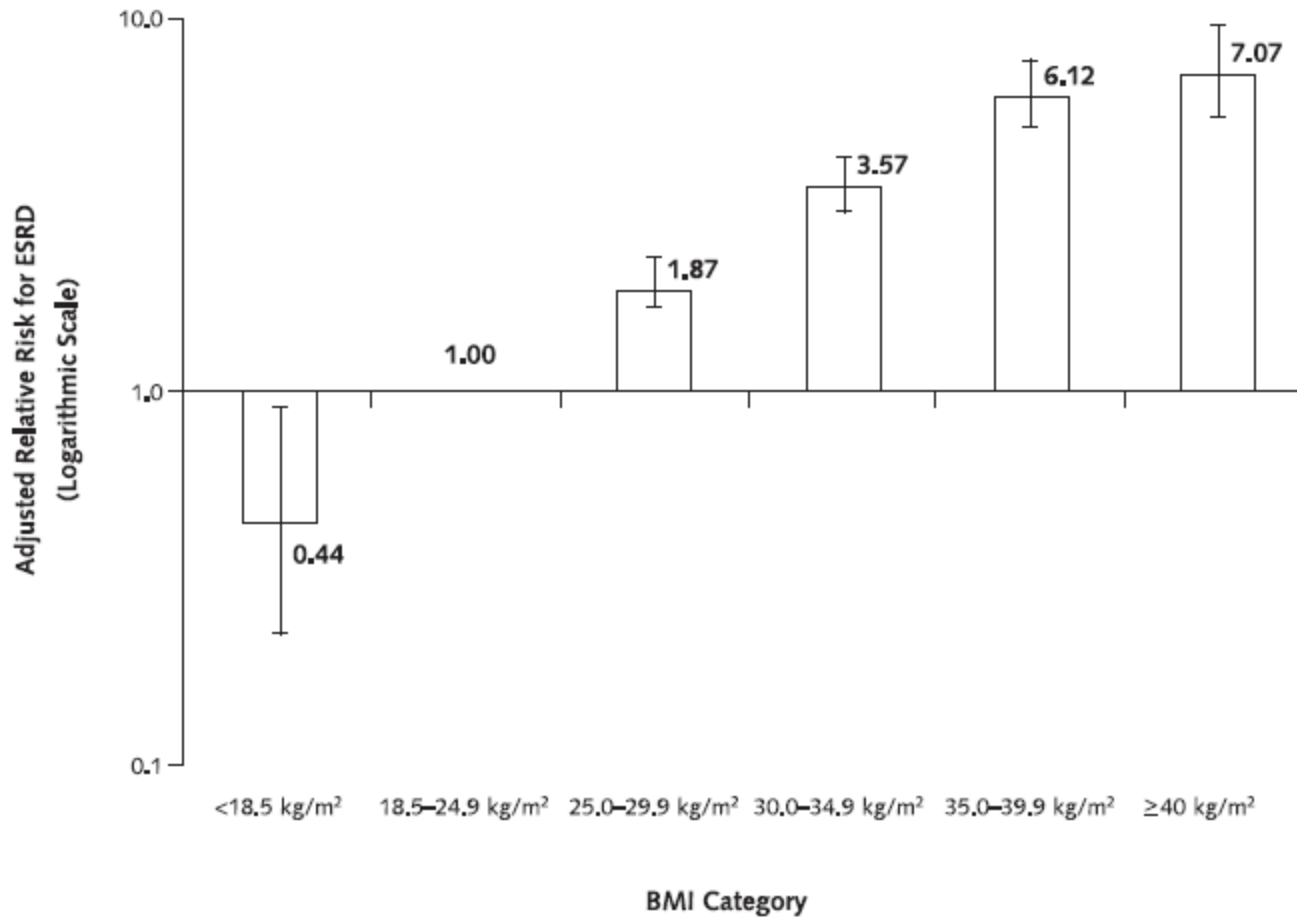
B White Men



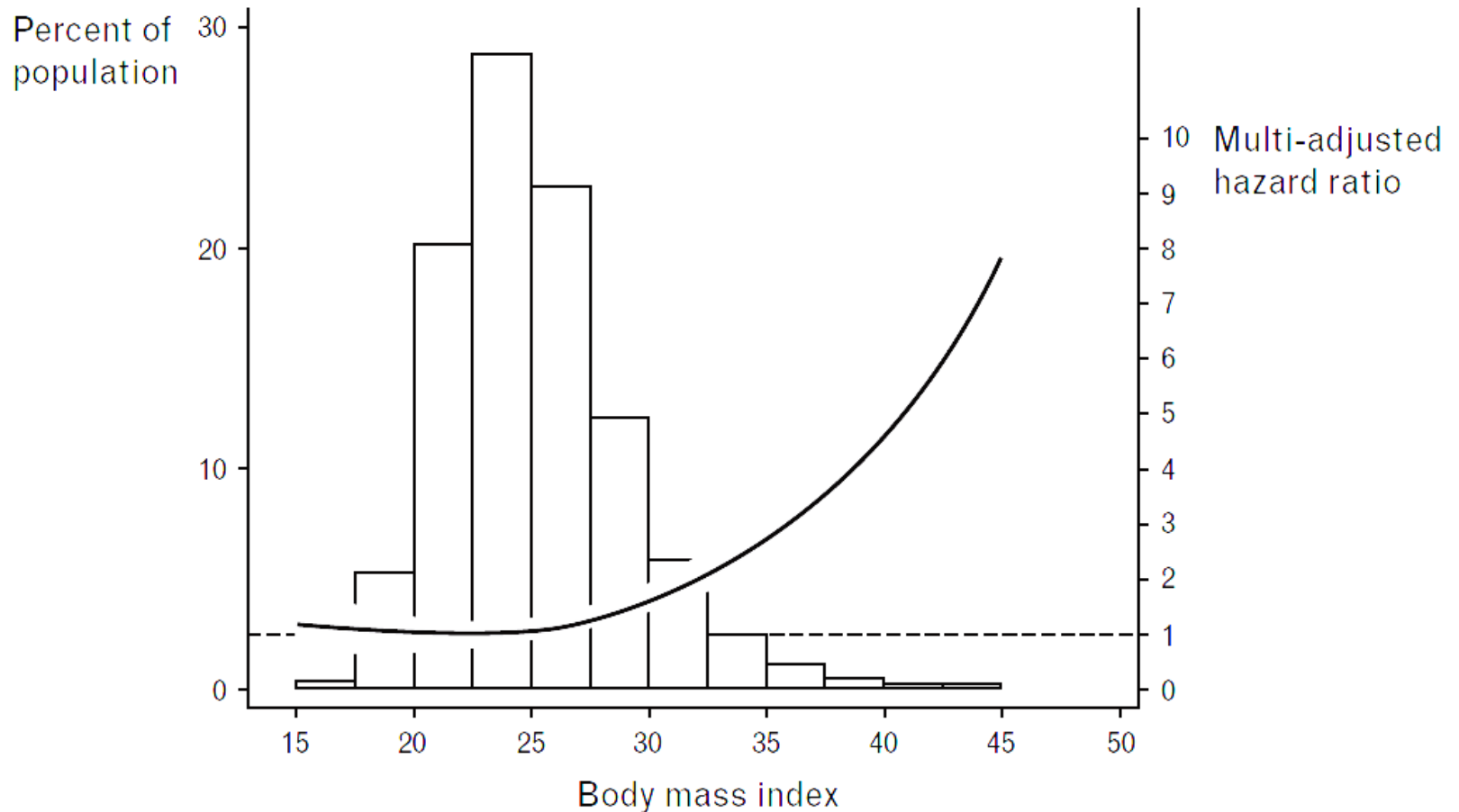
The cluster of co-morbidities associated with and aggravated by obesity



BMI- an independent predictor of end-stage renal disease

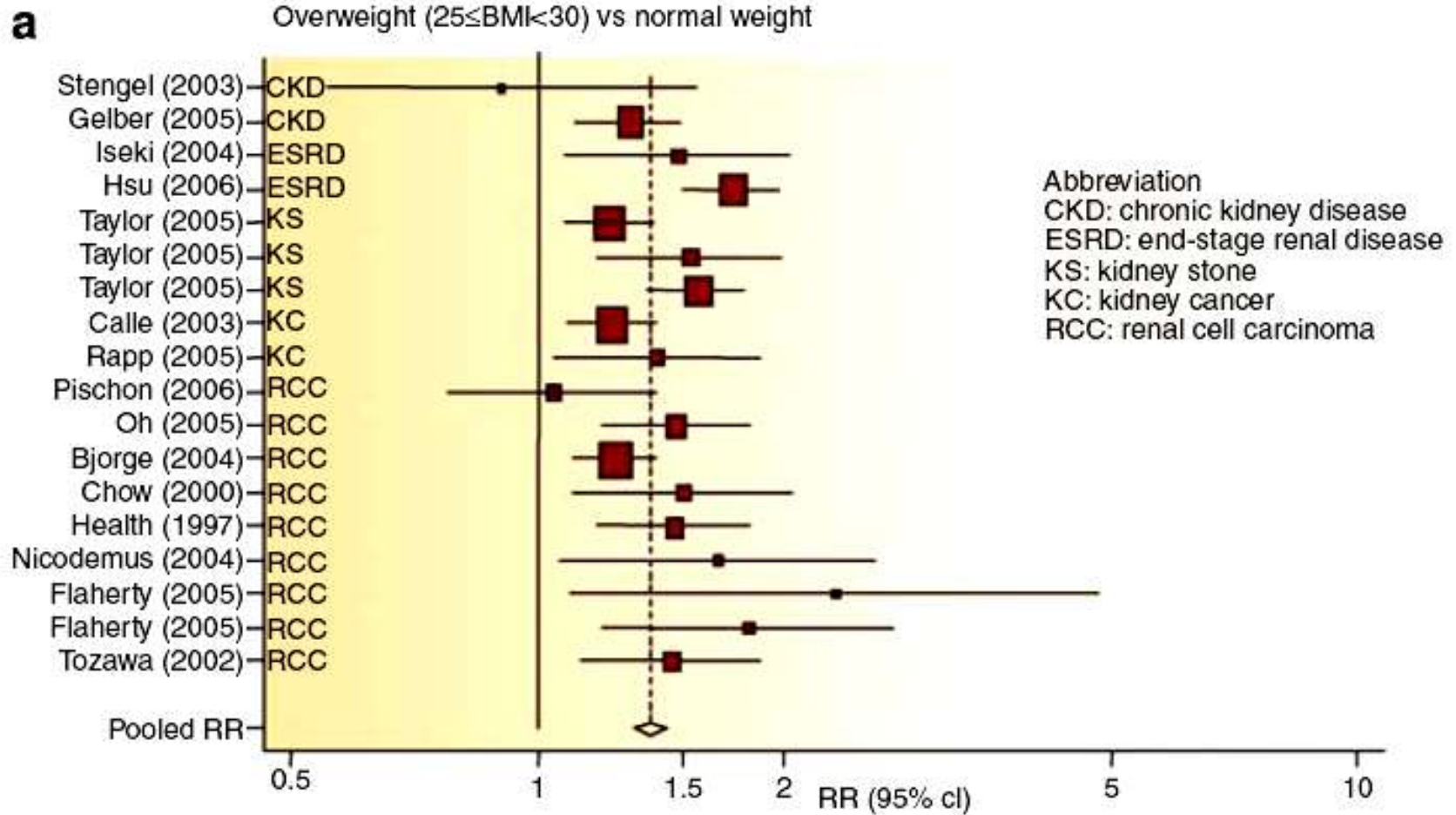


Risk of CKD/ESDR increases with BMI



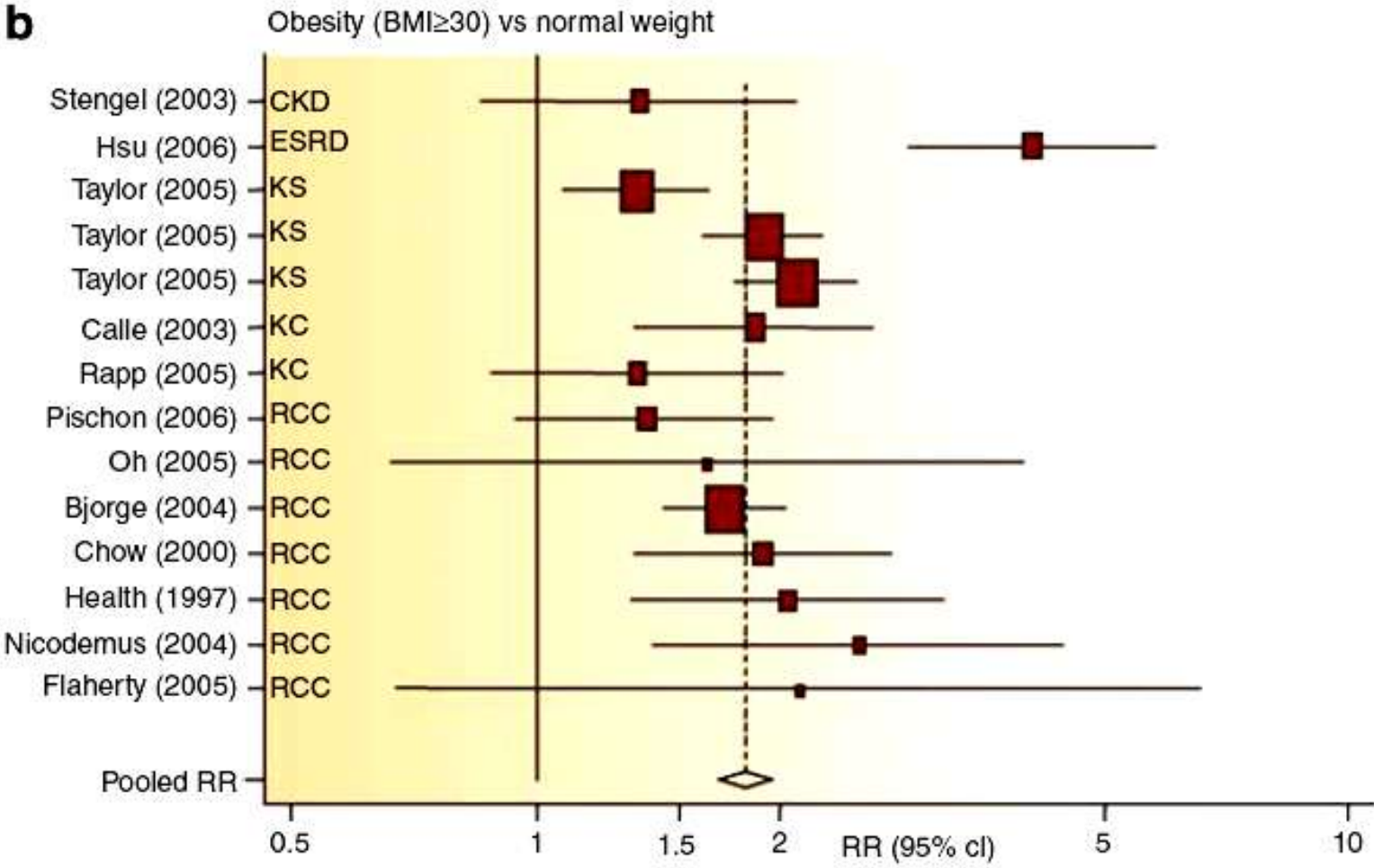
Left axis and bar graph: distribution of BMI in the study population of 74986 adults in the HUNT Study in Norway
Right axis: hazard ratio for treated ESDR or CKD-related death by BMI (multiadjusted for age, sex, smoking status, physical activity, socioeconomic status)

Association between **overweight** and **kidney disease** based on cohort studies in the general populations - overweight ($25 < \text{BMI} < 30$) vs normal weight.



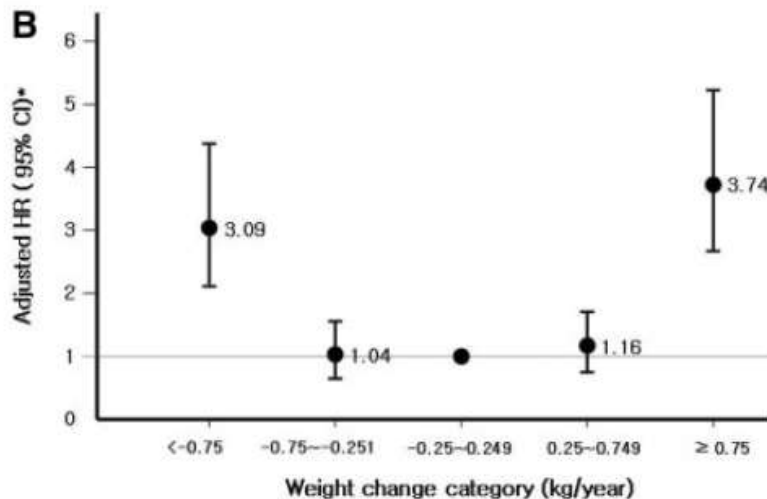
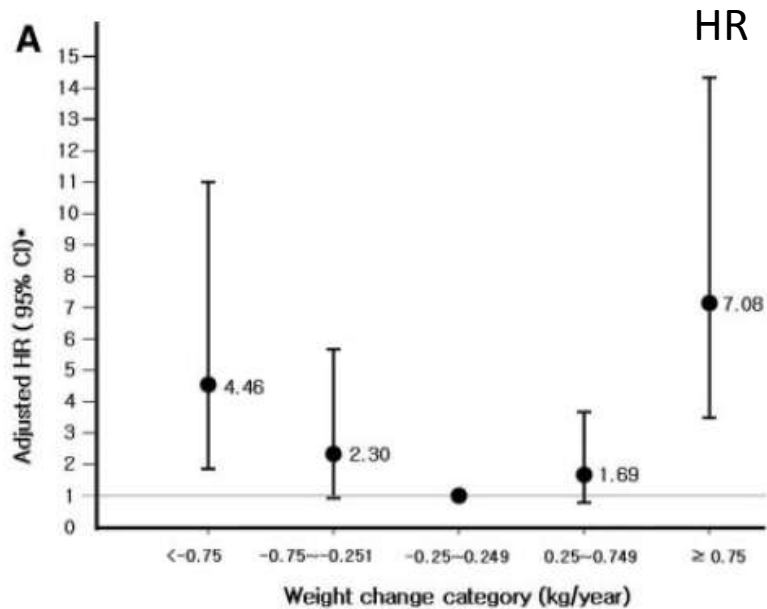
Test for heterogeneity: $Q=37.11$, $P=0.003$; Pooled RR (95% CI): 1.40 (1.30-1.50).

Association between **obesity** and **kidney disease** based on cohort studies in the general populations – obesity (BMI>30) vs normal weight.

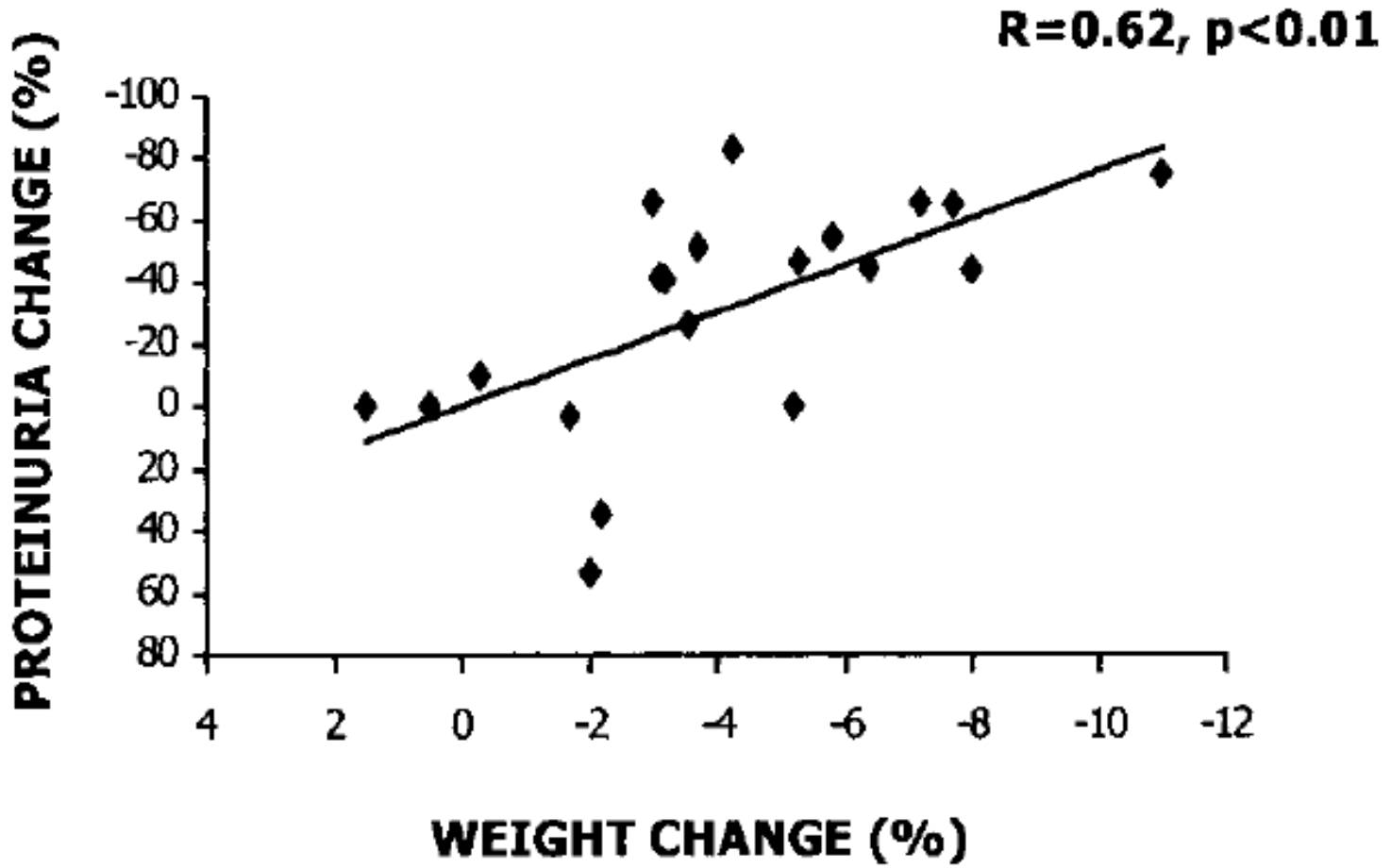


Test for heterogeneity: $Q=40.96$, $P=0.001$; Pooled RR (95% CI): 1.83 (1.57-2.13).

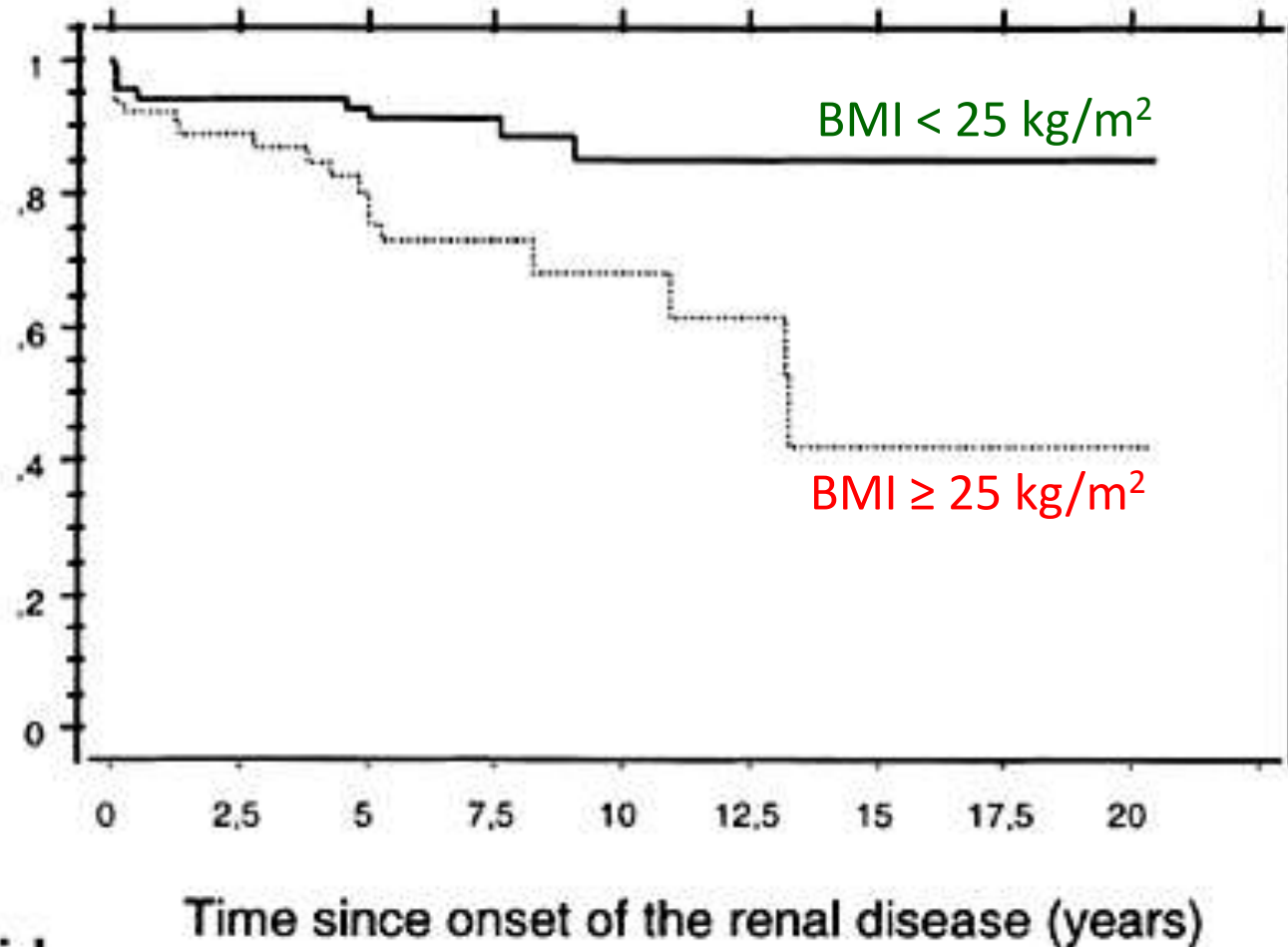
Association between the development of CKD (estimated GFR 64 ml/min per 1.73 m²) and weight change per year



Relationship of proteinuria and weight changes in diet-group patients



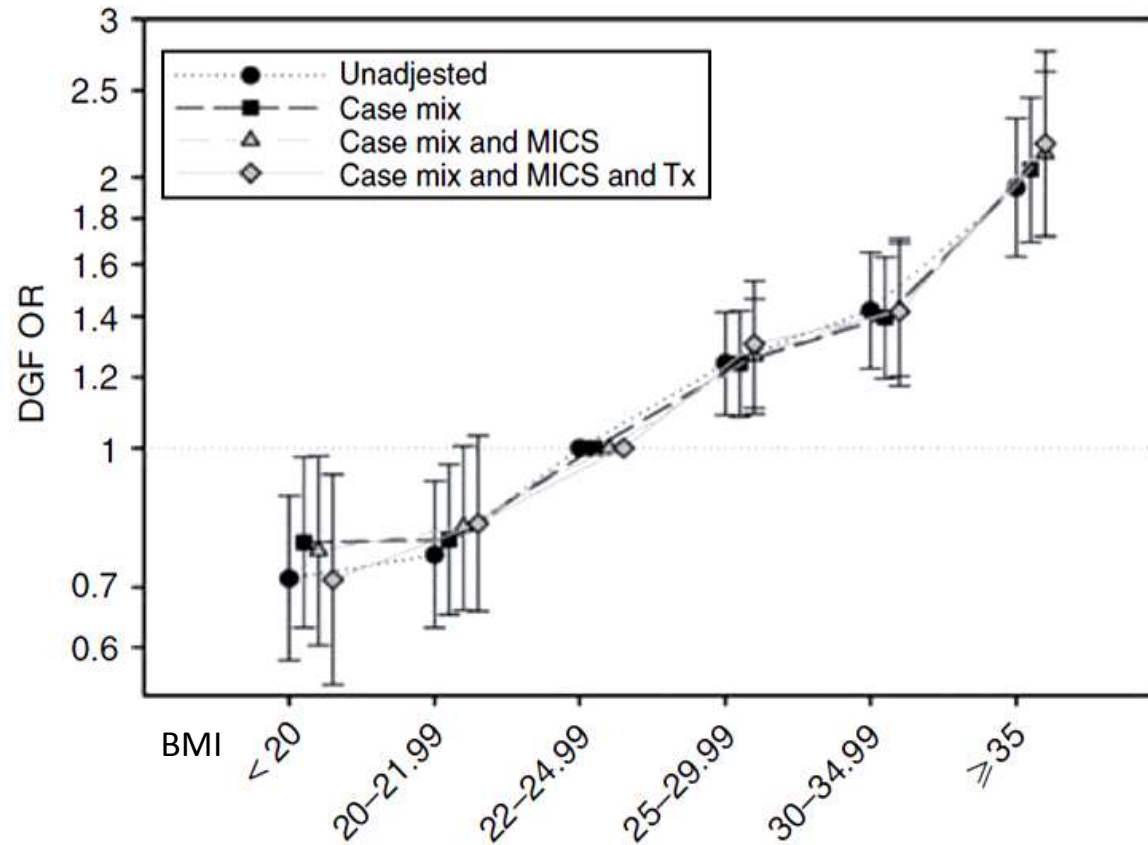
Overweight significantly increase risk of IgA nephropathy progression



CRF-free survival rate according to the presence of an elevated BMI at the initial renal biopsy.

Higher recipient BMI is associated with post-transplant delayed kidney graft function

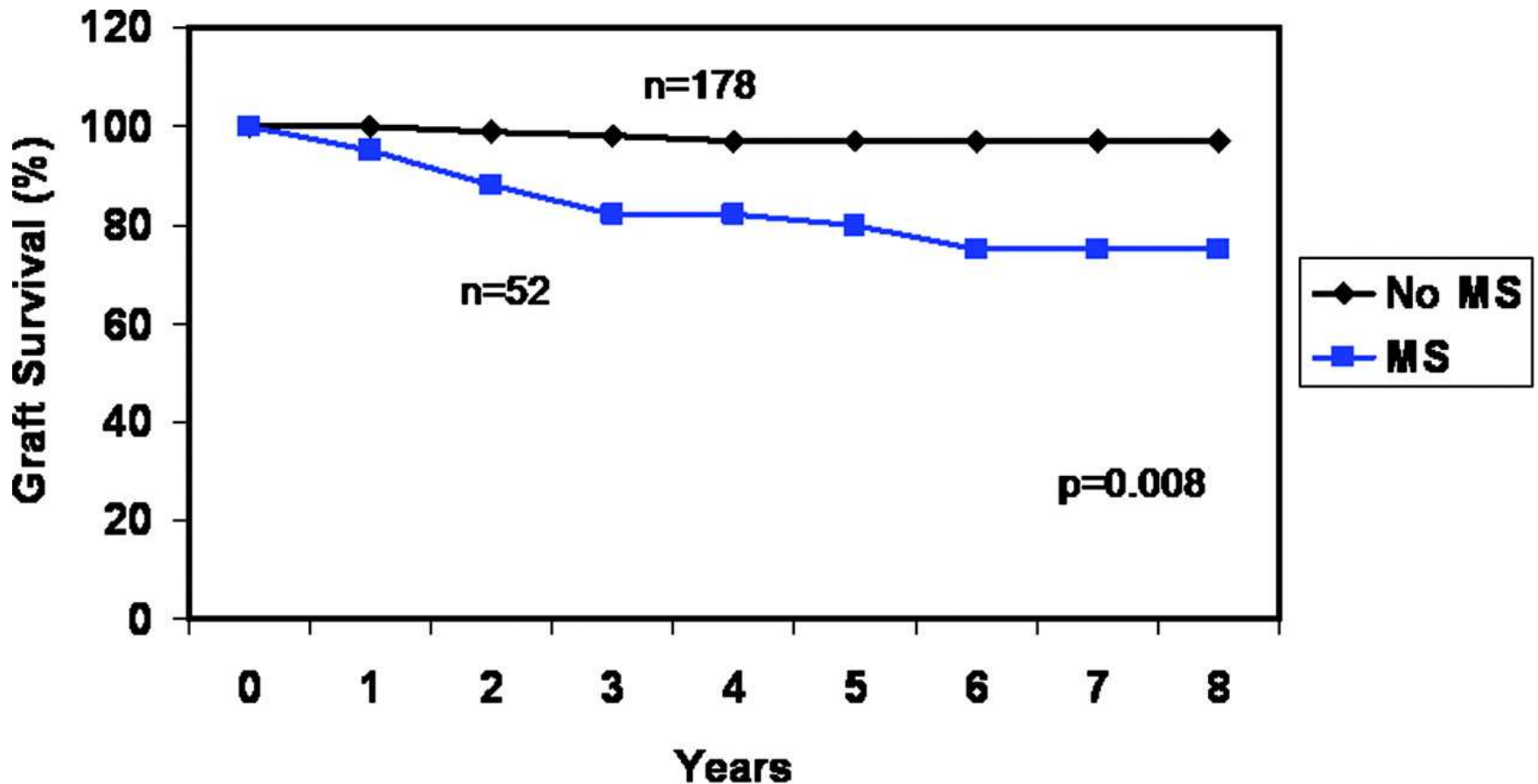
Analysis of 11,836 hemodialysis patients who underwent kidney transplantation



MICS- malnutrition–
inflammation complex
syndrome;
Tx- transplanted covariates

Multivariate analysis of logistic regression models showing pretransplant body mass index (BMI) and odds ratio of delayed graft function (DGF) in four different models

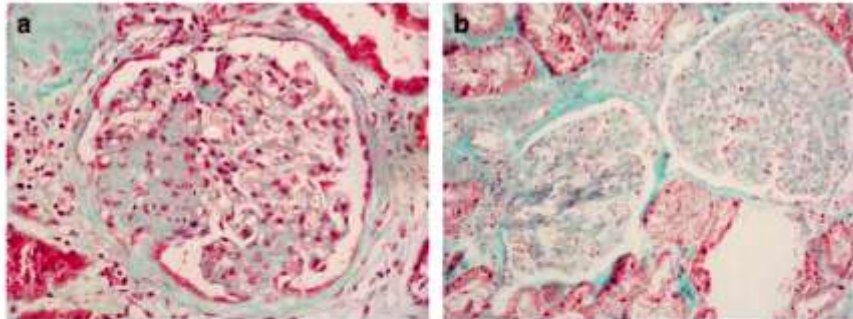
Allograft survival rates in kidney transplant recipients with and without metabolic syndrome (MS)



Hricik D E CJASN 2011;6:1781-1785

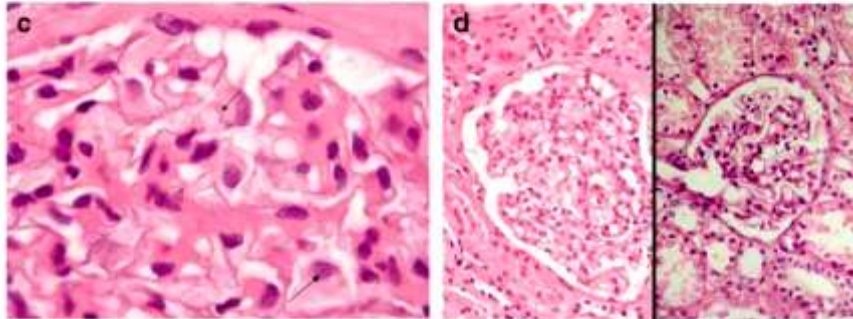
Obesity-Related Glomerulopathy

Focal and segmental glomerulosclerosis



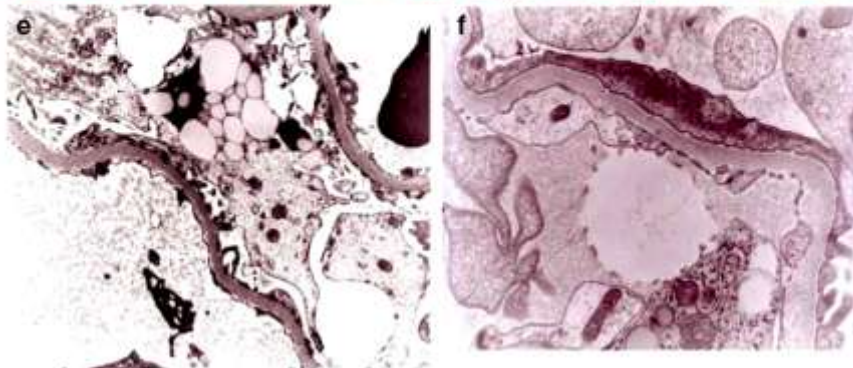
Global mesangial matrix increase in both glomeruli

Hypertrophic podocytes that contain intracytoplasmic droplets of fat resorption (arrow) and prominent nucleoli (arrow)



Glomerulus with glomerulomegaly from an extremely obese patient and glomerulus without glomerulomegaly from a control of the same age

Electron microscopy. Large-sized podocyte with intracytoplasmic lipids and focal foot process fusion (uranyl acetate and lead citrate stain, original magnification)



Mild fusion of podocytes and condensations of cytoskeletal filaments with a parallel orientation to the glomerular basement membrane

Renal biopsy findings in OB-FSFS and I-FSGS

	Per cent of normal glomeruli	Per cent of glomeruli with FSG lesions	Per cent of glomeruli with GGS	Glomerular diameter (μm)
OB-FSG (n=15)	61 \pm 24	19 \pm 23	18 \pm 18	256 \pm 24
I-FSG (n=15)	57 \pm 20	24 \pm 12	18 \pm 20	199 \pm 26
				P<0.001

Obesity-associated focal segmental glomerulosclerosis (OB-FSGS)

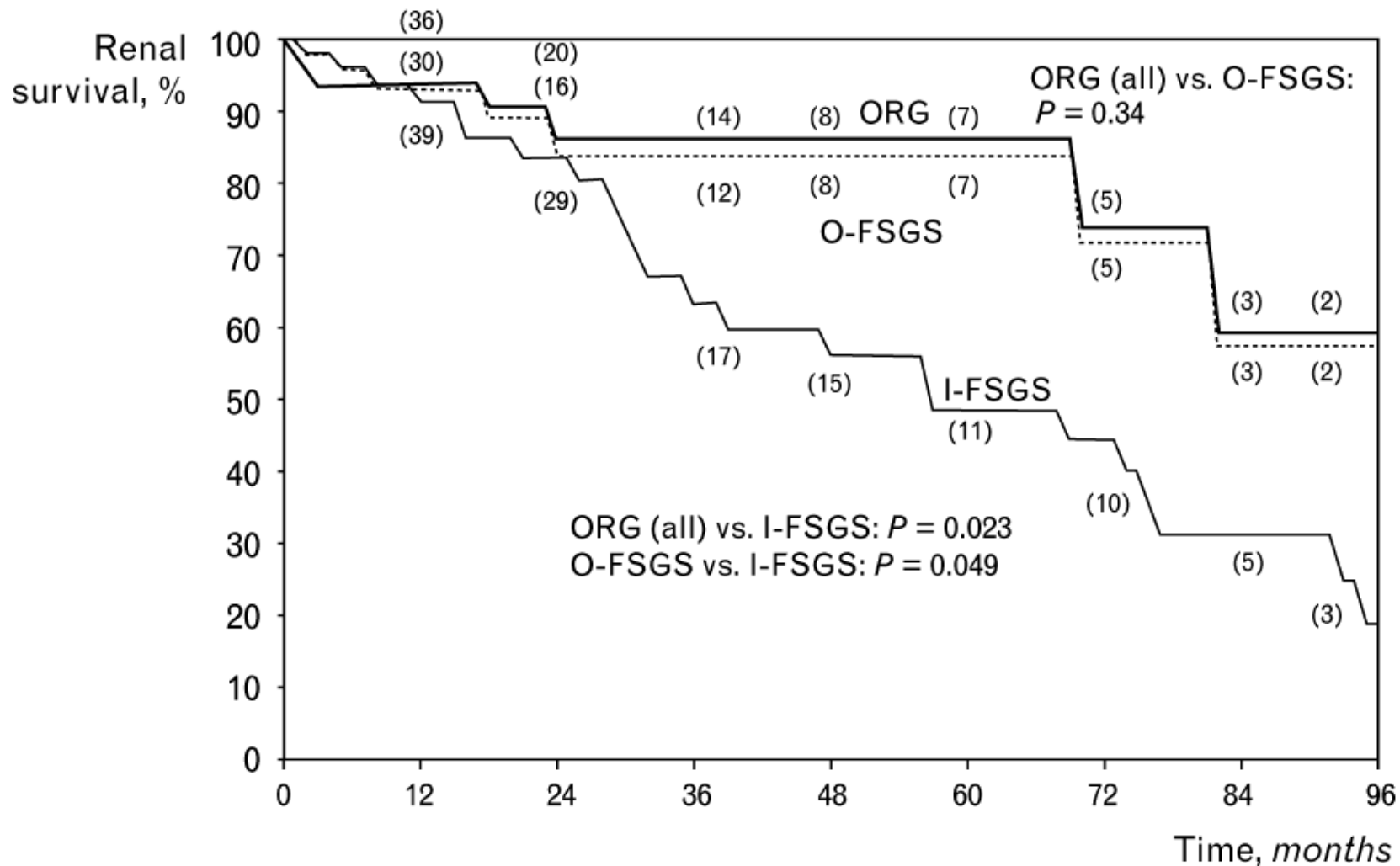
- Proteinuria (frequently in nephrotic range)
- Lack of oedema, hypoalbuminemia, hypoproteinemia and lipids disorders
- Decrease GFR in 50% patients
- Histopathology
 - Glomerulomegaly
 - FSGS
- Treatment:
- loss on weight, ACEI / ARBs

Praga M. et al., Nephrol. Dial. Transplant., 2001, 16, 1790-1798

Praga M. et al., Nephrol. Dial. Transplant., 2002, 17, 1157-1159

Renal survival in patients with obesity related glomerulopathy

Obesity-related vs idiopathic focal glomerulosclerosis



Renal survival- doubling of serum creatinine or end-stage renal disease

Factors implicated in the pathogenesis of CKD in obesity

- ❖ ↑ renin angiotensin system
- ❖ ↑ aldosterone
- ❖ ↑ sympathetic nervous system
- ❖ ↑ insulin resistance
- ❖ ↑ salt intake
- ❖ Altered adipokines: ↑ leptin, ↑ fetuin A, ↑ resistin, ↓ adiponectin, ↑ tumor necrosis factor, ↑ free fatty acids
- ❖ ↑ endothelin 1
- ❖ ↓ brain natriuretic protein
- ❖ ↑ plasminogen activator inhibitor 1
- ❖ Infiltrating macrophage phenotypic switch

Obesity and renal hemodynamic, renal reabsorption and neurohormonal activity

Model	Arterial pressure	Heart rate	Cardiac output	Renal sympathetic activity	Plasma renin activity	Na ⁺ balance	Renal tubular reabsorption	GFR ^a
Obese rabbits (high fat diet)	↑	↑	↑	↑	↑	↑	↑	↑
Obese dogs (high fat diet)	↑	↑	↑	↑	↑	↑	↑	↑
Obese humans	↑	↑	↑	↑	↑	↑	↑	↑

GFR, glomerular filtration rate. ^aThe GFR changes refer to the early phases of obesity before major loss of nephron function has occurred.

Effects of overweight and obesity on the kidney

❖ Hemodynamic

- ↑ Effective plasma flow
- ↑ glomerular filtration rate
- ↑ glomerular filtration fraction
- ↑ albuminuria

❖ Structural

- ↑ kidney weight
- ↑ glomerular planar surface
- Mesangial expansion
- Podocyte injury

❖ Pathologic

- Glomerulomegaly
- Glomerulosclerosis
- Obesity related glomerulopathy

❖ Chronic kidney disease

- ↑ onset of kidney disease
- ↑ progression to kidney failure
- ↑ proteinuria

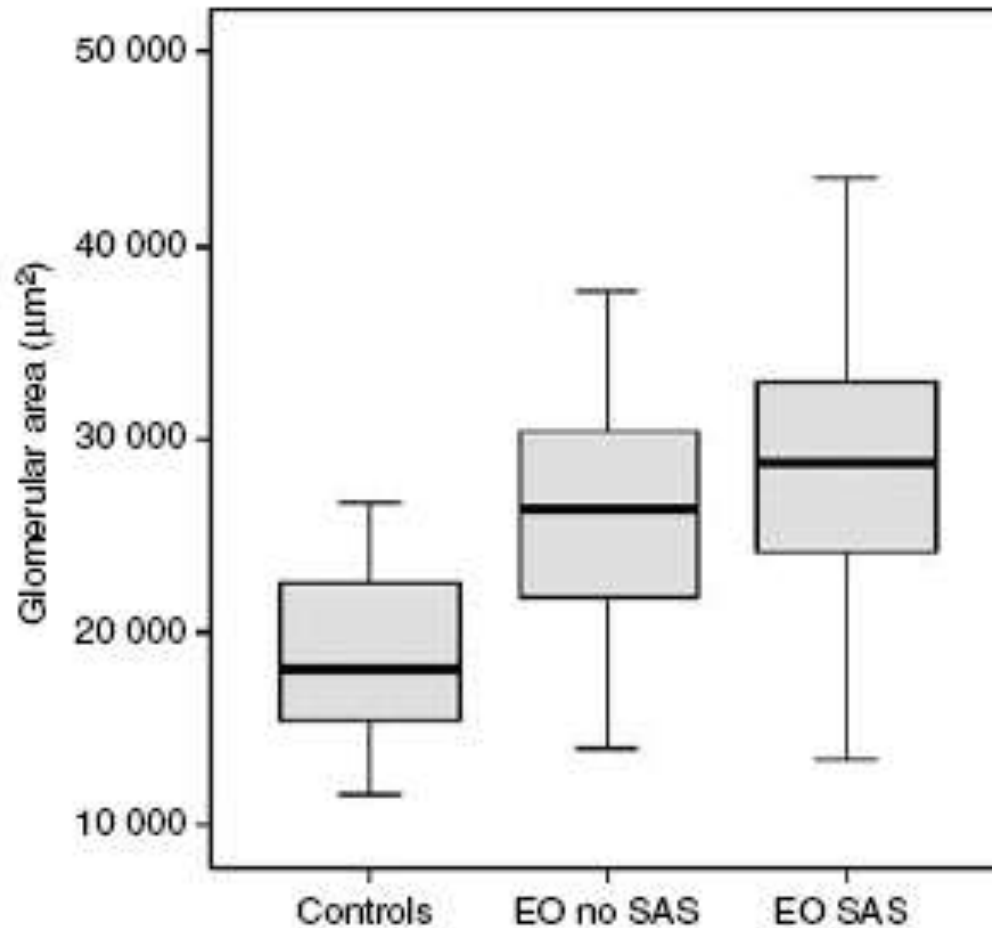
❖ End-stage renal disease

- ↑ incidence and prevalence
- Survival advantage in hemodialysis
- ↑ graft loss in kidney transplant recipients

❖ Other

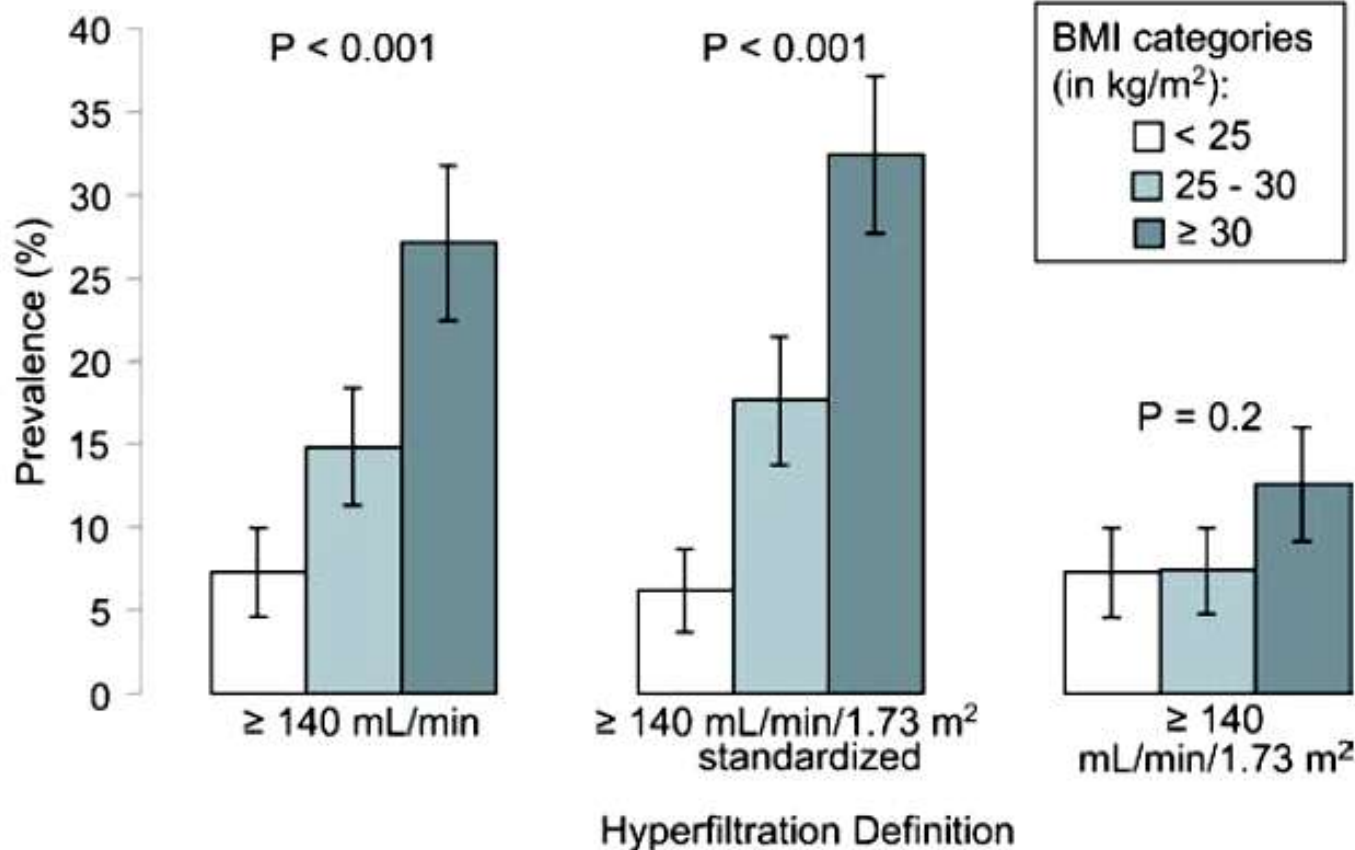
- ↑ renal cell carcinoma
- ↑ nephrolithiasis

Glomerular areas in extremely obese (EO) patients with or without sleep apnea syndrome (SAS) and in controls

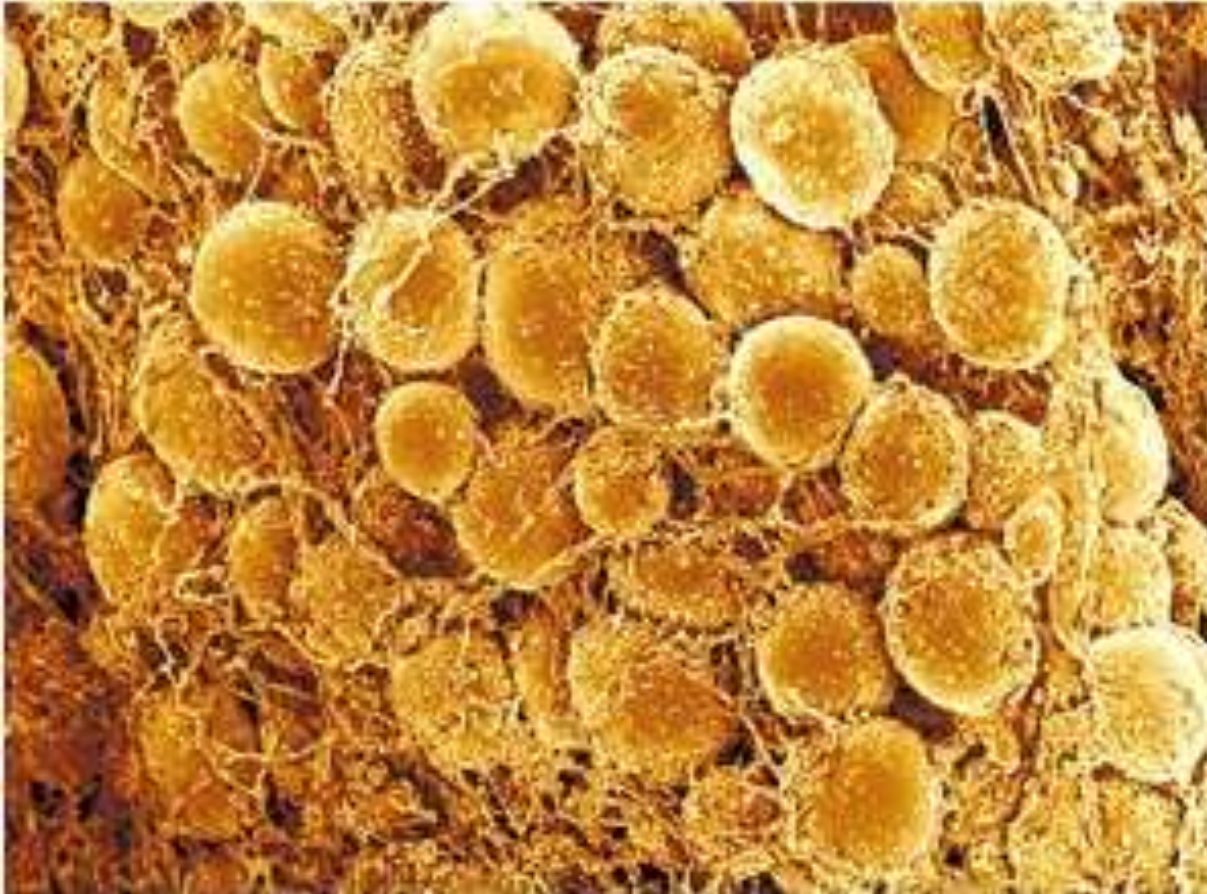


Marked Association Between Obesity and Glomerular Hyperfiltration: A Cross-sectional Study in an African Population

Prevalence of glomerular hyperfiltration with or without indexing to body surface area



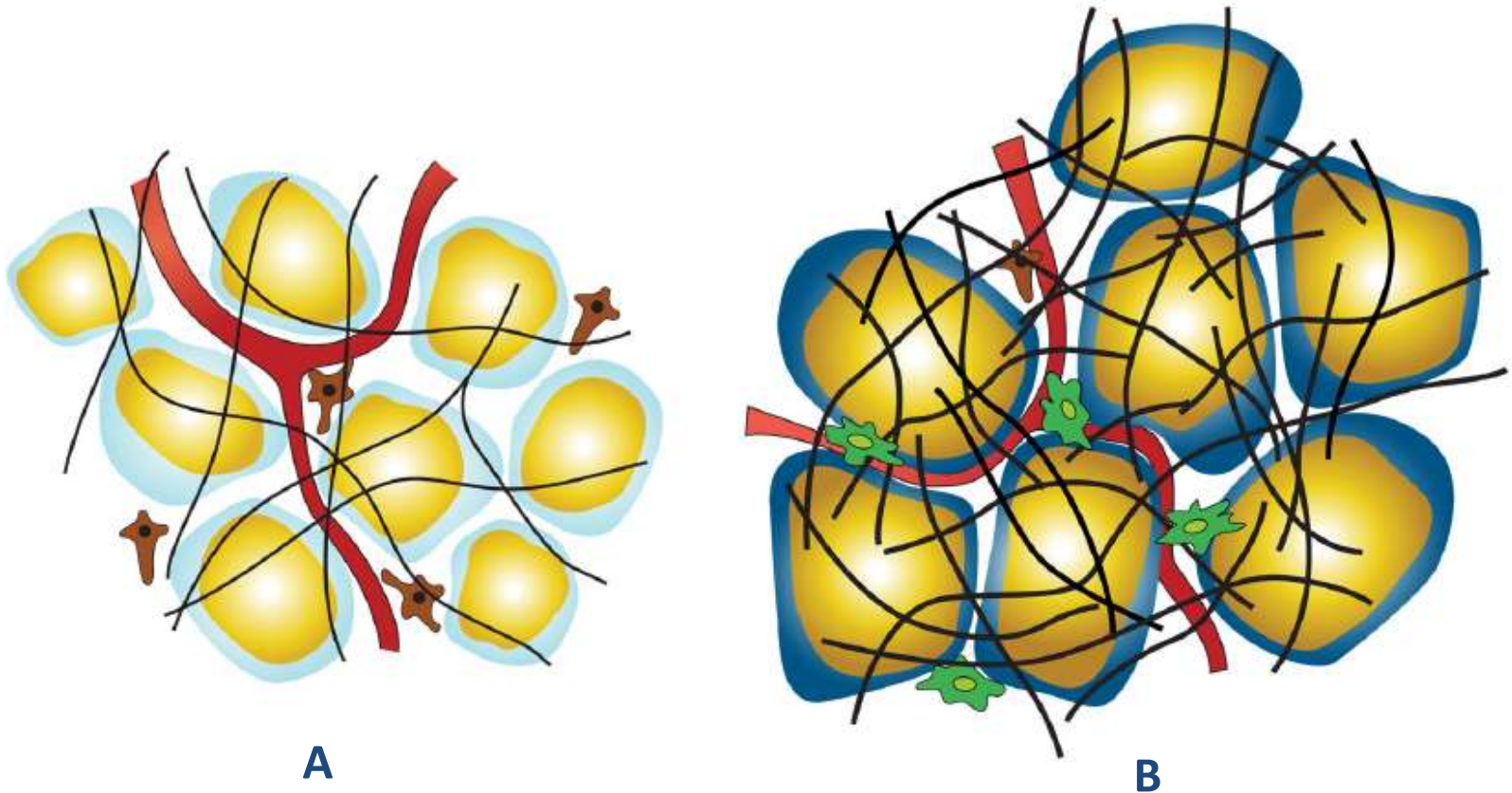
**Color-Enhanced Scanning Electron Micrograph
of Adipose Tissue, Showing Adipocytes.**



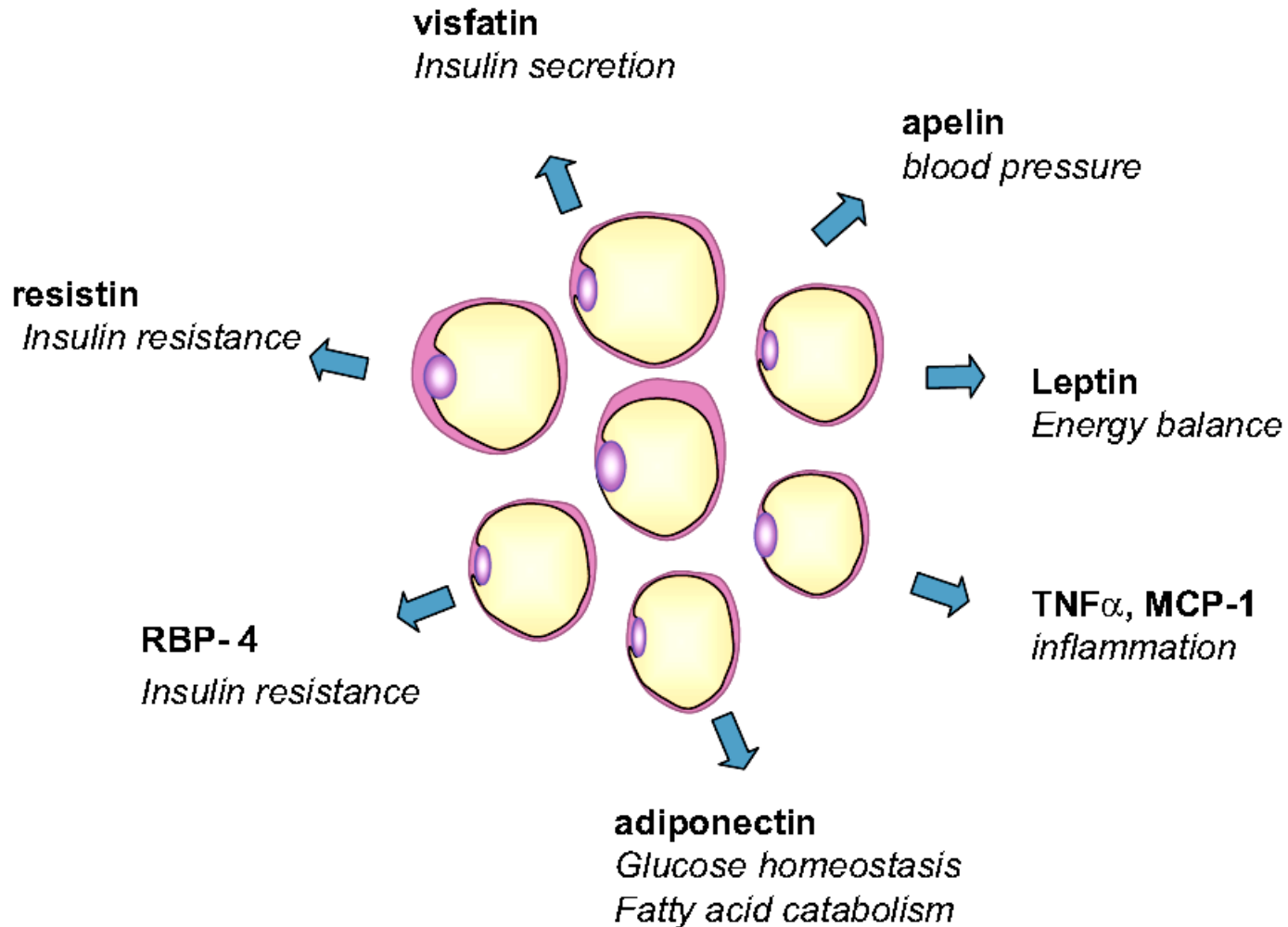
N. Engl. J. Med. 2006, 354, 1011-1012

White adipose tissue in the lean (A) vs. obese (B) state

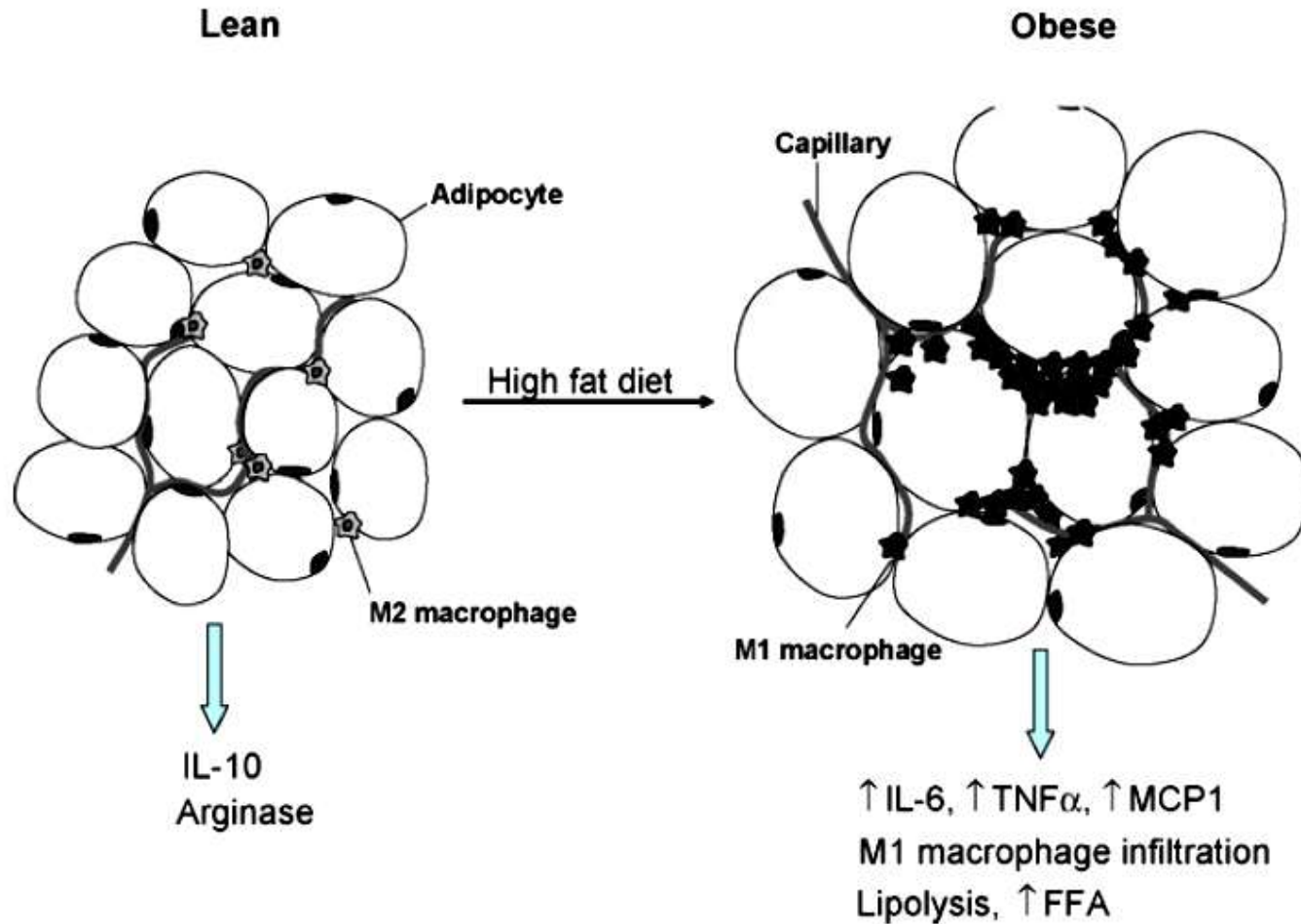
Adipocytes are shown with yellow triglyceride droplets and blue cytoplasm. In the lean state the light blue cytoplasm represent a state of normoxia, whereas the dark blue in the obese state represents a hypoxic state. Pre adipocytes are shown in brown, macrophages in green, blood



Adipose tissue as endocrine organ



Infiltration and polarization of macrophages in fat tissue in obese patients



Obesity and adipocyte response. Protein factors secreted from white adipose tissue during energy equilibrium and obesity

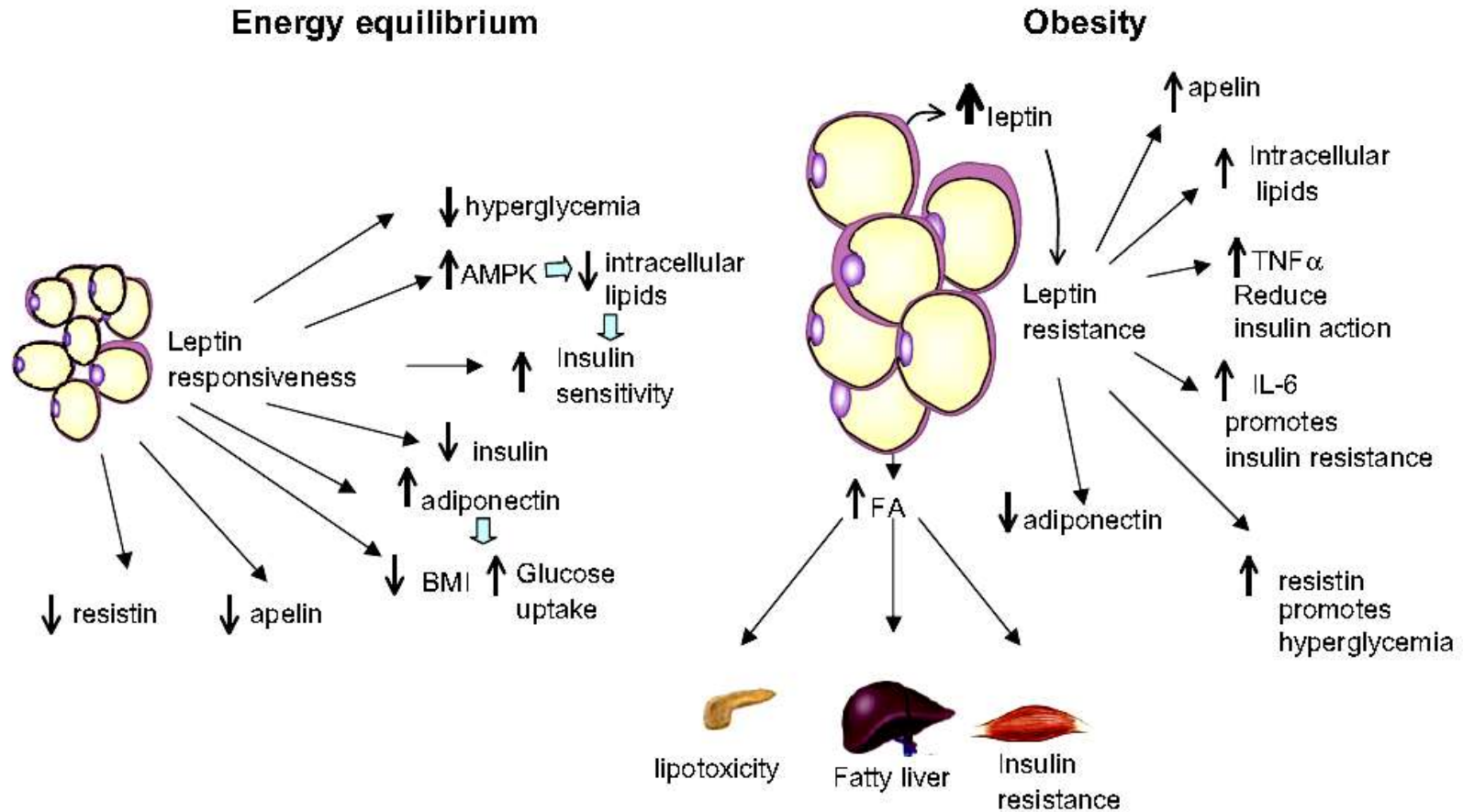
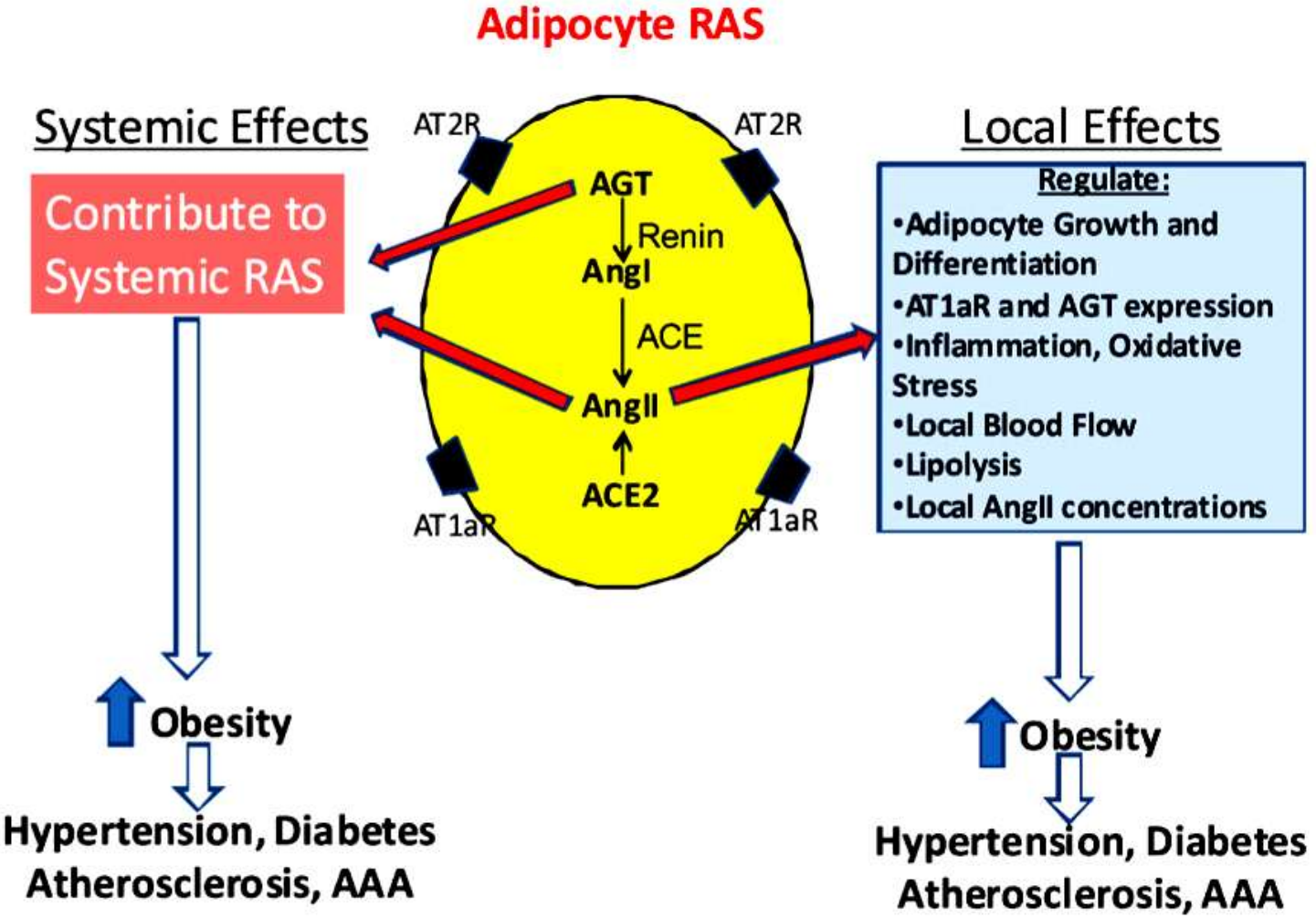


Table 1. List of hormones, cytokines, chemokines, growth factors and complement proteins produced by the adipose tissue

- Leptin
 - Adiponectin
 - Visfatin
 - Apelin
 - Resistin
 - Agouti signalling protein
 - Acylation stimulating protein
 - Nitric oxide (NO)
 - Renin
 - Angiotensin II
 - PAI-1
 - Tumour necrosis factor- α (TNF- α)
 - Interleukins-1 β , 6, 8, 10
 - Monocyte chemoattractant protein-1 (MCP-1)
 - Migration inhibitory factor (MIF)
 - Prostaglandin E₂ (PGE₂)
 - Hepatocyte growth factor (HGF)
 - Vascular endothelial growth factor (VEGF)
 - Nerve growth factor (NGF)
 - Heparin-binding epidermal growth factor-like growth factor (HB EGF)
 - Insulin-like growth factor-1 (IGF-1)
 - Complement factor D (adipsin)
- * Obestatin (2008)
-

Physiologic/pathophysiologic significance of an adipocyte RAS



Beyond effect of leptin on appetite and energy homeostasis, leptin exerts effect on the:

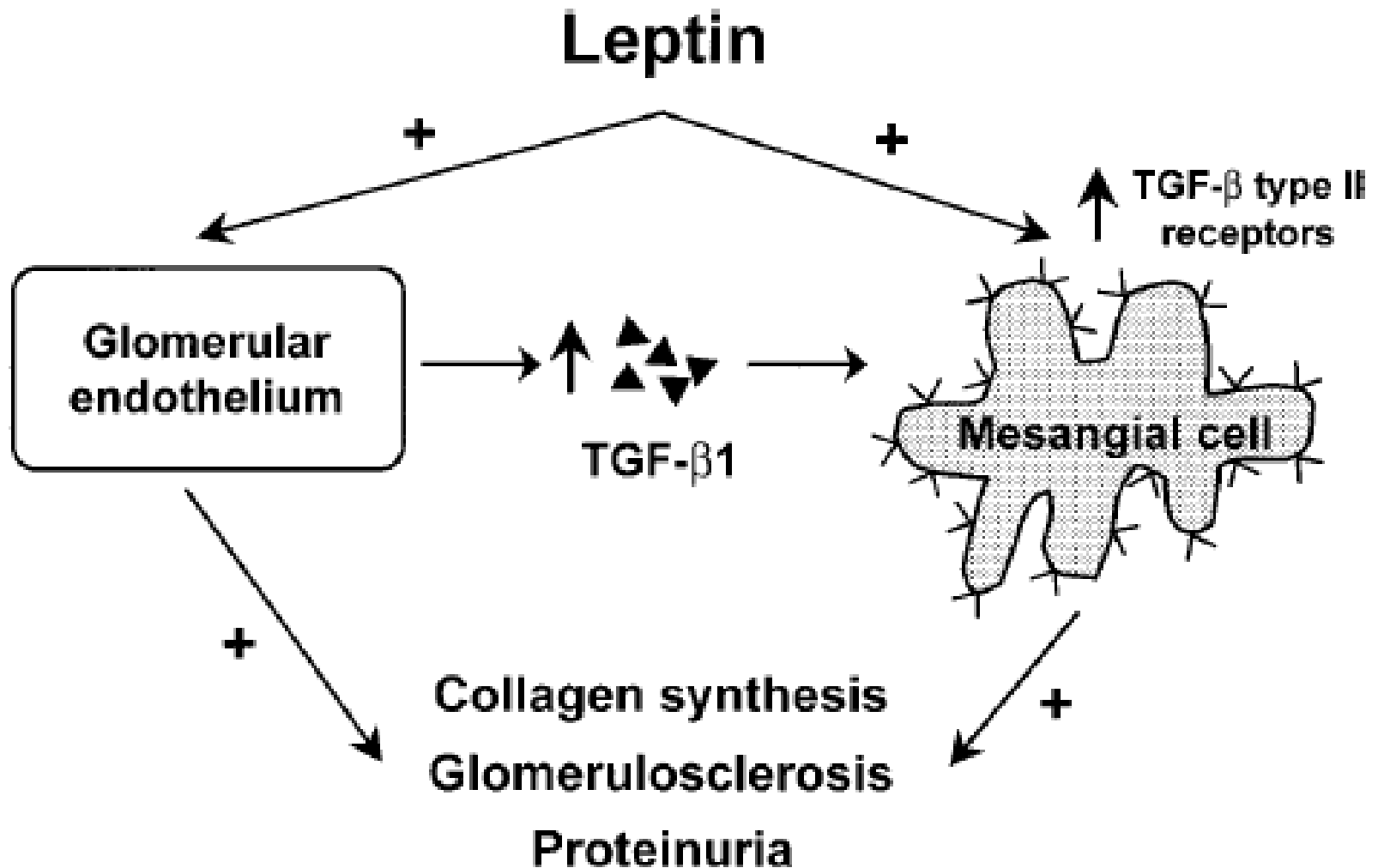
- kidneys (regulation of sodium homeostasis, obesity related hypertension and glomerulopathy)
- angiogenesis
- erythropoiesis
- immune function
- neuroendocrine function and
- bones

A role for leptin in glomerulosclerosis ?

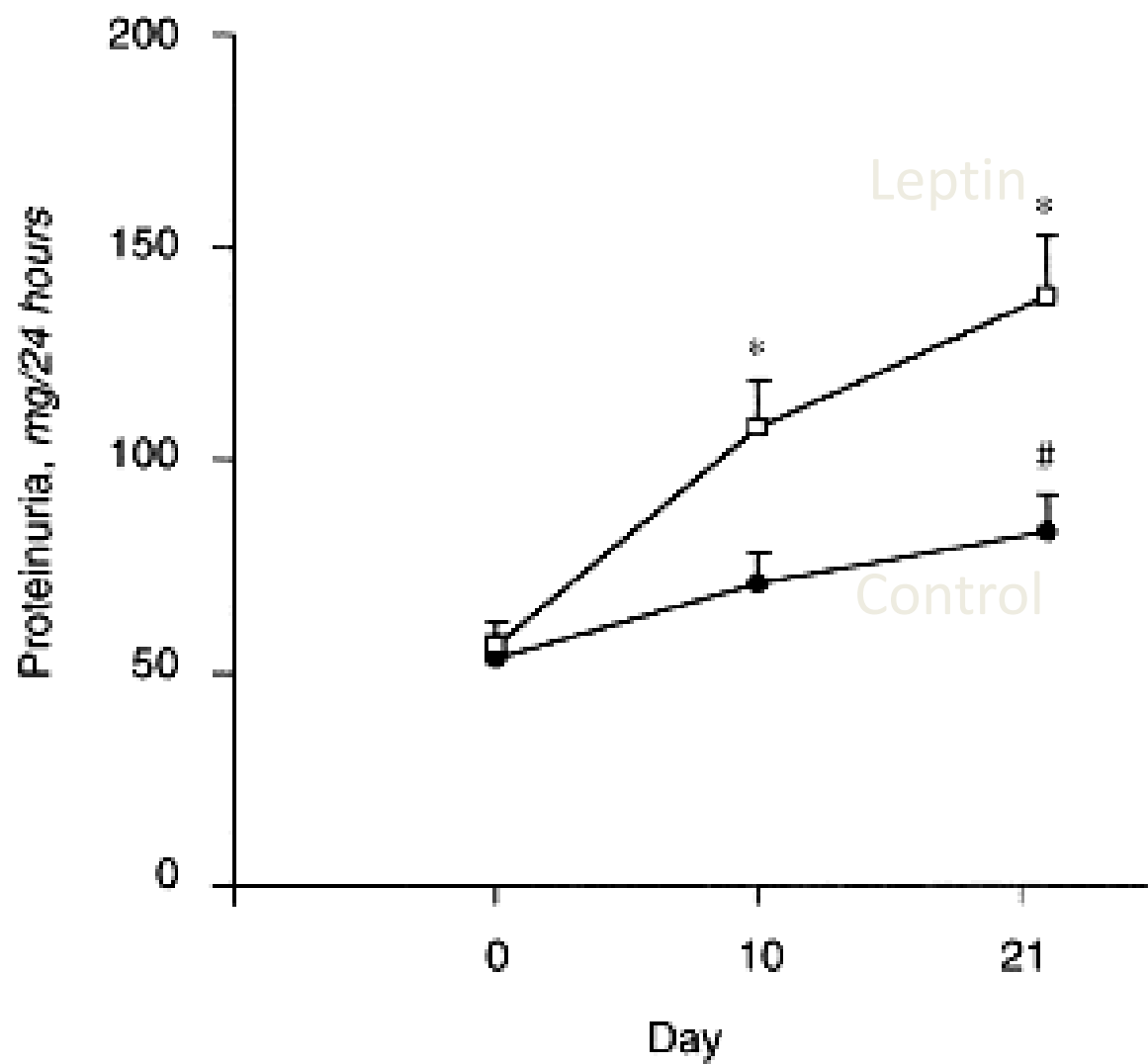
- Leptin stimulates glomerular endothelial cell proliferation in vitro and in vivo and transcription and secretion of transforming growth factor b1 (TGFb1), a fibrosis – indicating cytokine
- Leptin administration in rats causes proteinuria and glomerular mesangial matrix expansion

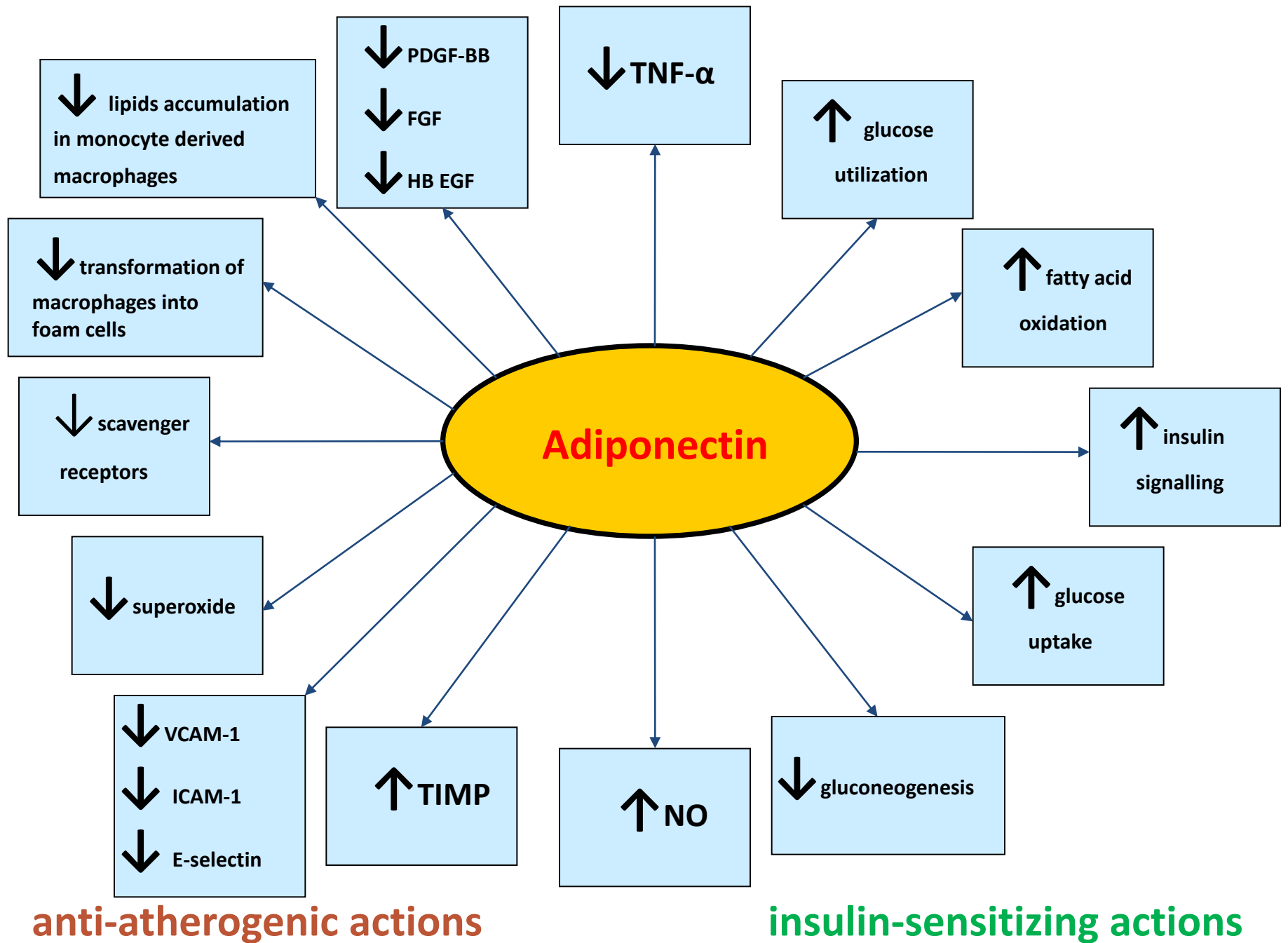
Wolf G. et al., Kindey Int. 1999, 56, 860-872

Paracrine TGF- β pathways between glomerular endothelial and mesangial cells mediated by leptin

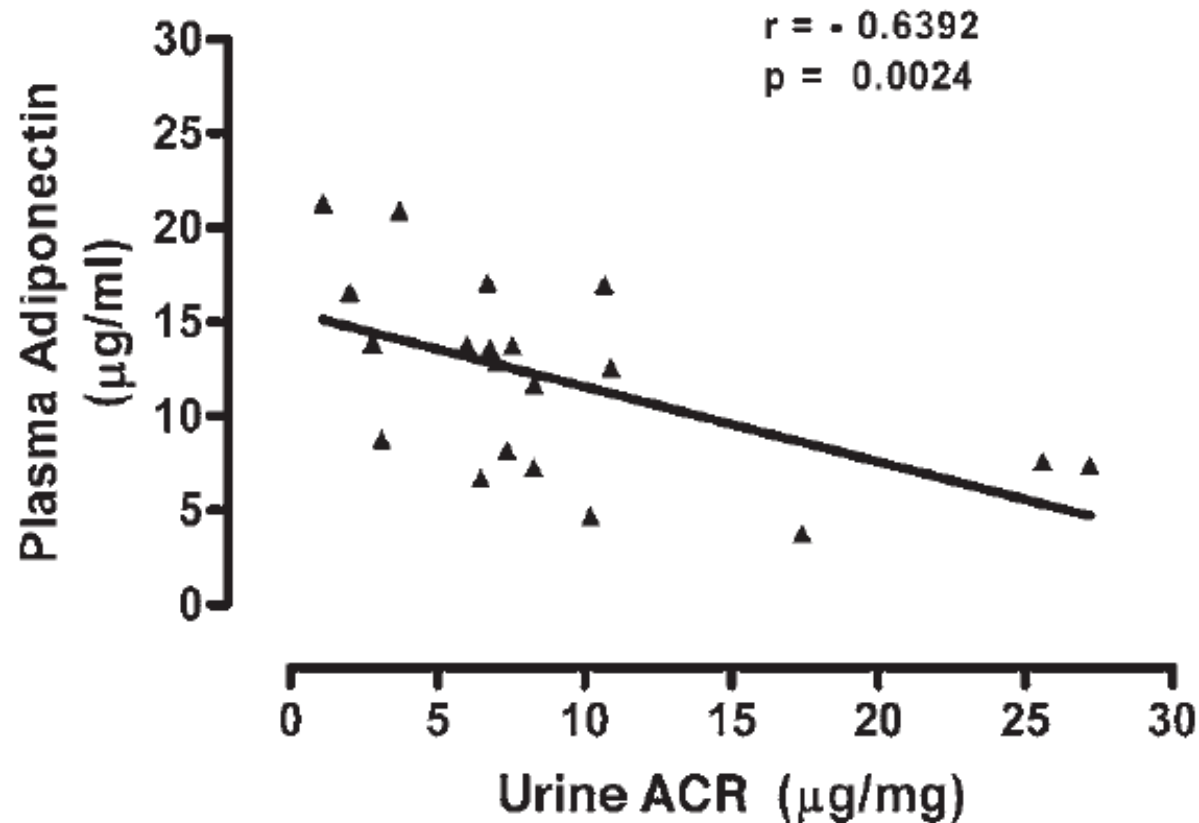


Leptin induced proteinuria –effect of 3 weeks leptin infusion

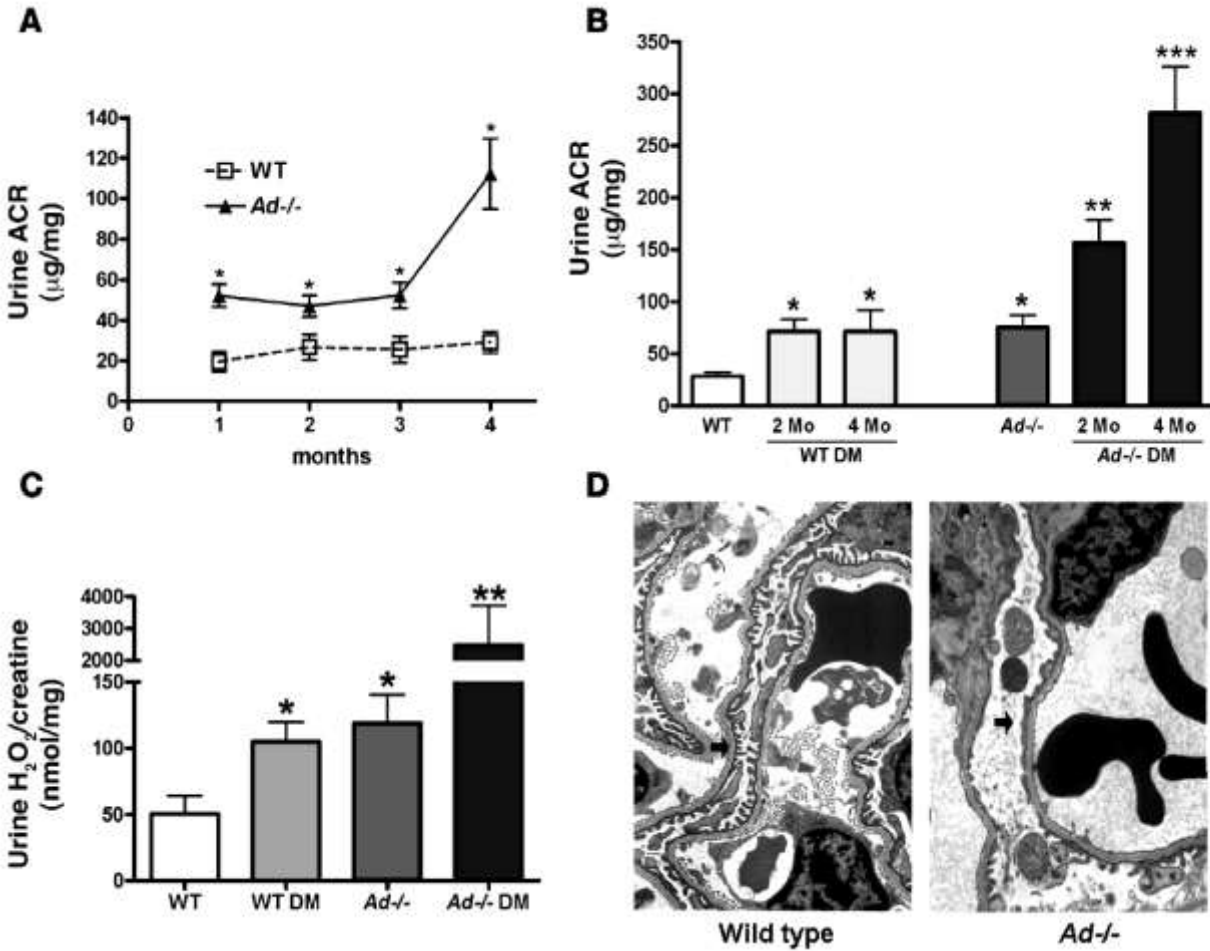




Negative correlation between albuminuria and plasma adiponectin levels in obese adults African Americans.

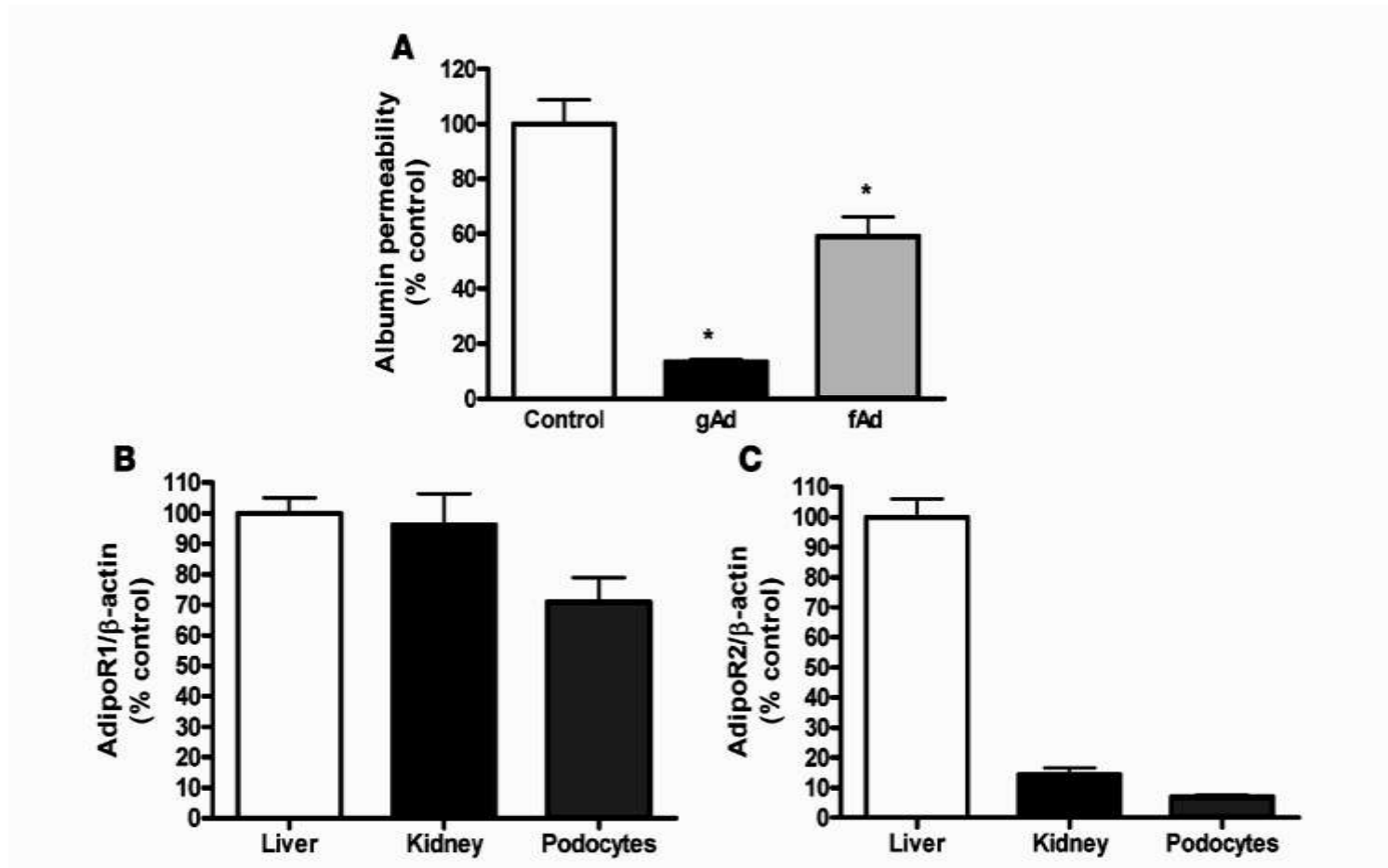


Ad^{-/-} mice exhibit increased albuminuria, oxidant stress, and podocyte dysfunction



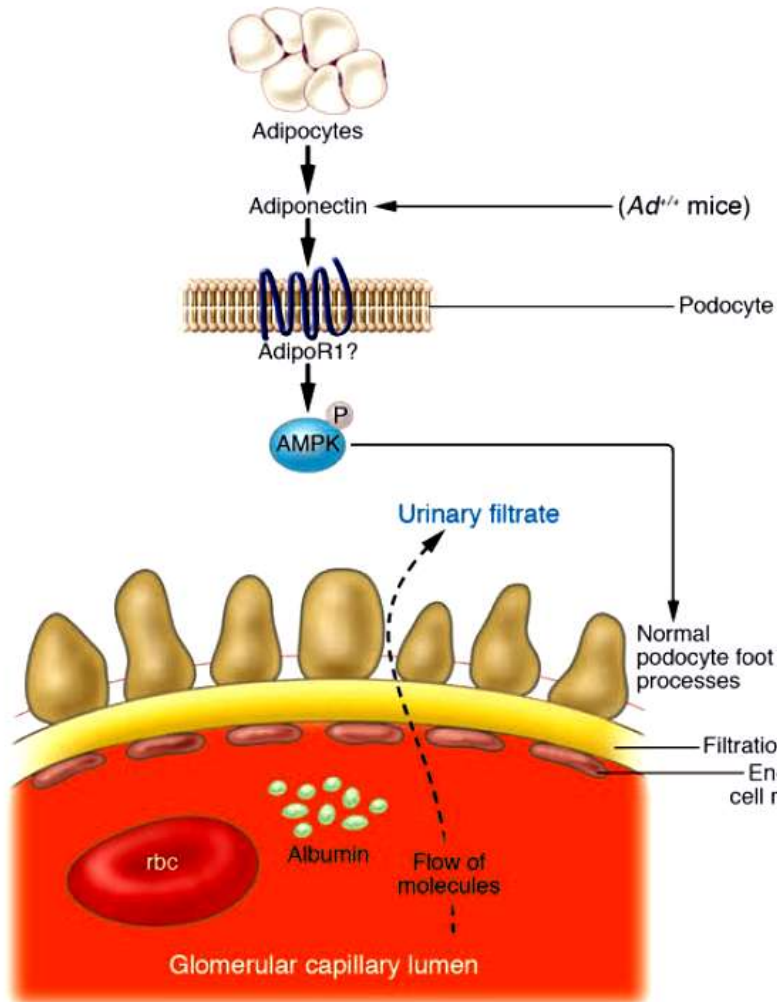
Adiponectin inhibits permeability across a podocyte monolayer

Direct action of adiponectin on podocytes independent of the systemic and/or metabolic effects of adiponectin

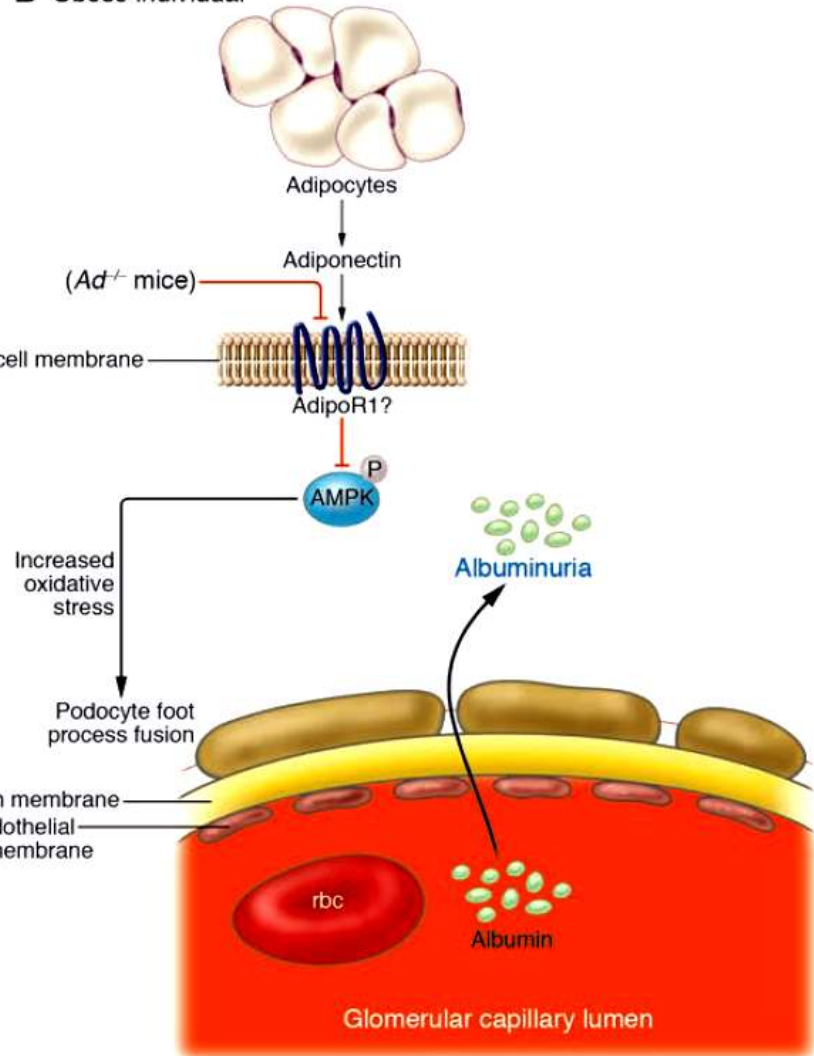


Effects of adiponectin on podocytes

A Lean individual



B Obese individual



Conditions and mediators known to regulate adiponectin levels

Down-regulation

Abdominal obesity

Type 2 diabetes

Polycystic ovary
syndrome

Hyperinsulinaemia

TNF- α

Glucocorticoids

Testosterone

β -receptor agonists

Conjugated linoleic acid

Up-regulation

Weight loss

Type 1 diabetes

Kidney failure

Anorexia nervosa

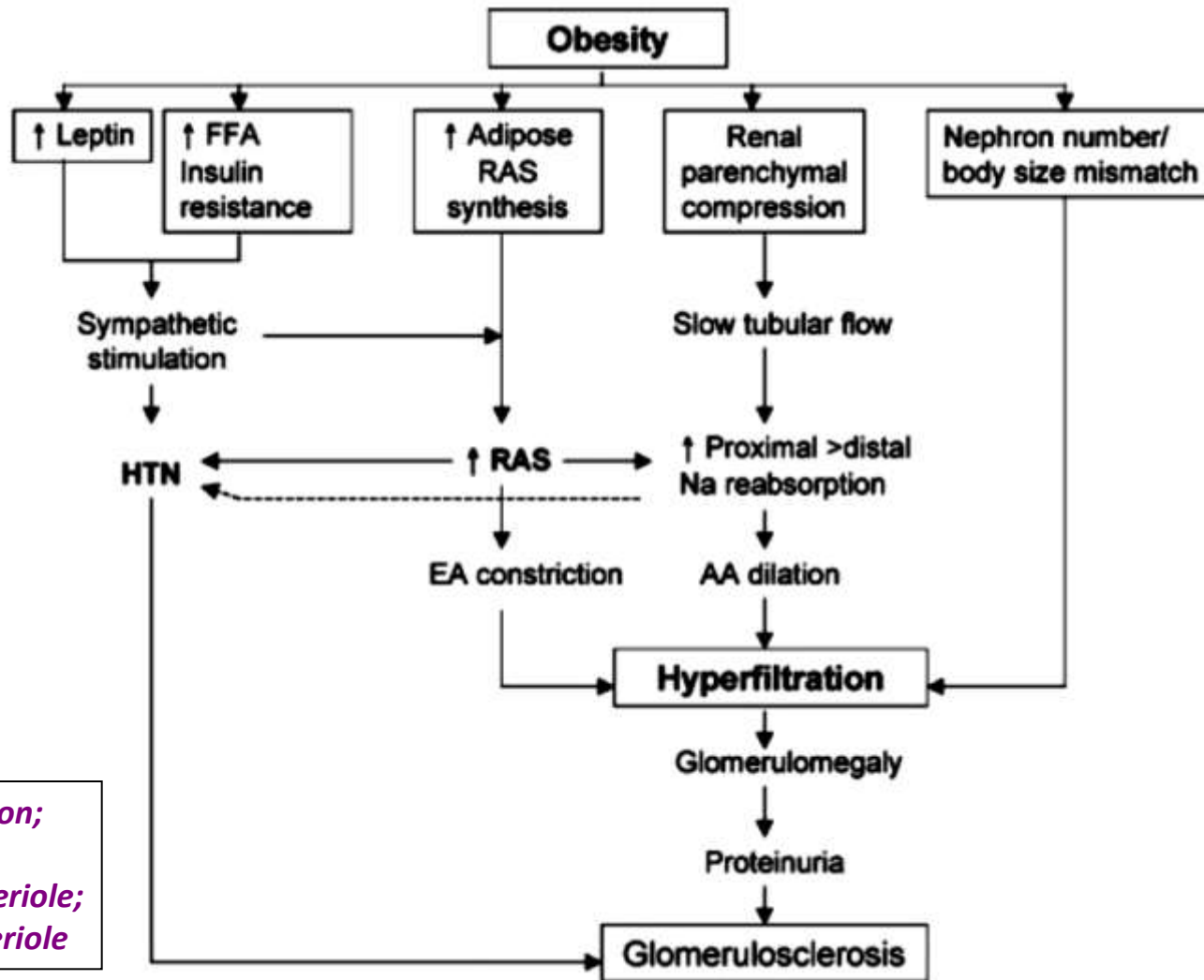
Leptin

Thiazolidinediones

Renin–angiotensin blockade

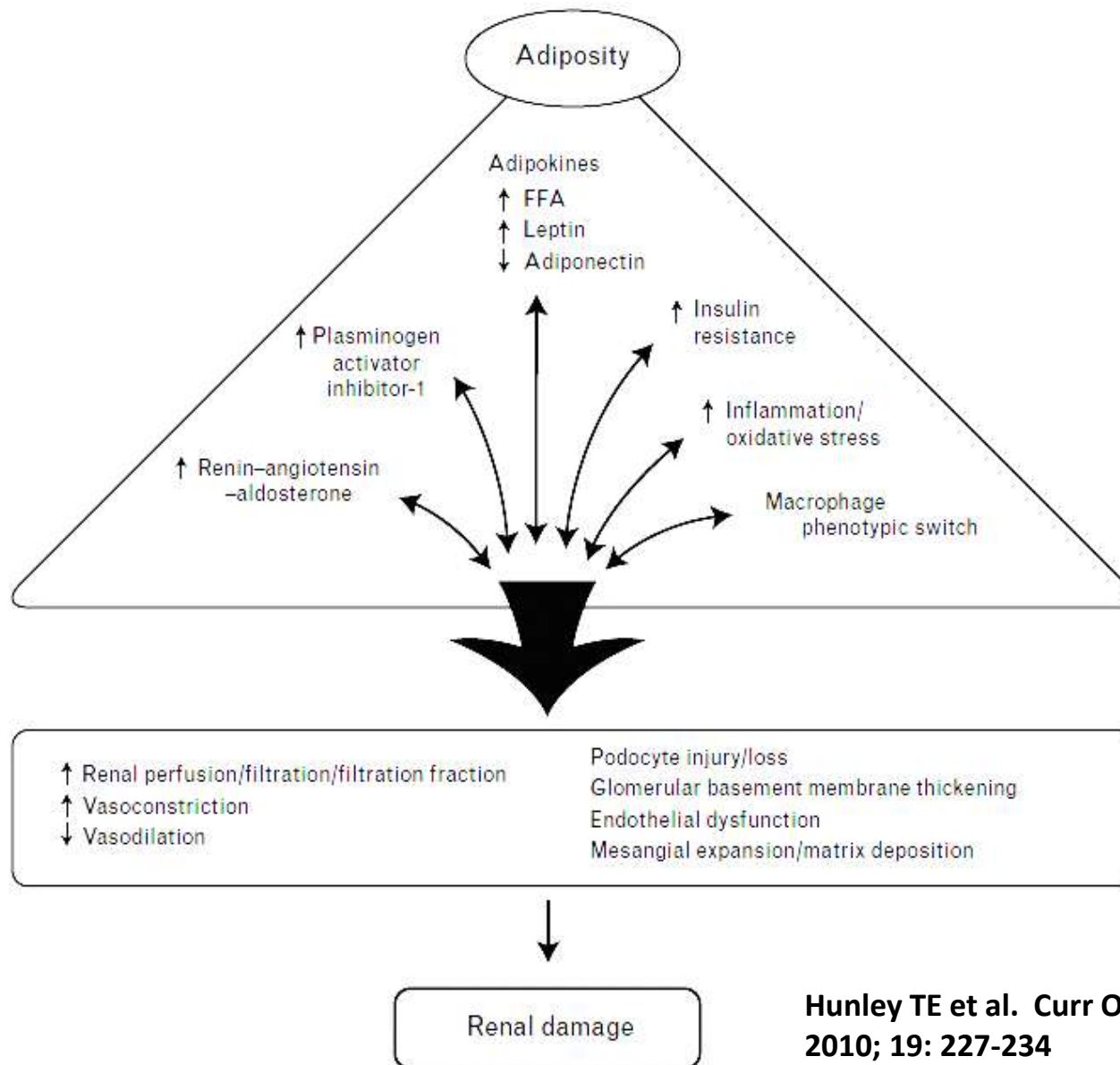
Cannabinoid type 1 receptor
antagonists

Hyperfiltration and hypertension- hemodynamic consequences of obesity



*HTN, hypertension;
Na, sodium;
AA, afferent arteriole;
EA, efferent arteriole*

Mechanisms of obesity related renal disease



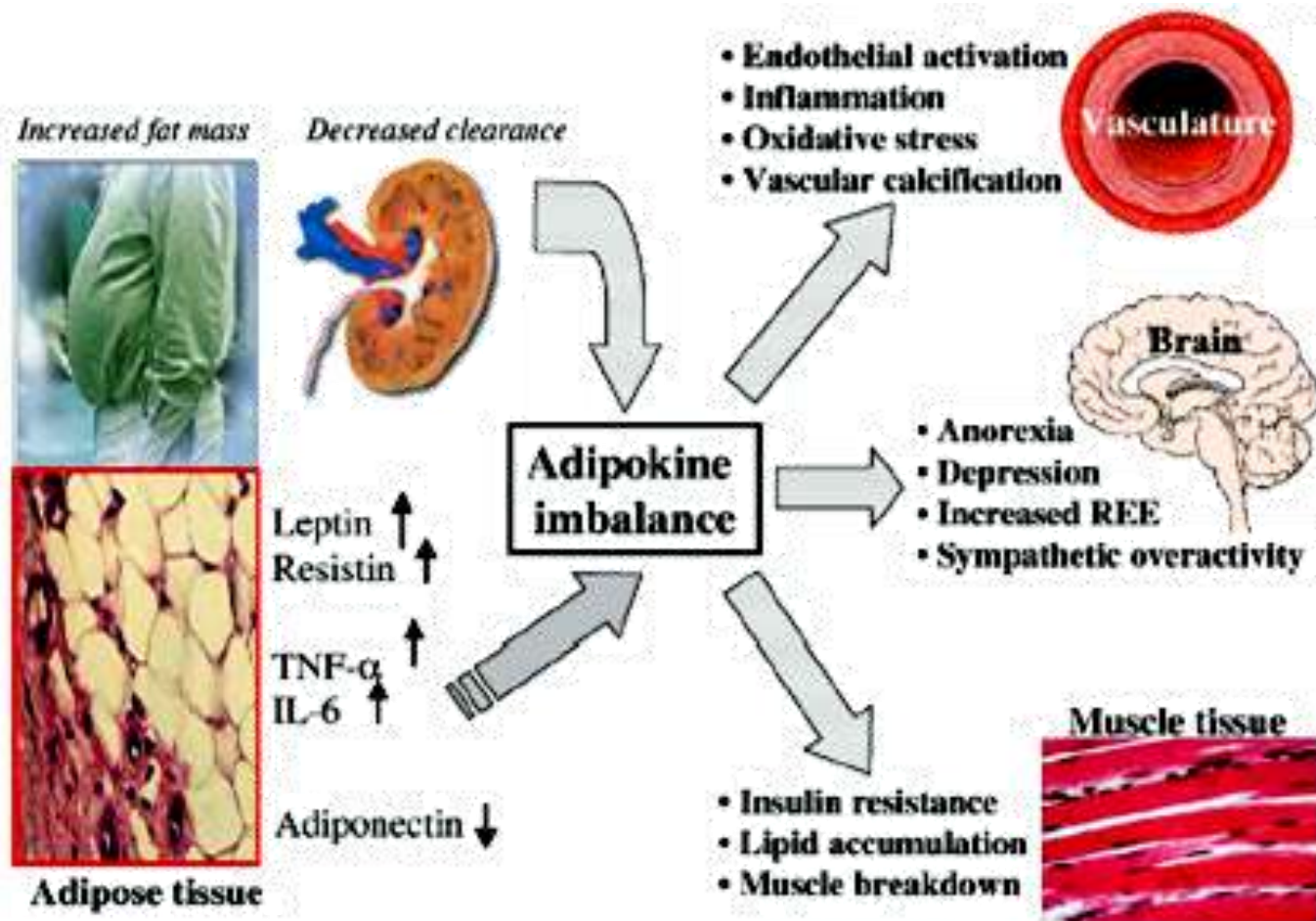


Figure 1. Adipose tissue secretes many adipokines that stimulate NF- κ B and affect insulin sensitivity, such as resistin, TNF- α , and IL-6. These effects may be balanced in part by the insulin-sensitizing hormone adiponectin, which by inhibition of NF- κ B has anti-inflammatory effects. It could be speculated that decreased renal mass may contribute to adipokine imbalance because all of these factors are retained in chronic kidney disease. Retention and an imbalance of proinflammatory adipokines may have vascular endothelial effects as well as effects on the central nervous system, and may contribute to wasting and insulin resistance.

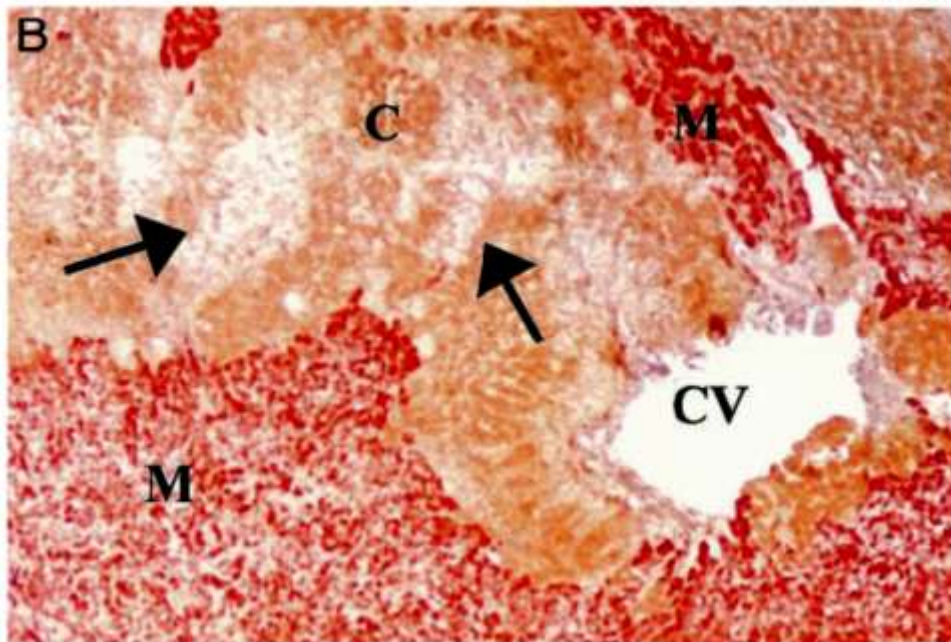
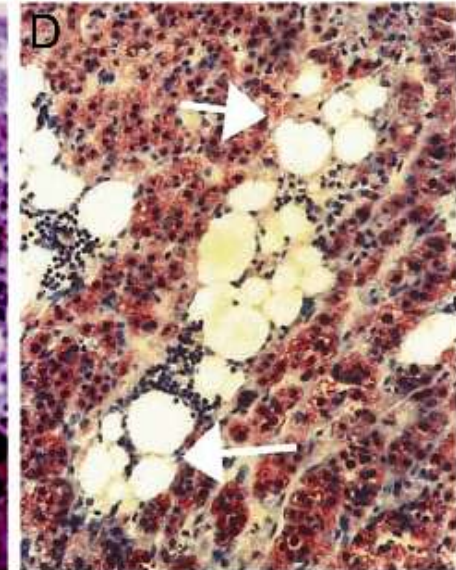
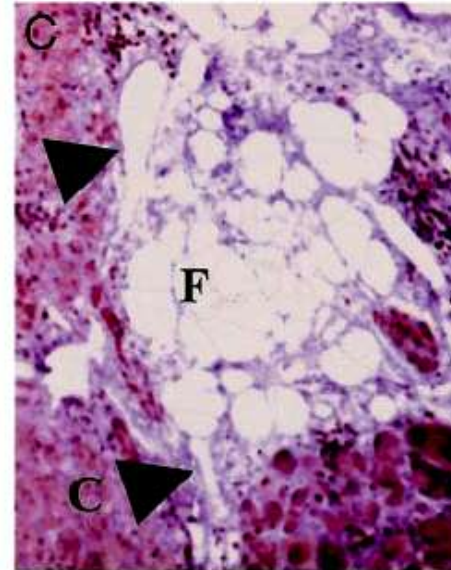
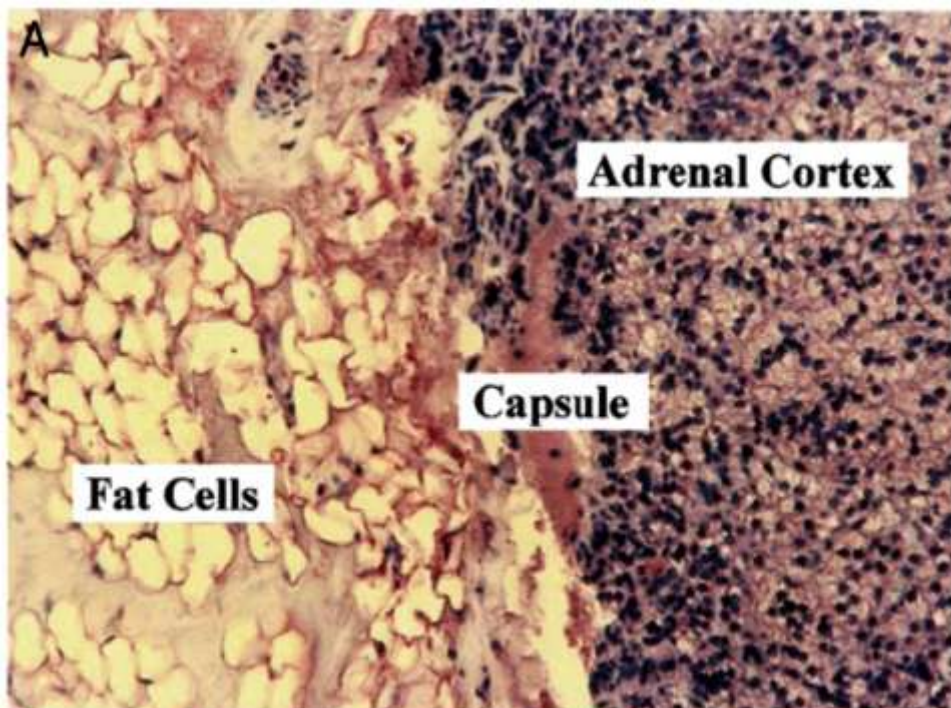


Fig. 5. Paraffin sections of normal human adrenal gland. (A) Human adrenals are embedded in periadrenal fat. (B–D) Adrenocortical cells are immunostained (brown) with an antibody against 17α -hydroxylase; in B, chromaffin cells are immunostained with an antibody against chromogranin A (red staining). (C) Adipose tissue may accompany adrenal vessels (arrow heads) or occur within the adrenal cortex in direct contact with adrenocortical cells (arrows in B and D). C, adrenal cortex; M, adrenal medulla; CV, central vein; arrows demonstrate clusters of fat cells.

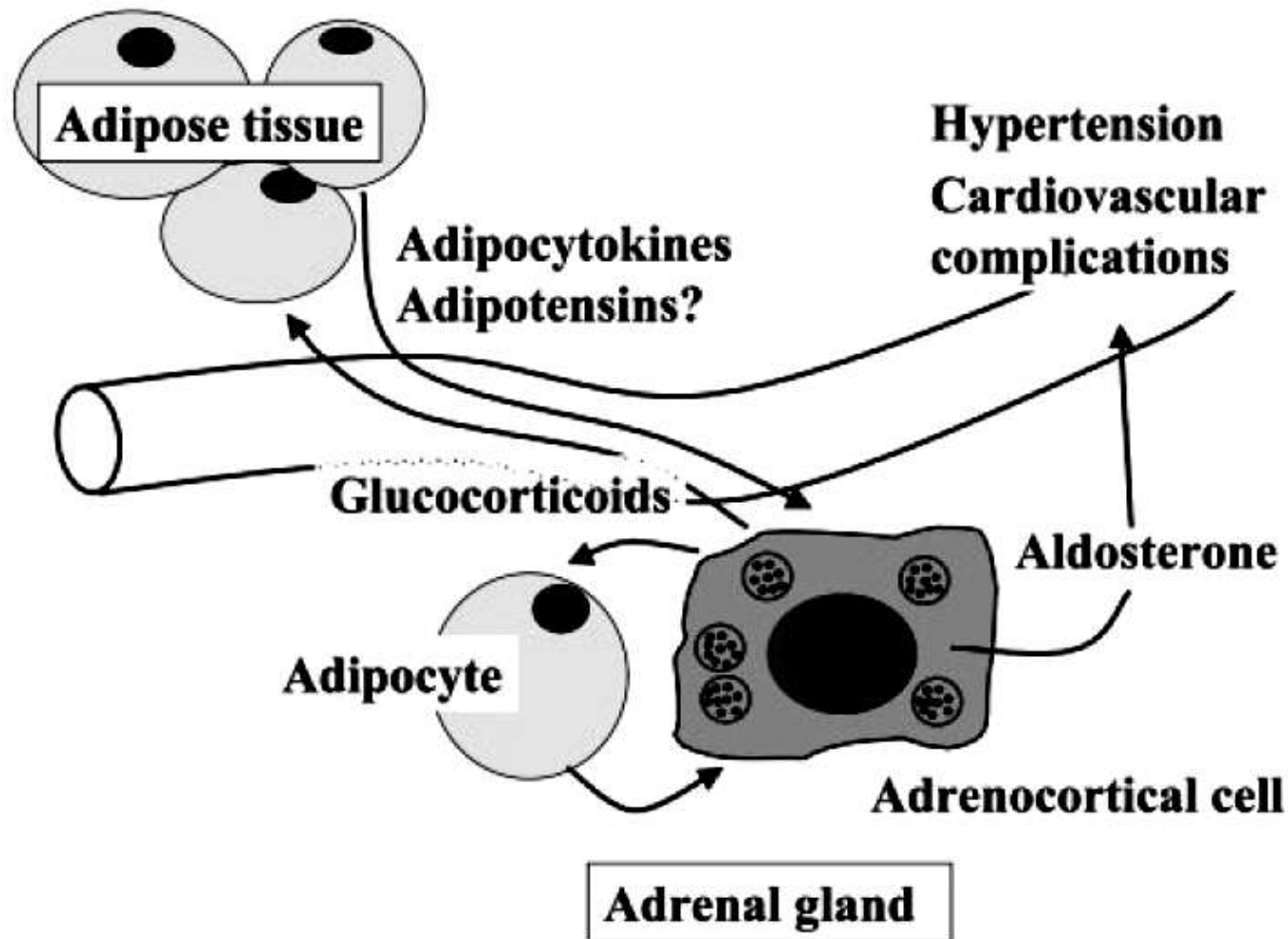
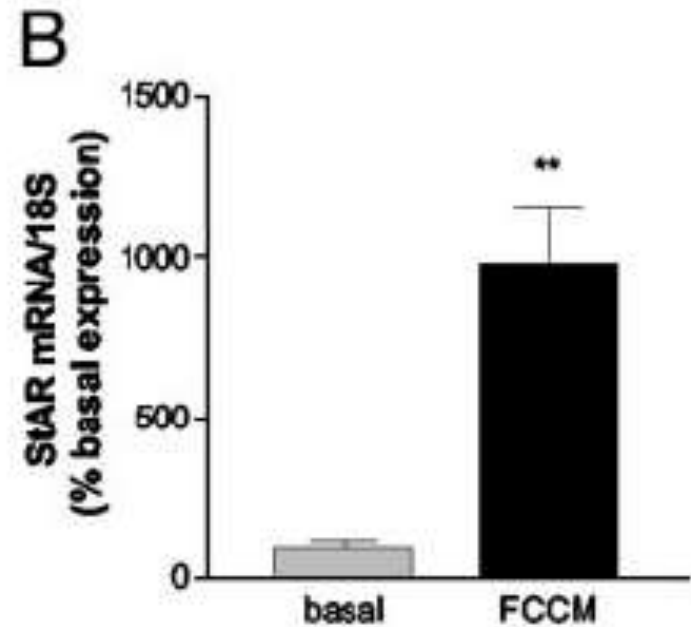
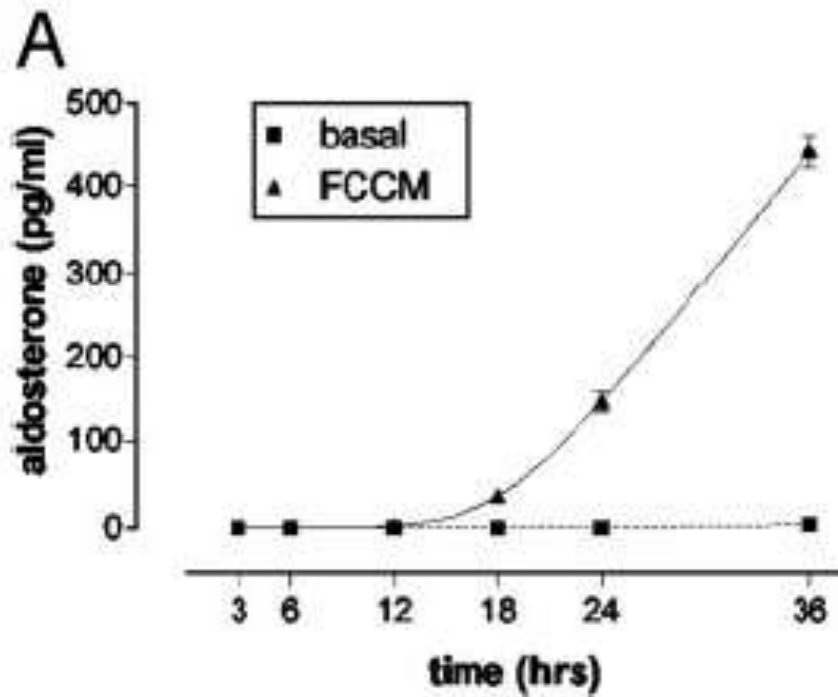
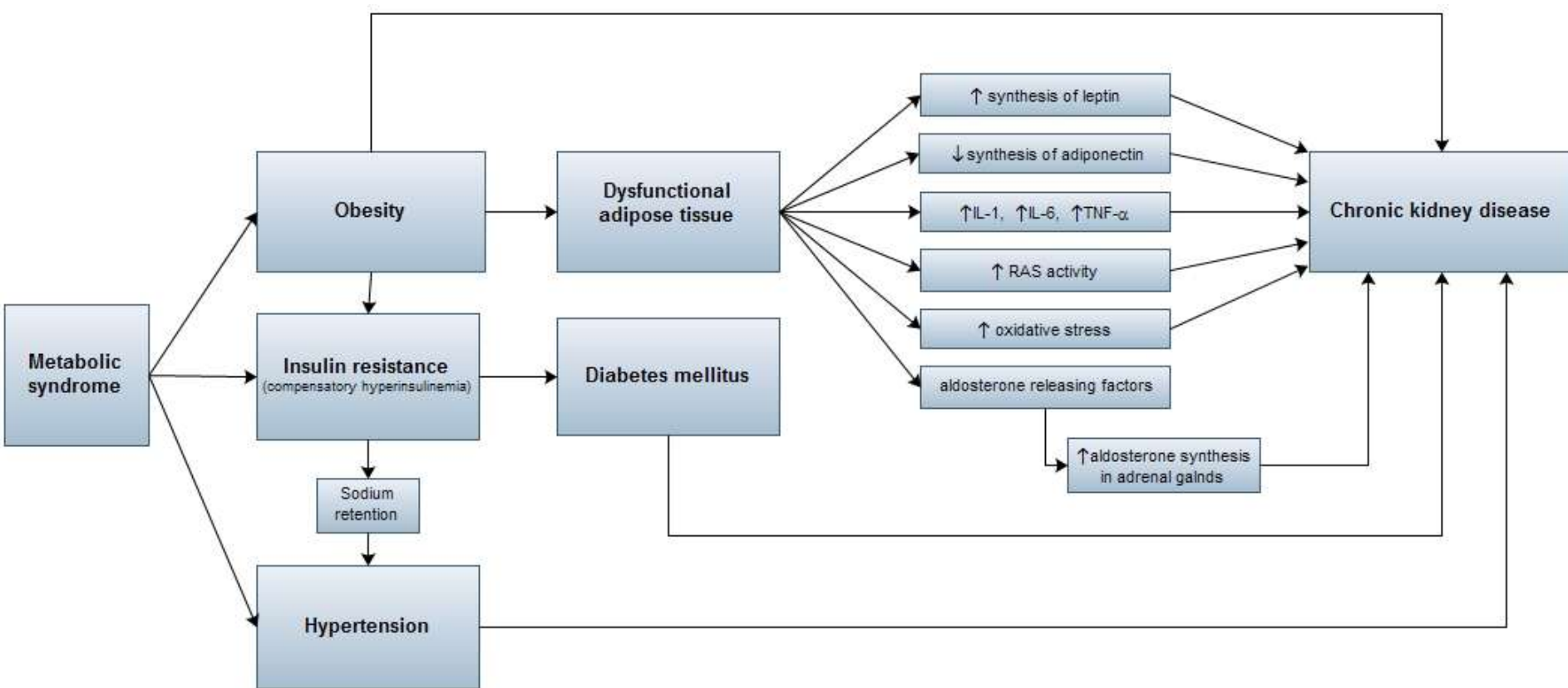


Fig. 6. Adipocytes release secretagogues that stimulate adrenocortical steroidogenesis with a potent effect on mineralocorticoid secretion. Enhanced aldosterone levels may be responsible for hypertension and cardiovascular complications associated with obesity. Adrenal glucocorticoids stimulate fat cell growth and proliferation. Arrows indicate stimulation.

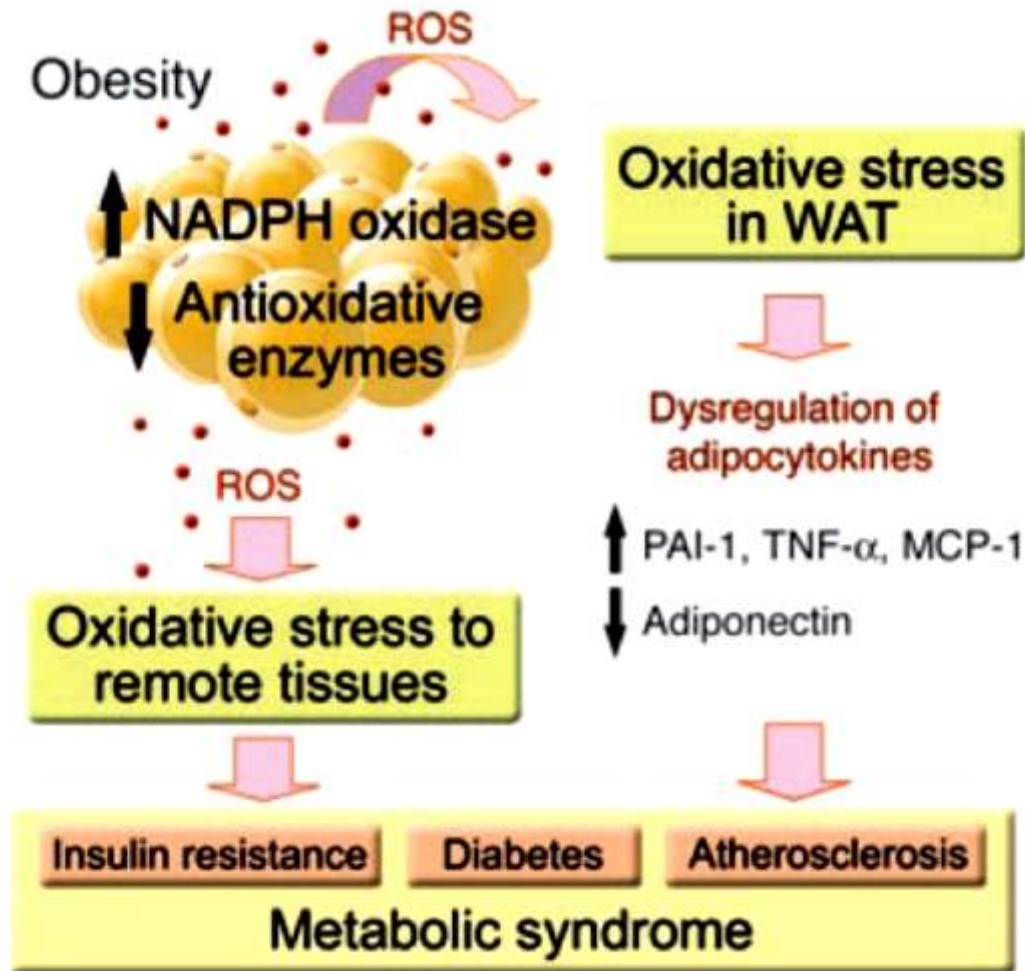
Secretory products from isolated human adipocytes stimulate aldosterone synthesis by human adrenocortical cells



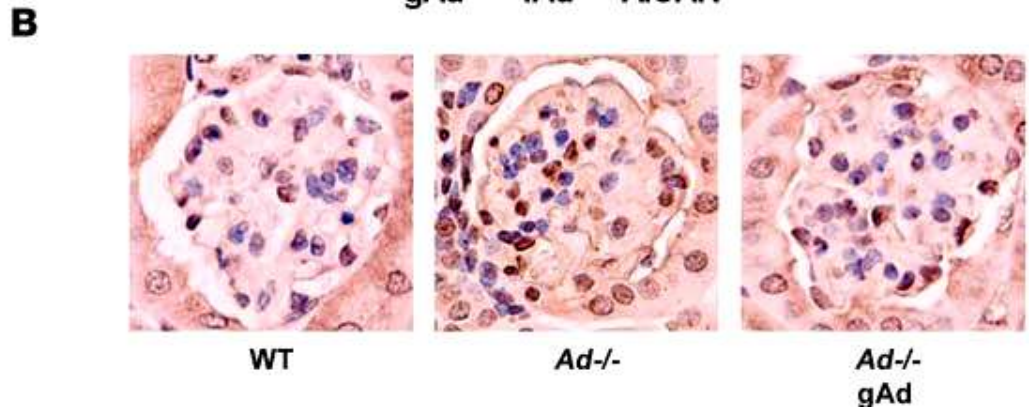
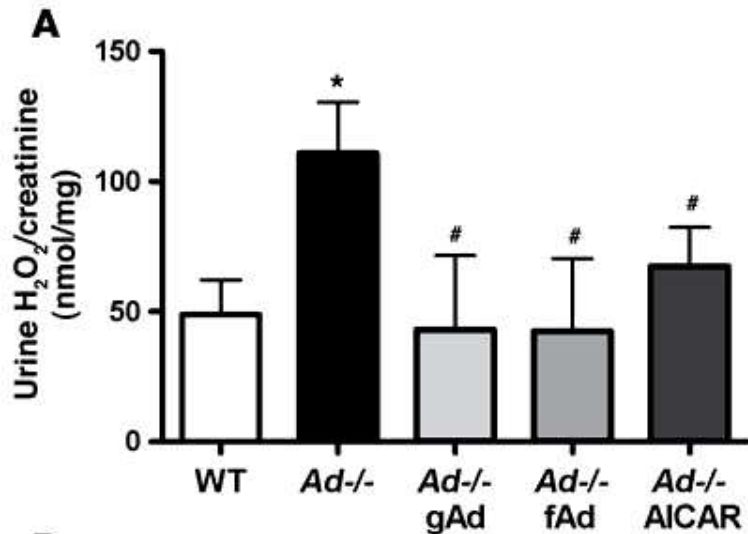
Mechanisms linking metabolic syndrome and chronic kidney disease



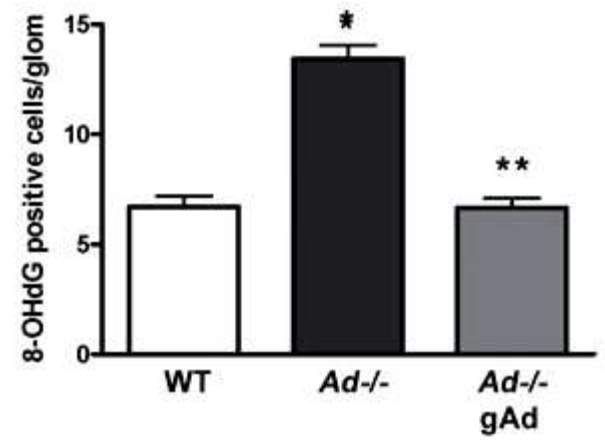
Oxidative stress in adipose tissue in obese patients



Regulation of oxidant stress and by adiponectin

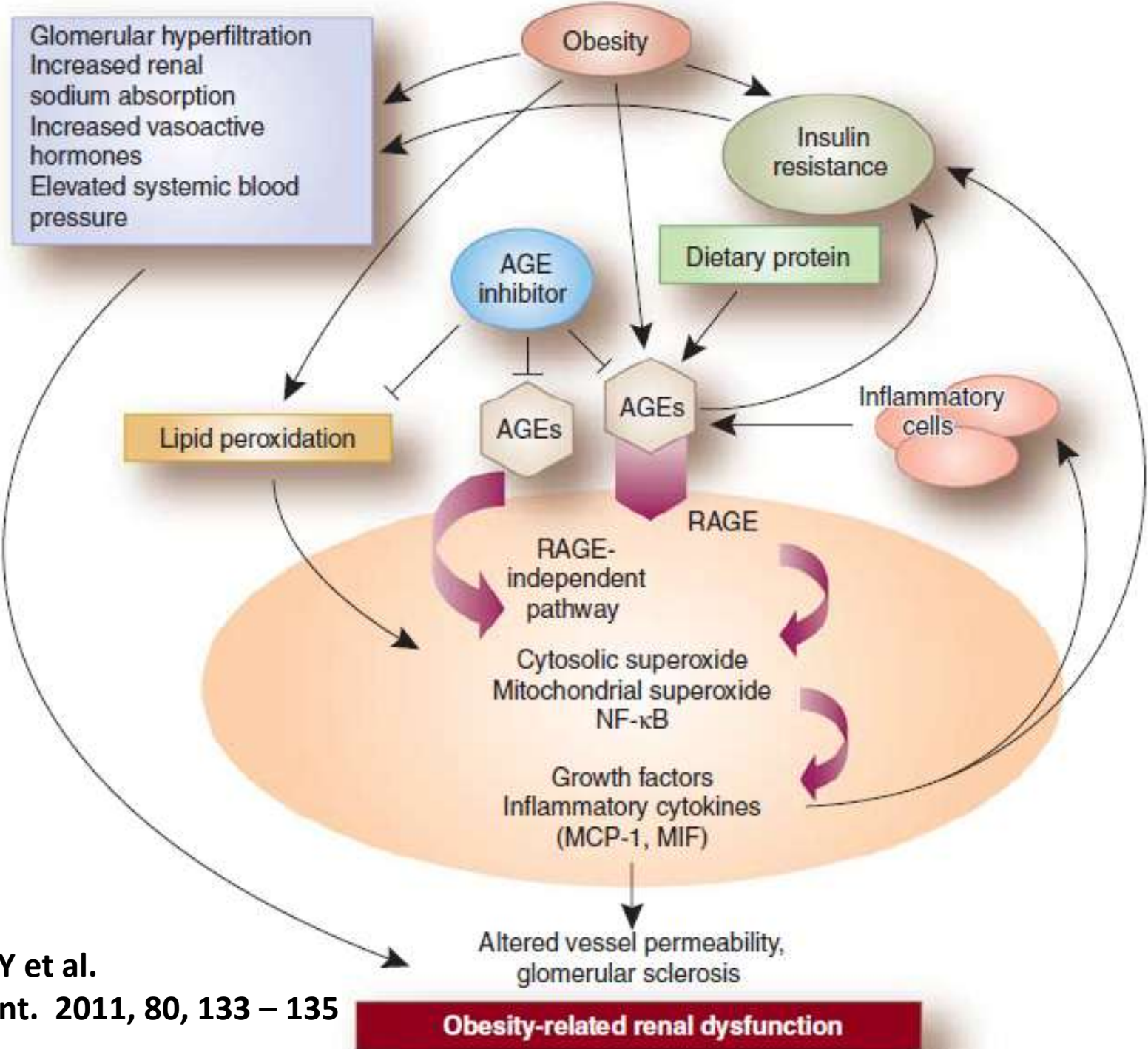


Glomerular 8-OHdG was increased in Ad^{-/-} kidneys and reduced with gAd, demonstrated by light microscopy immunostain and quantitation of 8-OHdG-positive cells



Advanced glycation endproducts (AGEs)

- ❖ Dietary fat and processed foods are extremely high in a group of sugar modifications known as advanced glycation endproducts (AGEs).
- ❖ These molecules improve taste, reduce food spoilage, and promote longer shelf life.
- ❖ Excessive dietary intake of AGEs has recently been shown to contribute to renal and cardiovascular diseases and the development of type 2 diabetes
- ❖ Once in circulation, dietary AGEs may cause inflammation and free oxygen radical production by modulation of specific receptors, including the receptor for AGE (RAGE).
- ❖ The kidney is the main organ responsible for the removal of AGEs from the bloodstream.
- ❖ This high exposure of the kidney to AGEs is likely to make the organ particularly susceptible to AGE-mediated damage.

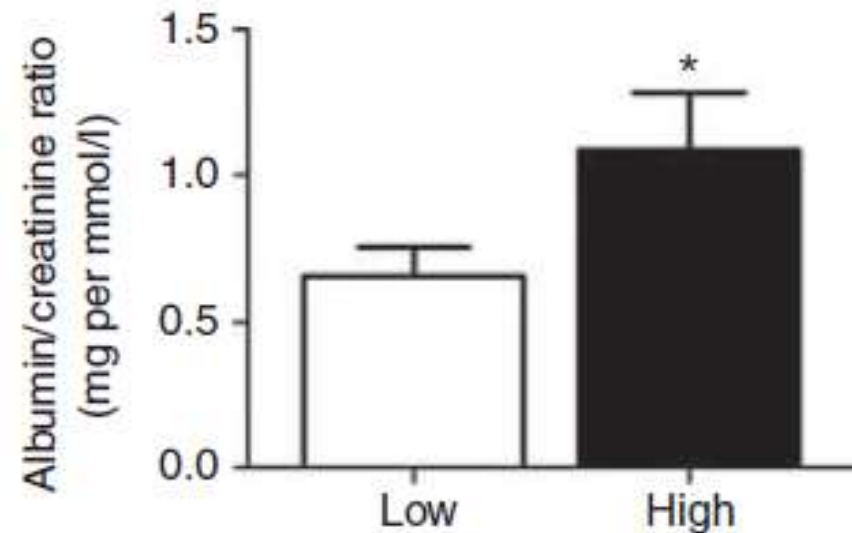


Tomino Y et al.
Kidney Int. 2011, 80, 133 – 135

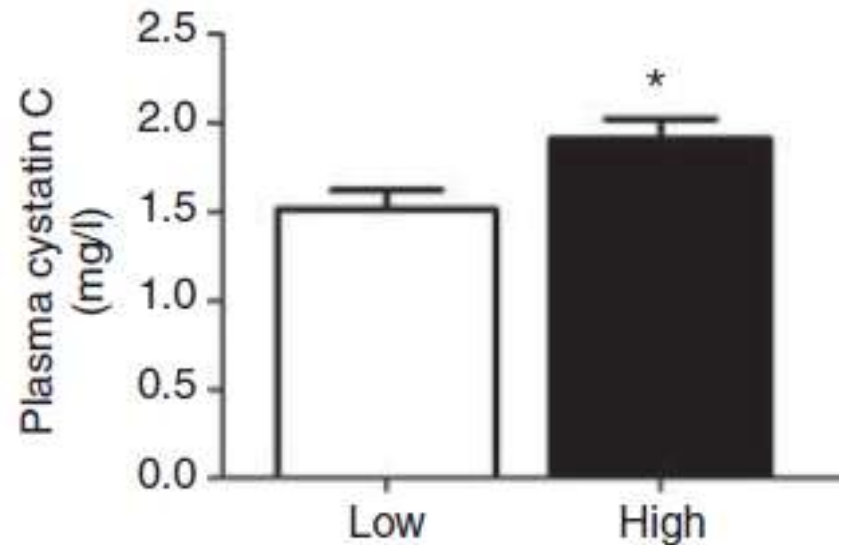
Targeted reduction of advanced glycation improves renal function in obesity

- randomized, crossover clinical trial involving 2 weeks each on a low- and a high-AGE-containing diet, 11 overweight and obese individuals (BMI 26–39 kg/m²)

Albumin/creatinine ratio



Plasma cystatin C



Low – low GE-containing diet

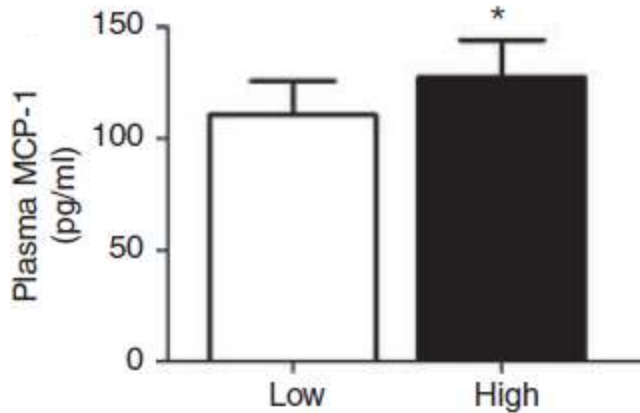
High - high-AGE-containing diet

* p<0.05

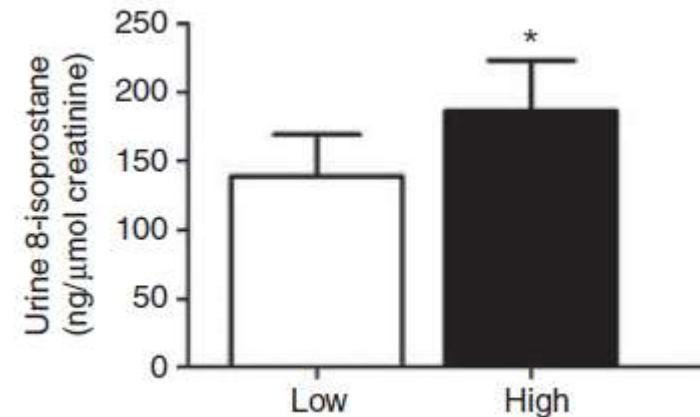
Targeted reduction of advanced glycation improves inflammatory parameters in obesity

- randomized, crossover clinical trial involving 2 weeks each on a low- and a high-AGE-containing diet, 11 overweight and obese individuals (BMI 26–39 kg/m²)

Plasma MCP-1
(monocyte chemotactic protein-1)

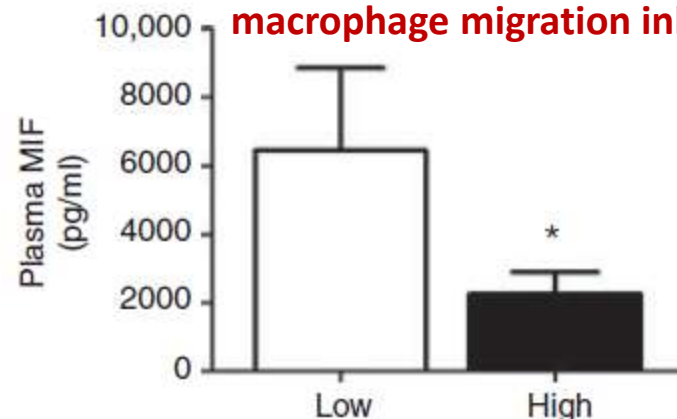


Urine 8-isoprostane



Plasma MIF

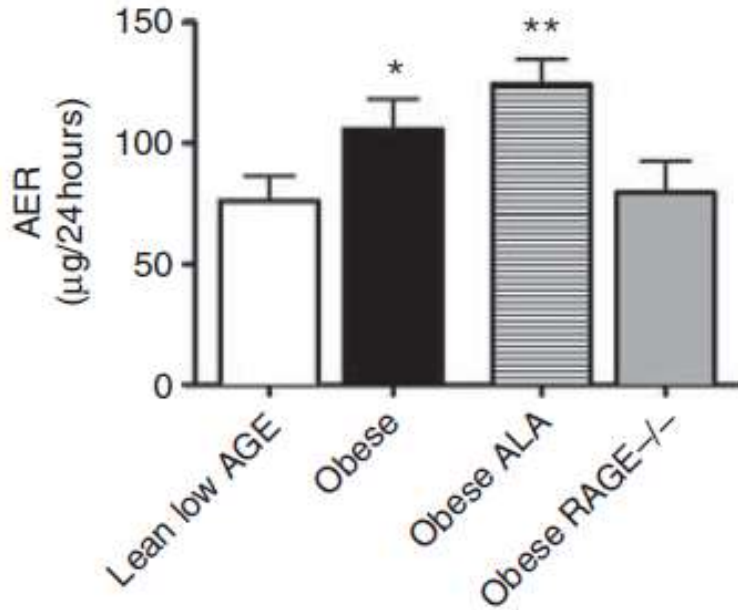
macrophage migration inhibitory factor)



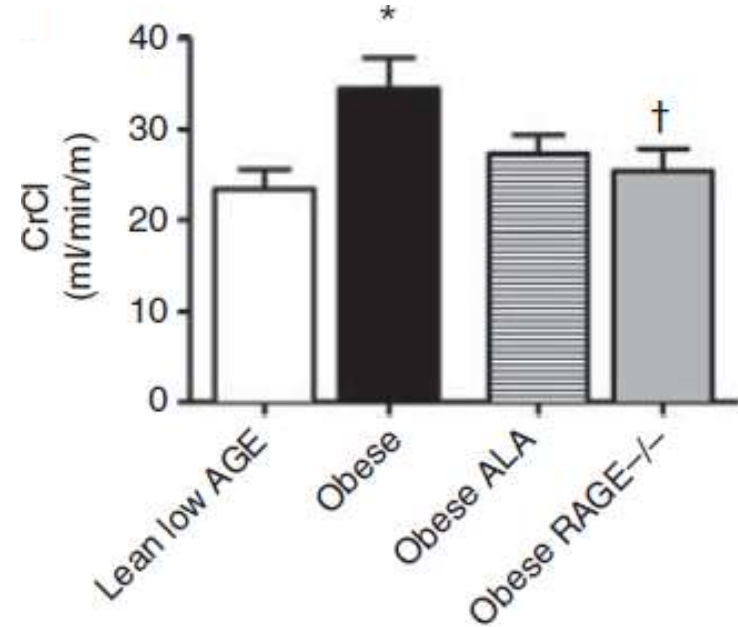
Low – low GE-containing diet
High - high-AGE-containing diet
* p<0.05

Advanced glycation endproducts (AGEs) – impact on renal function - murine study

Albumin excretion rate



Creatinine clearance



Lean low AGE– wild type mice, low-AGE containing diet, standard fat

Obese- wild type mice, high AGE/high-fat diet

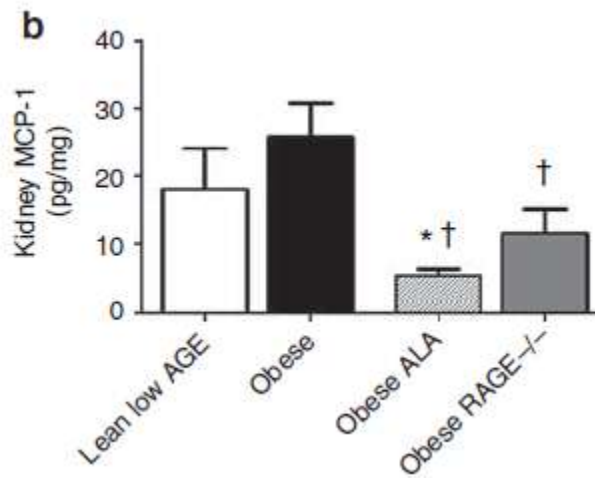
Obese ALA- wild type mice, high AGE/high-fat diet +AGE-lowering therapy, (alagebrium chloride 1 mg/kg/day)

Obese RAGE ^{-/-} mice with RAGE deletion, high AGE/high-fat diet

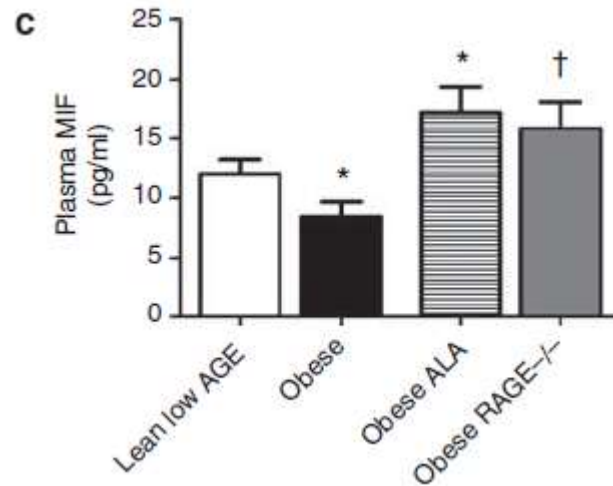
*p<0.05 vs lean low AGE, **p<0.01 vs lean low AGE, ***<p0.001 vs lean low AGE, †p<0.05 vs obese.

Advanced glycation endproducts (AGEs) – impact on inflammatory parameters- murine study

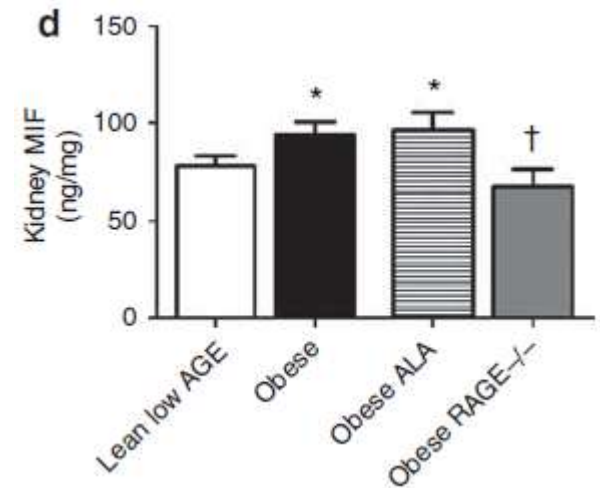
Kidney MCP-1 (monocyte chemotactic protein-1)



Plasma MIF (macrophage migration inhibitory factor)



Kidney MIF (macrophage migration inhibitory factor)



Lean low AGE– wild type mice, low-AGE containing diet, standard fat

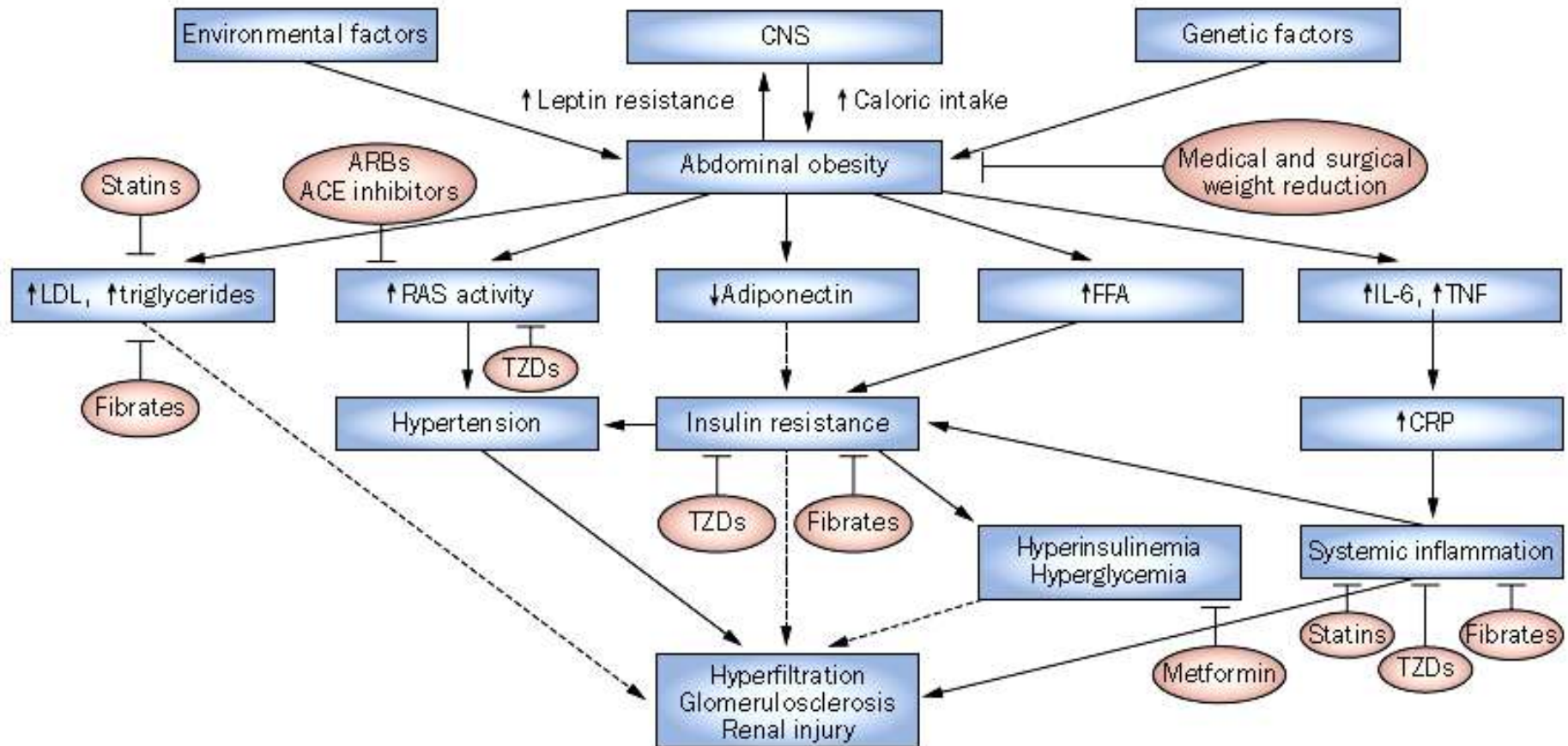
Obese- wild type mice, high AGE/high-fat diet

Obese ALA- wild type mice, high AGE/high-fat diet +AGE-lowering therapy, (alagebrium chloride 1 mg/kg/day)

Obese RAGE -/- mice with RAGE deletion, high AGE/high-fat diet

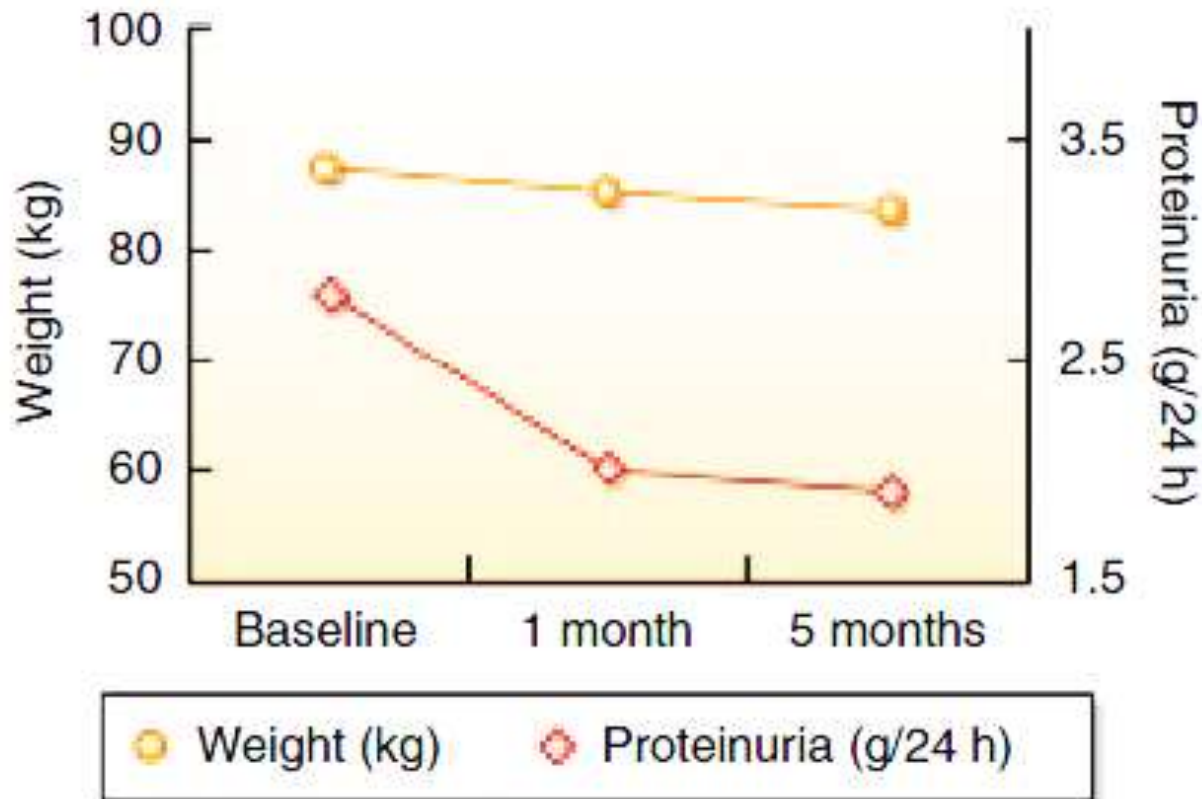
*p<0.05 vs lean low AGE, **p<0.01 vs lean low AGE, ***<p0.001 vs lean low AGE, †p<0.05 vs obese.

Mechanisms of metabolic-syndrome-induced renal injury and potential targeted treatments

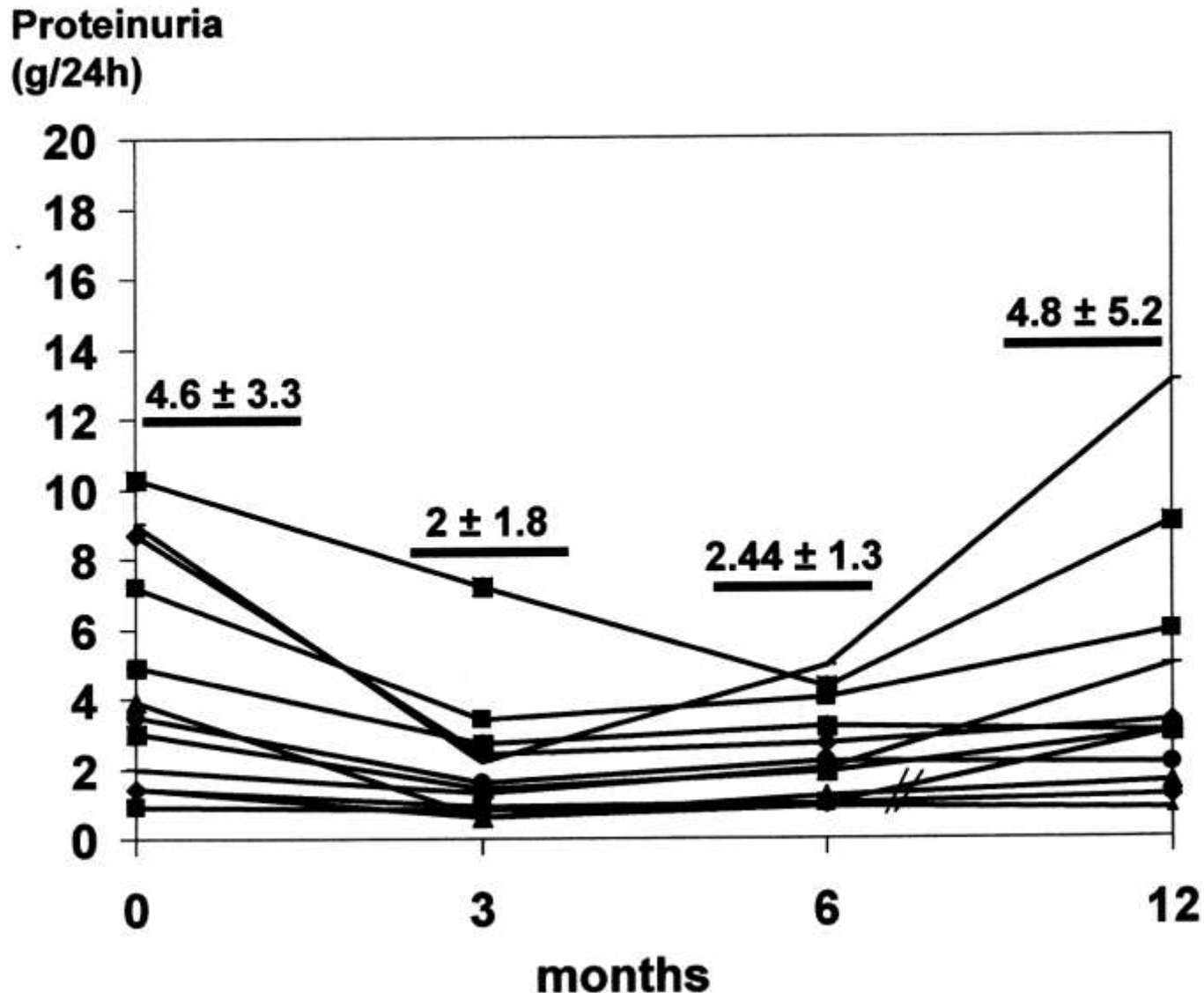


Reduction in proteinuria in a group of obese patients subjected to a low-calorie diet

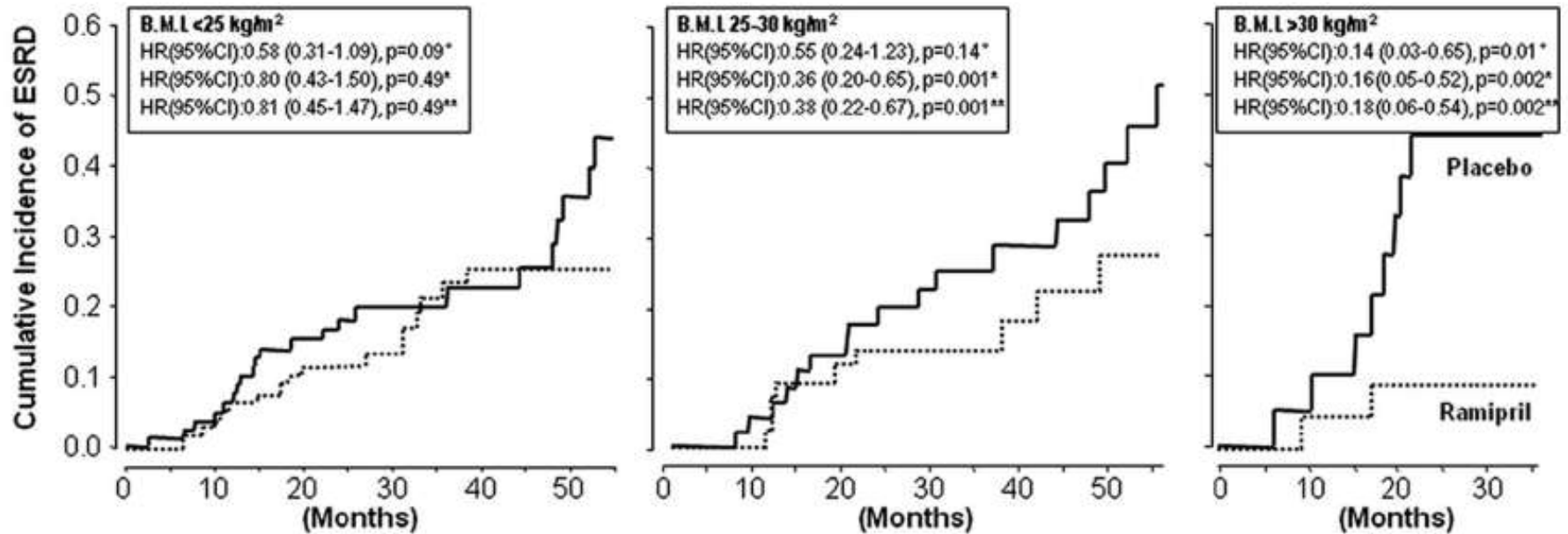
- ❖ One month after the onset of caloric restriction, proteinuria had decreased $26.4 \pm 30\%$ of baseline values (from 2.8 ± 1.4 to 2 ± 1.5 g per 24 h) in spite of a modest weight loss ($2.8 \pm 2.1\%$ of the baseline values)



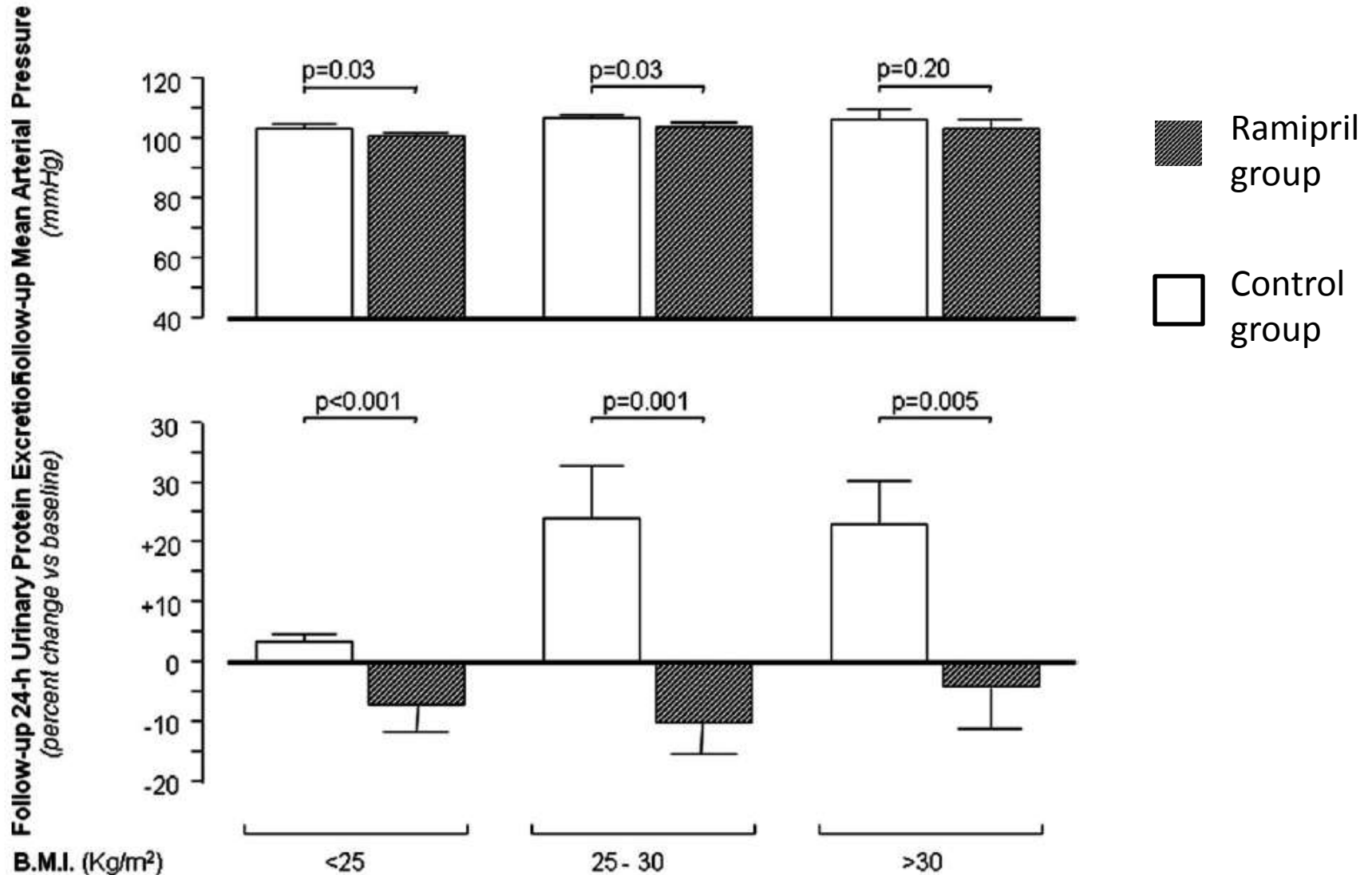
Evolution of proteinuria after ACE-I treatment in obesity associated FSGS



Ramipril markedly attenuates the risk of ESDR in overweight and obese patients

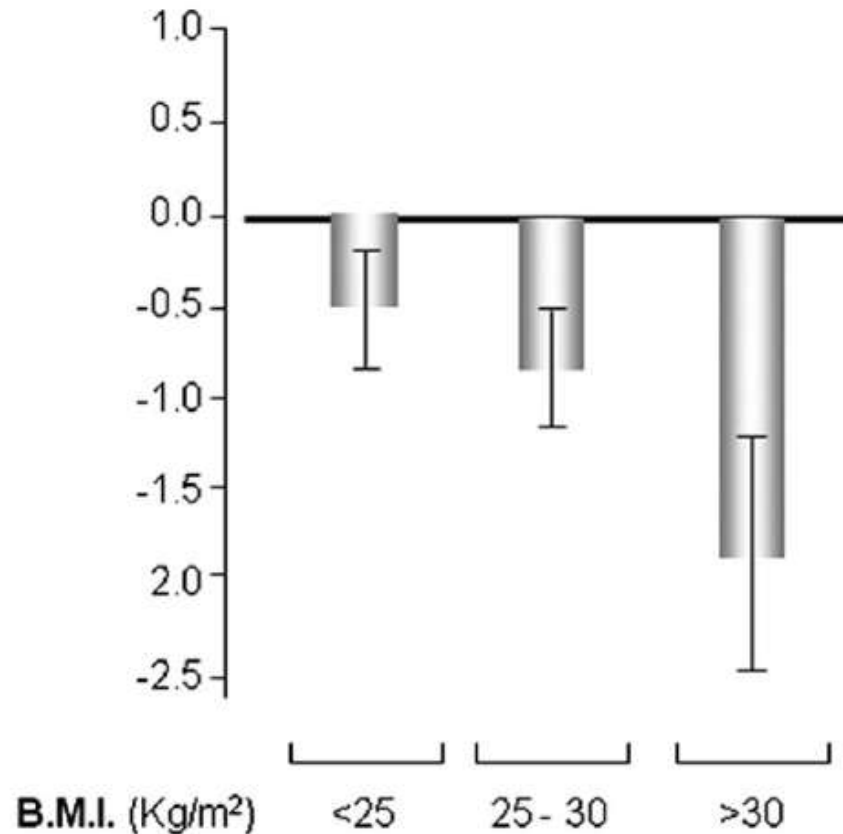


Ramipril prevents the rise in proteinuria in overweight and obese patients

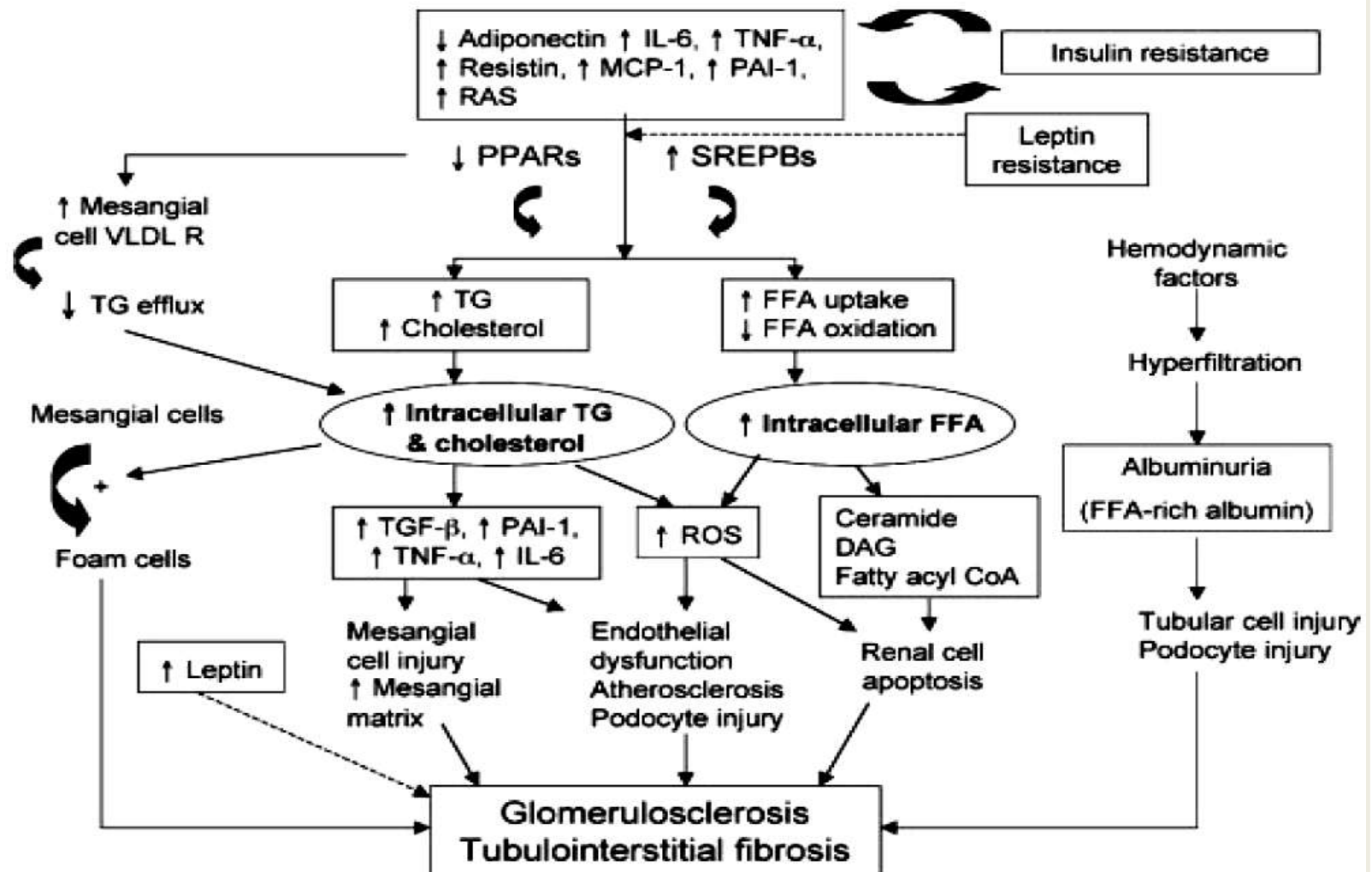


Anti-proteinuric effect of ramipril

Differences in Urinary Protein Excretion
(*Ramipril versus Placebo*)



Potential mechanisms of renal dysfunction related to inflammatory cytokines and lipotoxicity in obesity and obesity initiated metabolic syndrome



Thank you for your attention !

Andrzej Wiecek

Katowice

