



**The 17th Budapest Nephrology School**  
(Nephrology, Hypertension, Dialysis, Transplantation)

Under the auspices of **ISN, ERA-EDTA and ISP**  
**26-31 August, 2010**

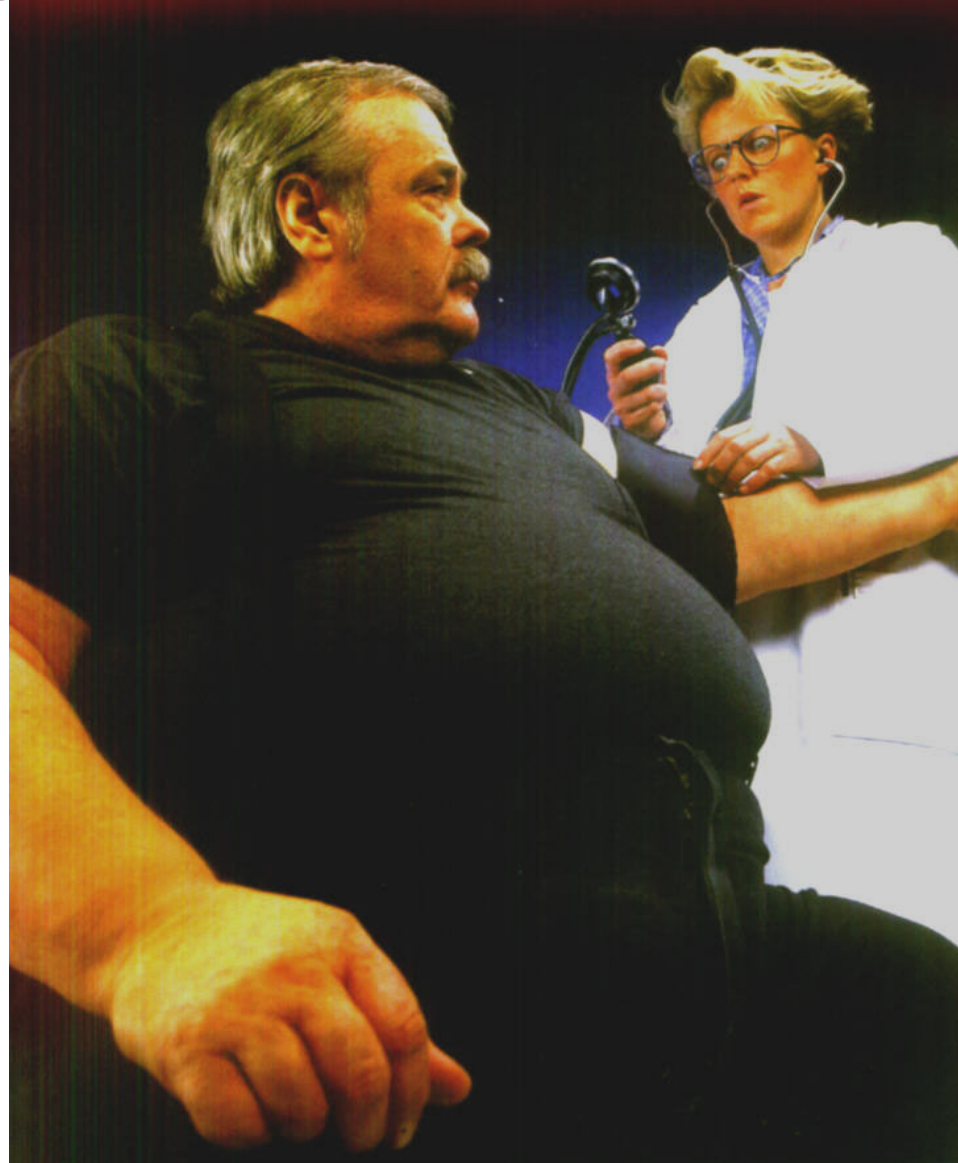
**Role of the fat tissue in the  
pathogenesis of arterial hypertension  
and chronic kidney disease**

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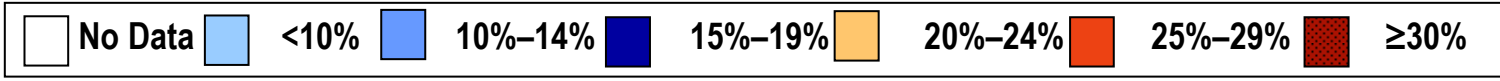
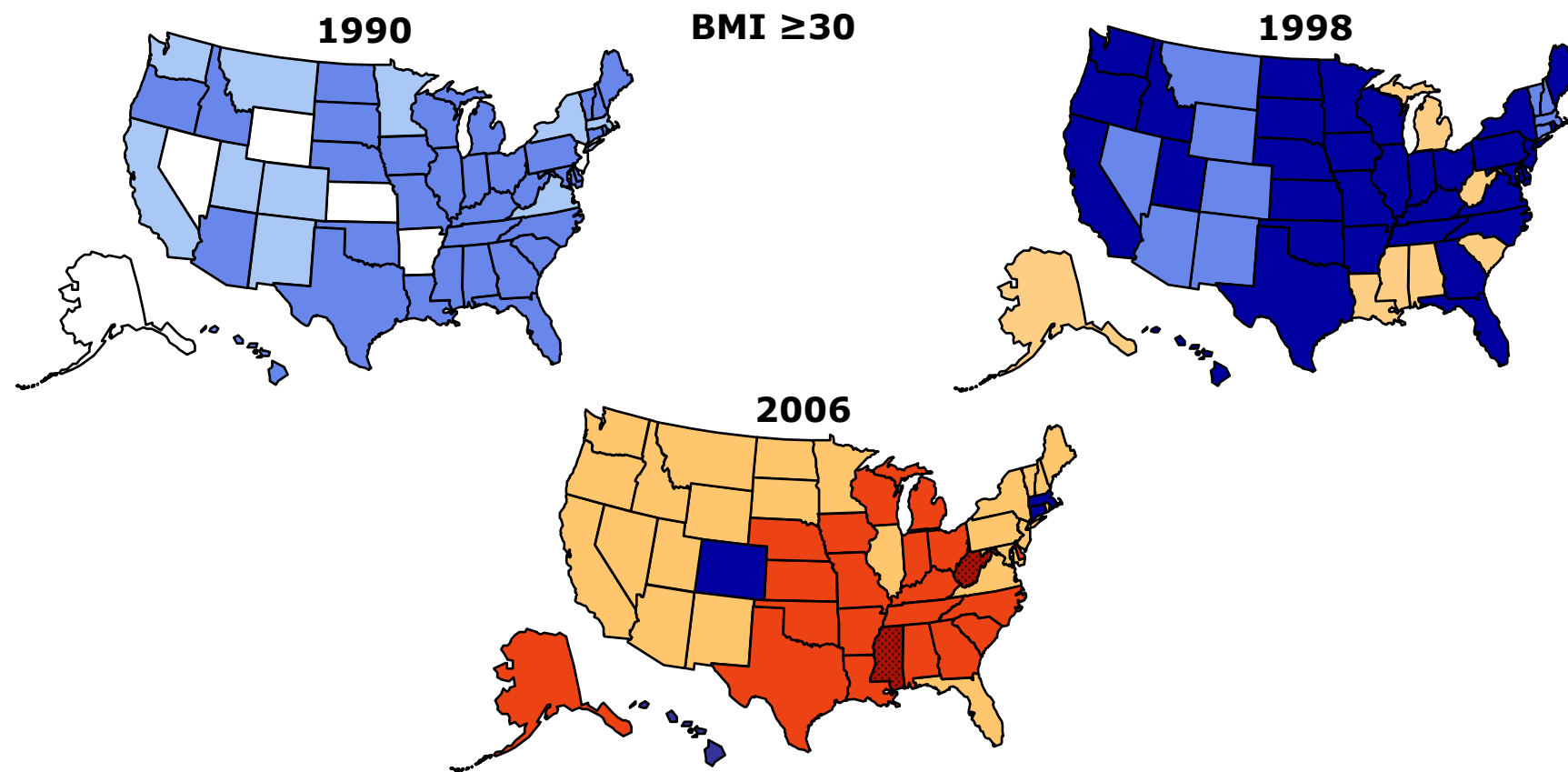
***e-mail: [awiecek@spskm.katowice.pl](mailto:awiecek@spskm.katowice.pl)***

# Obesity- the public health problem in Western Countries



# Obesity Trends Among U.S. Adults

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



**Obesity and hypertension  
are two complex disorders  
that are closely interrelated**

*Larimore J.W. A study of blood pressure in  
relation to type of bodily habitus.  
Arch Intern 1923; 31: 567-572.*

*Faber A. Readings of blood pressure of 1000  
healthy individuals age 20-25 years: An  
antropometric study.  
Scand Arch Physiol 1924; 45: 189-203.*



**Alessandro del Borro (XVII)**

Figure 1 - Relationship between body mass index and mean systolic and diastolic blood pressure in 22,354 Korean subjects. (Redrawn from Ref. 8).

Hall JE et al.: *Braz J Med. Biol Res.* 2000; 33, 605-618

Jones DW et al.: *J Hypertens* 1994, 12, 1433-1437

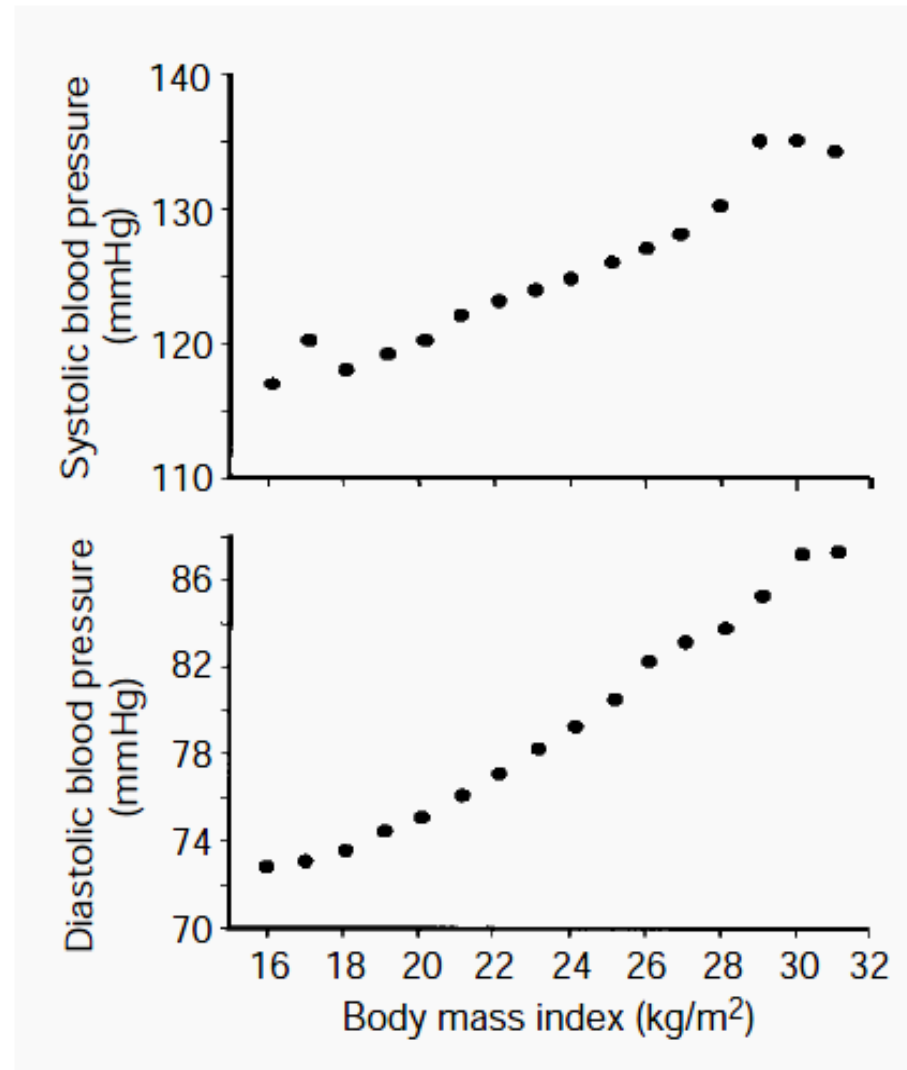
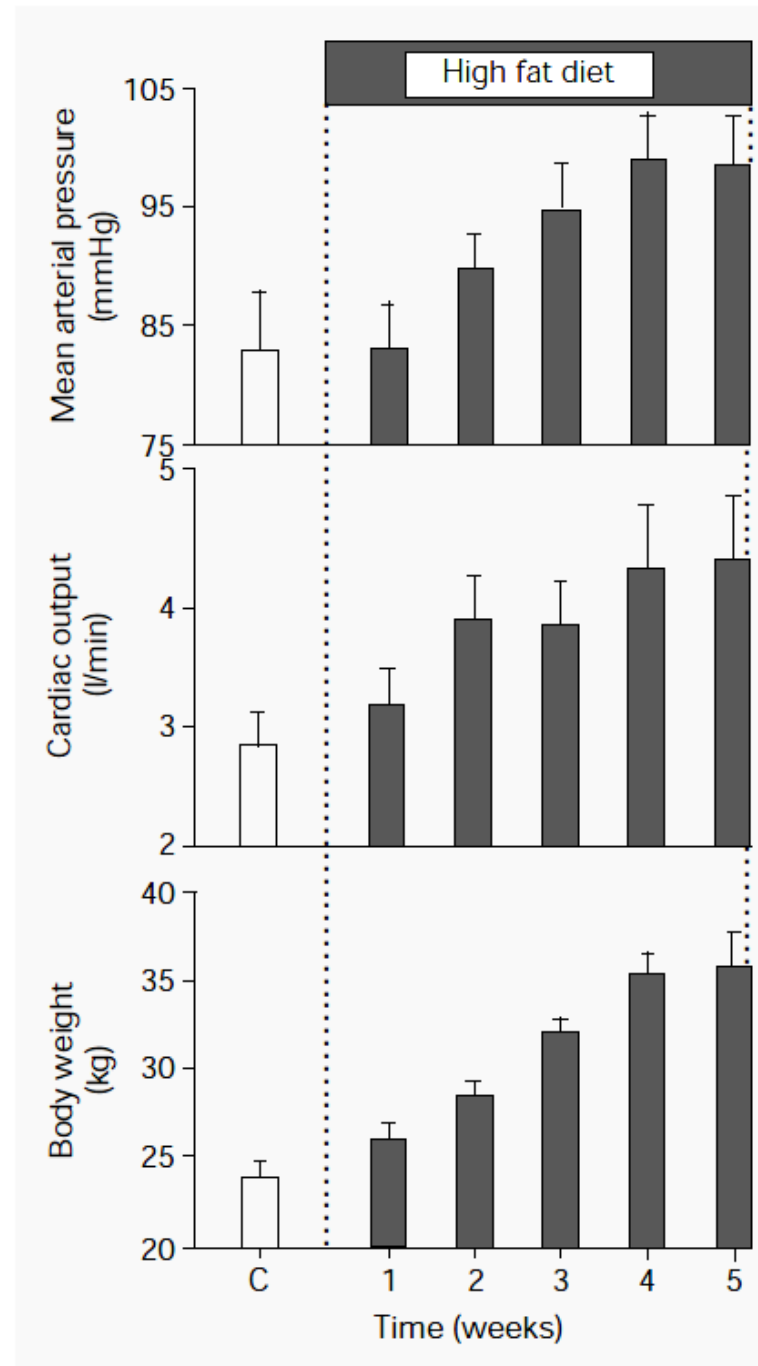


Figure 2 - Effects of 5 weeks of a high fat diet on mean arterial pressure, cardiac output, and body weight in dogs. C, Control. (Redrawn from Ref. 16).

Hall JE et al.: *Braz J Med Biol Res* 2000; 33, 605-618

Hall JE et al.: *Hypertension* 1994; 22, 292-299



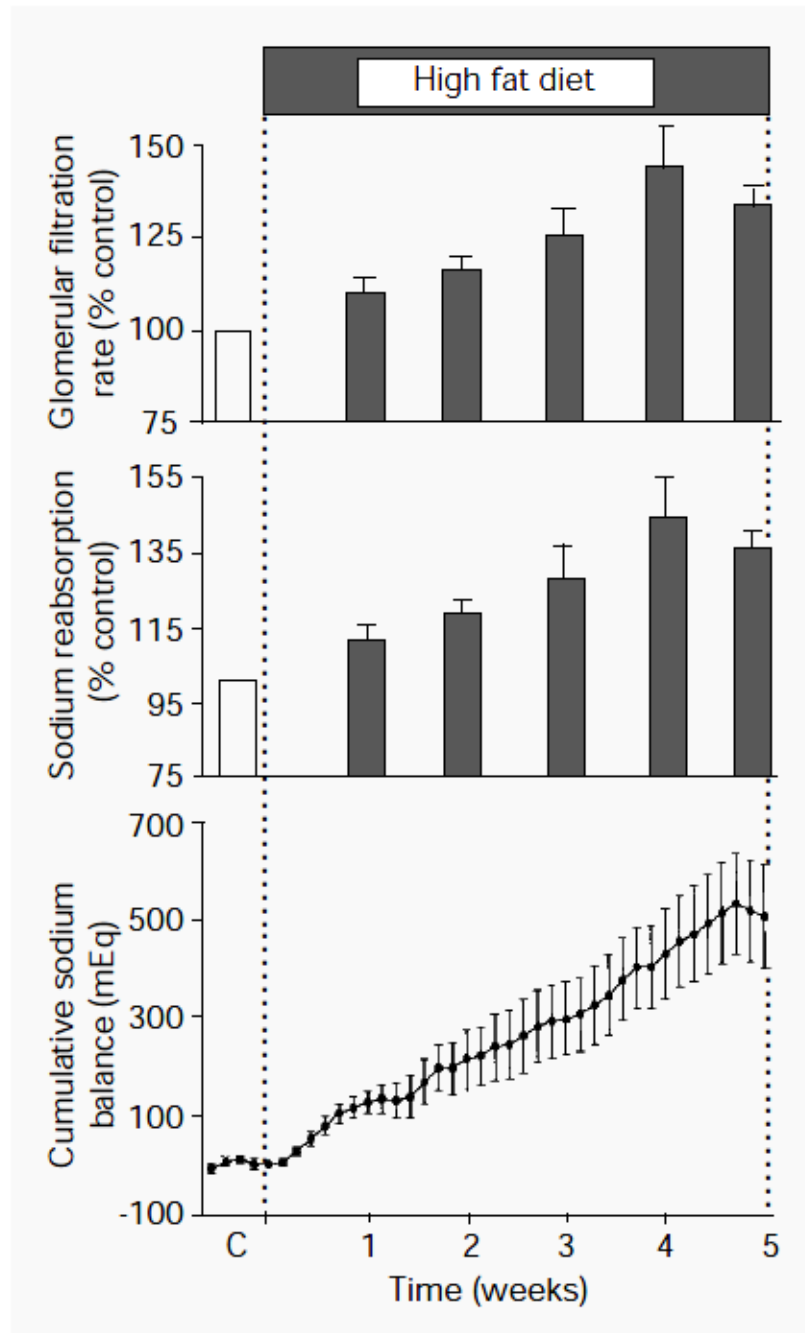


Figure 3 - Effects of 5 weeks of a high fat diet on glomerular filtration rate, renal sodium reabsorption, and cumulative sodium balance in dogs. C, Control. (Redrawn from Ref. 16).

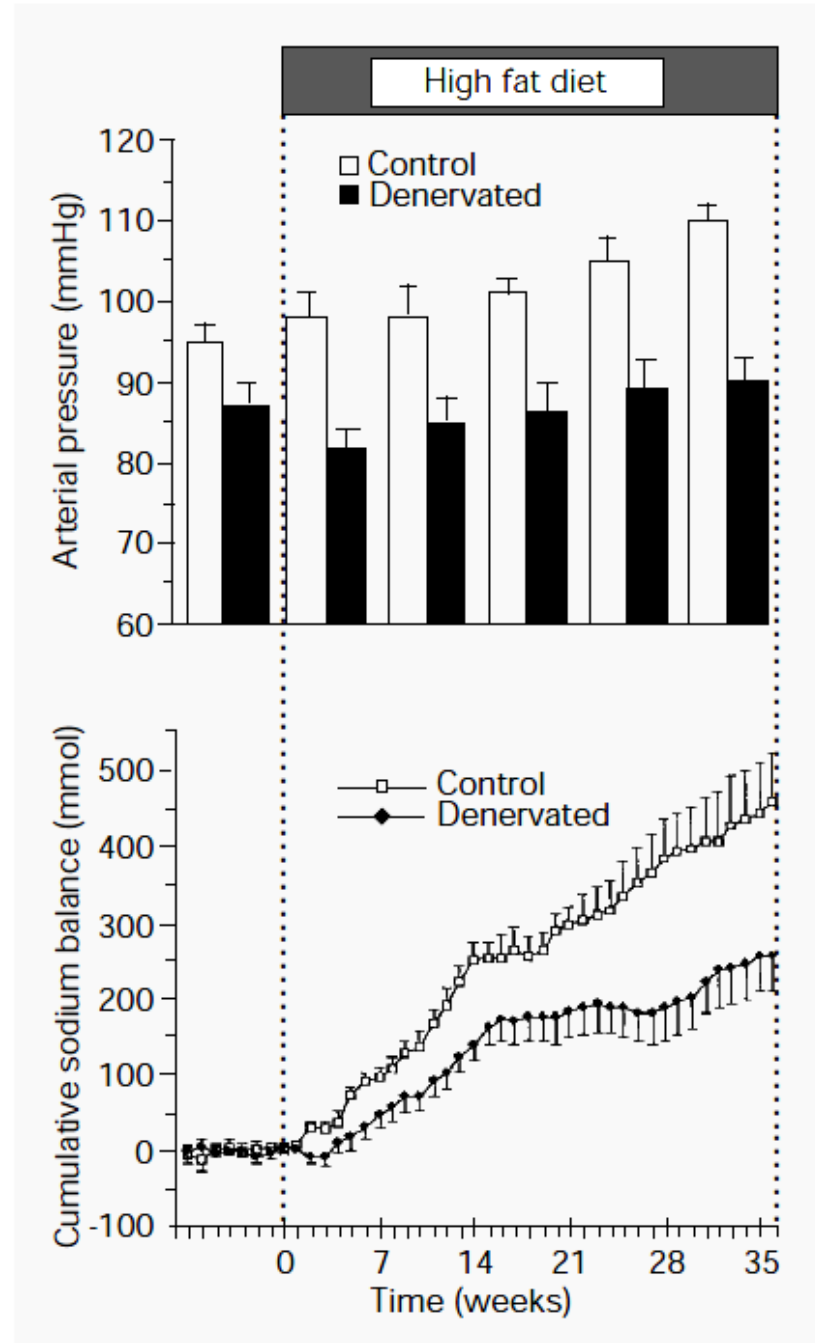
**Hall JE et al.: Braz J Med Biol Res 2000; 33, 605-618**

**Hall JE et al.: Hypertension 1994; 22, 292-299**

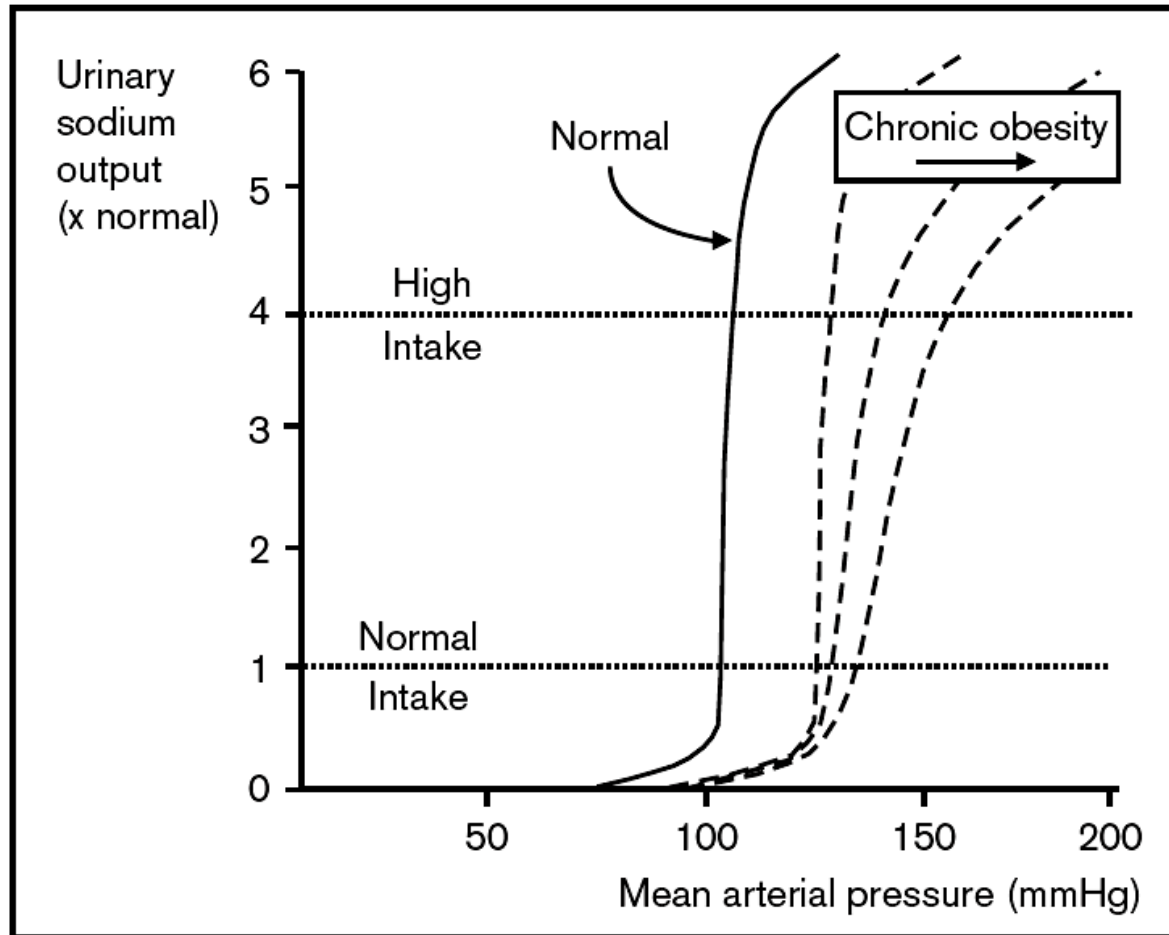
Figure 4 - Effects of 5 weeks of a high fat diet on mean arterial pressure and cumulative sodium balance in dogs with innervated kidneys (control) and bilaterally denervated kidneys (denervated). (Redrawn from Ref. 30).

Hall JE et al.: Braz J Med  
Biol Res 2000; 33, 605 -618

Hall JE et al.: Hypertension  
1994; 22, 292-299



# Effect of obesity to shift renal pressure natriuresis curve to



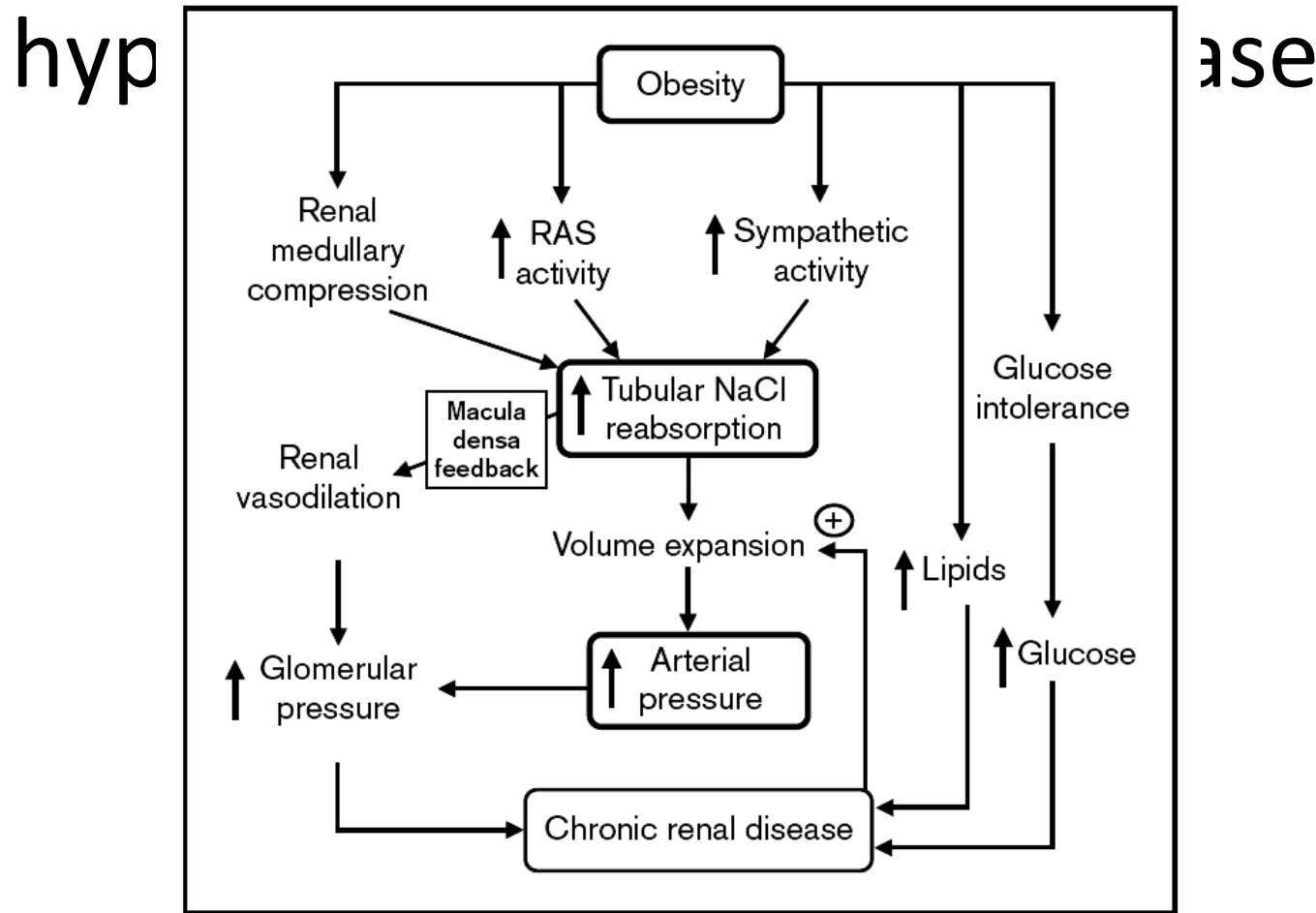
# Hemodynamic, neurohumoral, and renal changes in experimental obesity caused by a high fat diet and in human obesity

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

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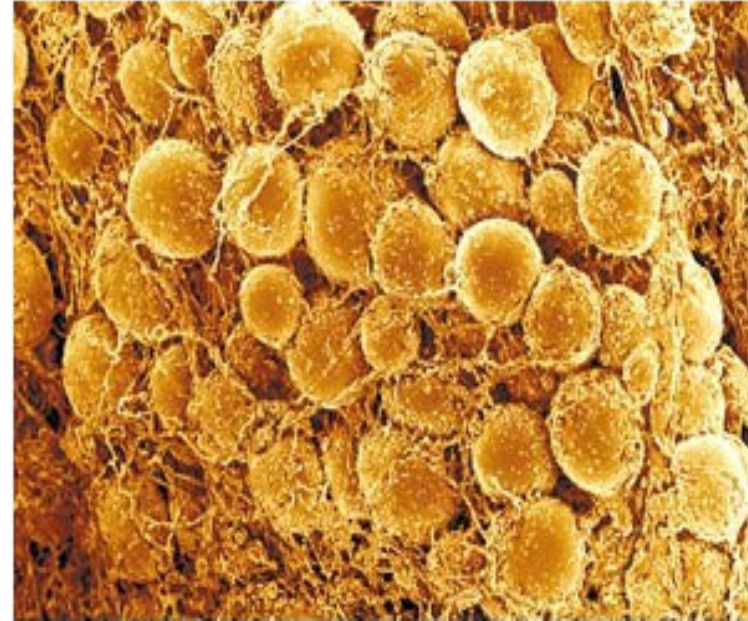
# Summary of the mechanisms of obesity-induced hypertension



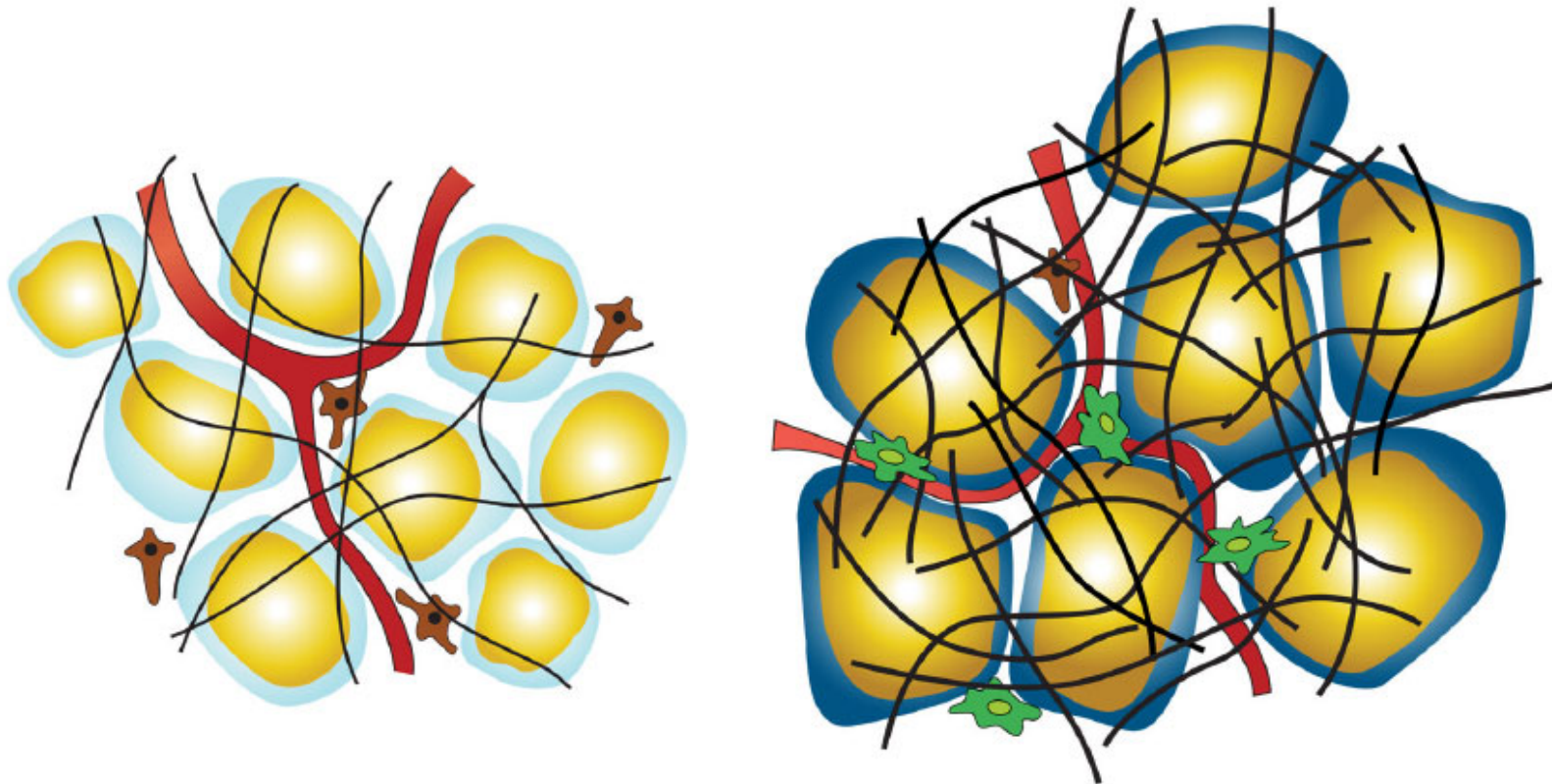
**Table 1.** List of hormones, cytokines, chemokines, growth factors and complement proteins produced by the adipose tissue

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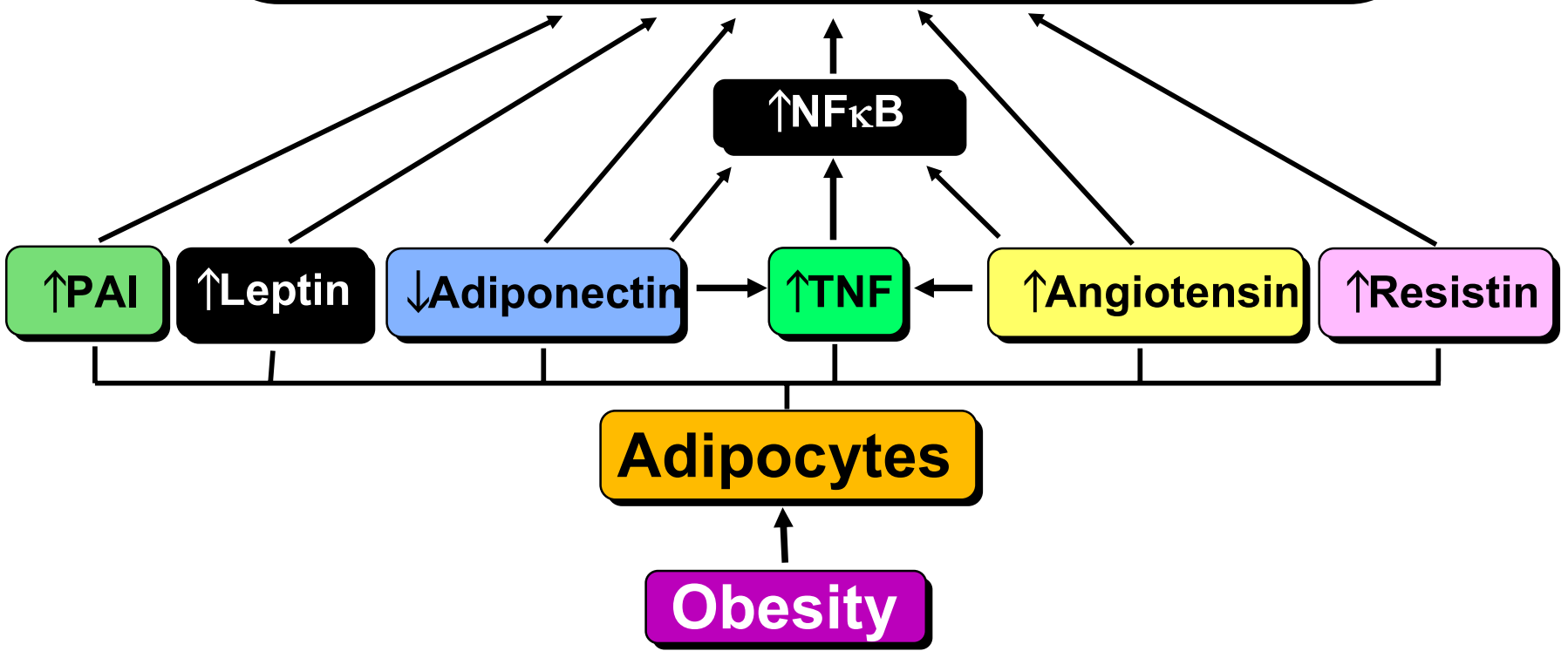
- Leptin
  - Adiponectin
  - Visfatin
  - Apelin
  - Resistin
  - Agouti signalling protein
  - Acylation stimulating protein
  - Nitric oxide (NO)
  - Renin
  - Angiotensin II
  - PAI-1
  - Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ )
  - Interleukins-1 $\beta$ , 6, 8, 10
  - Monocyte chemoattractant protein-1 (MCP-1)
  - Migration inhibitory factor (MIF)
  - Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)
  - 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)**
- 



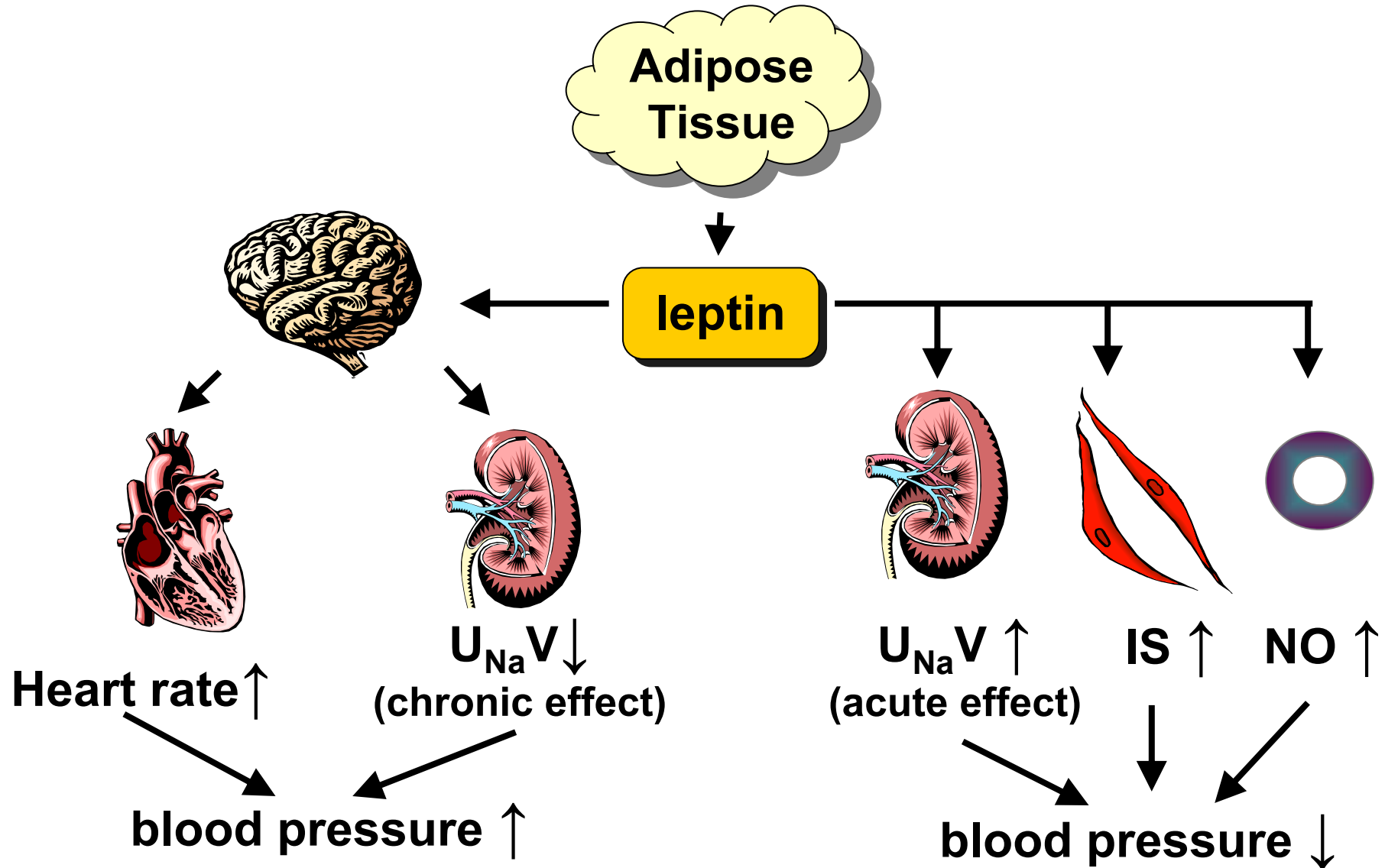
# White adipose tissue in the lean (left) vs. obese (right) state



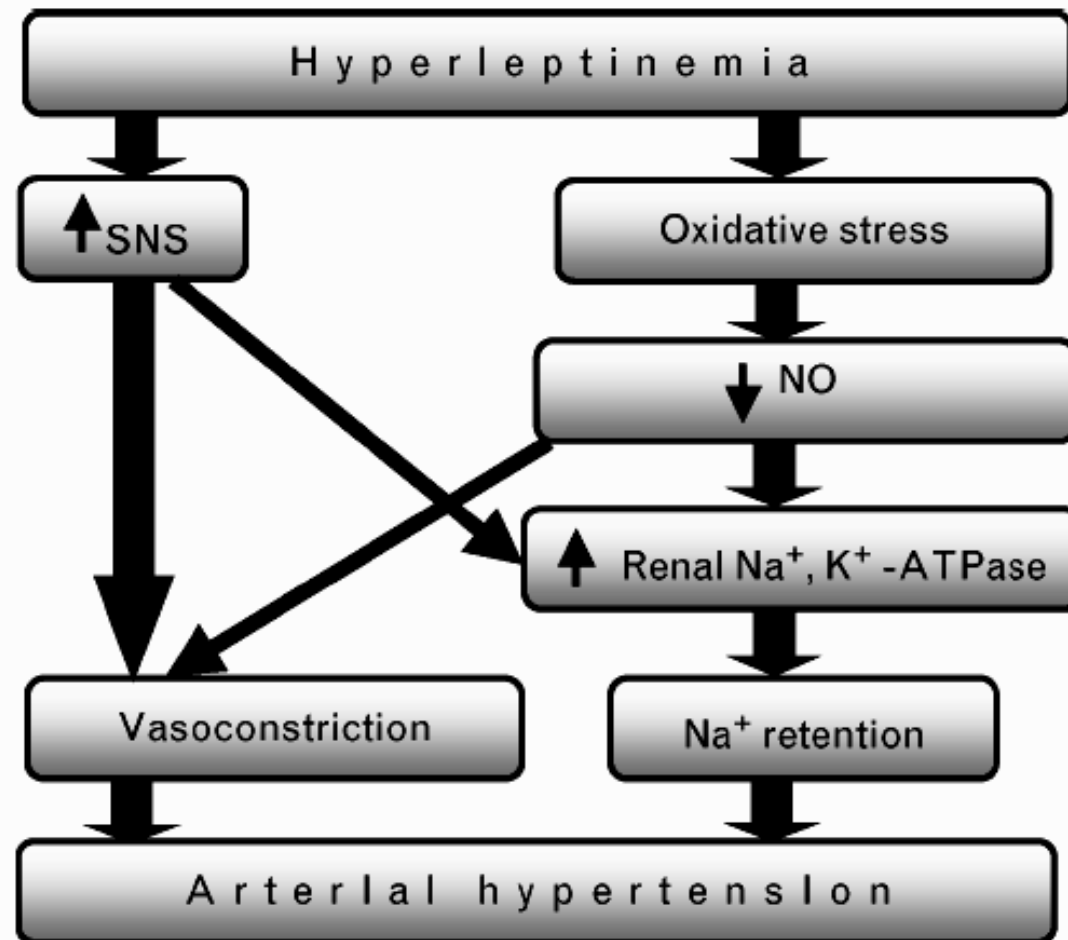
- Cardiovascular and reologic effects, sleep apnea
- Renal effects
- Activation of the sympathetic nervous system
- Metabolic effects (dyslipidemia, carbohydrate intolerance)
- Endocrine effects (hyperinsulinism, insulin resistance, hypercortisolism, increased erythropoietin secretion)
- Increased coagulation/decreased fibrinolysis ( ↑PAI)
- Haematologic effects



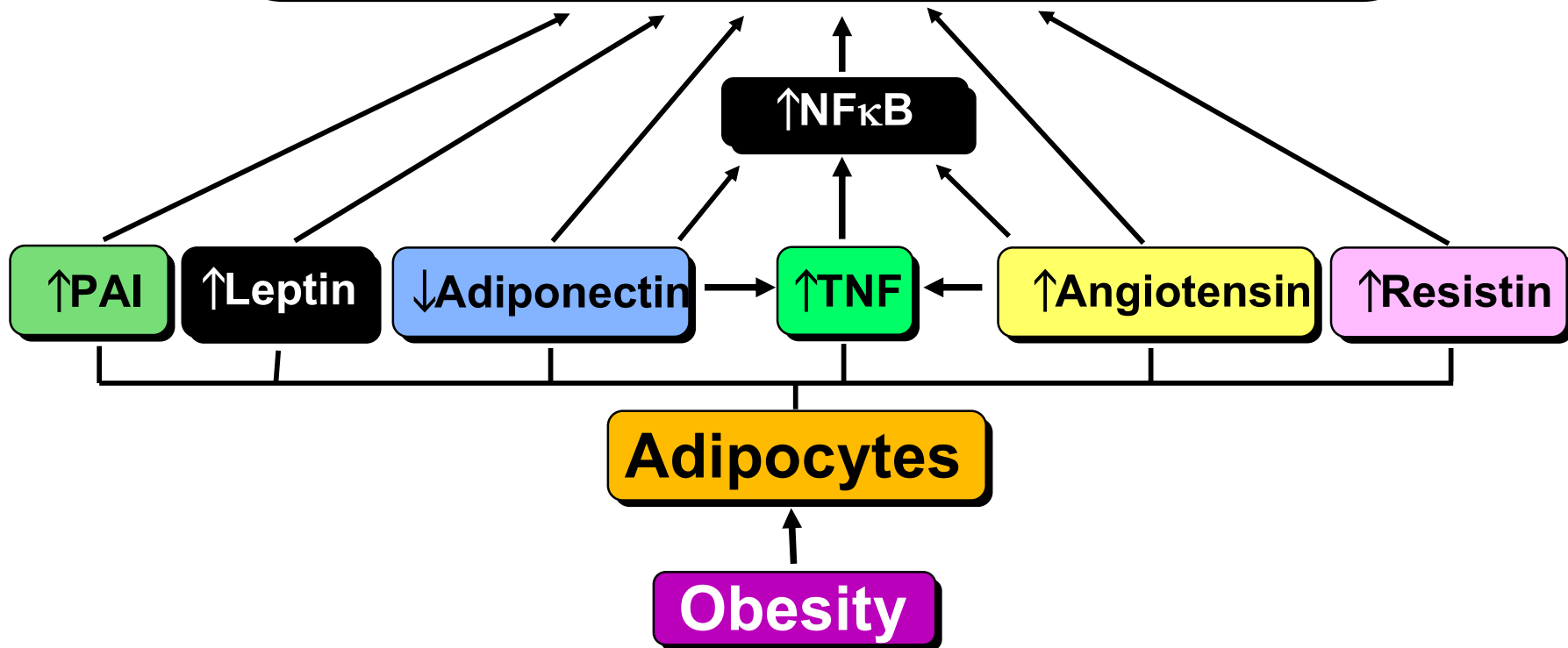
# Cardiovascular-renal actions of leptin

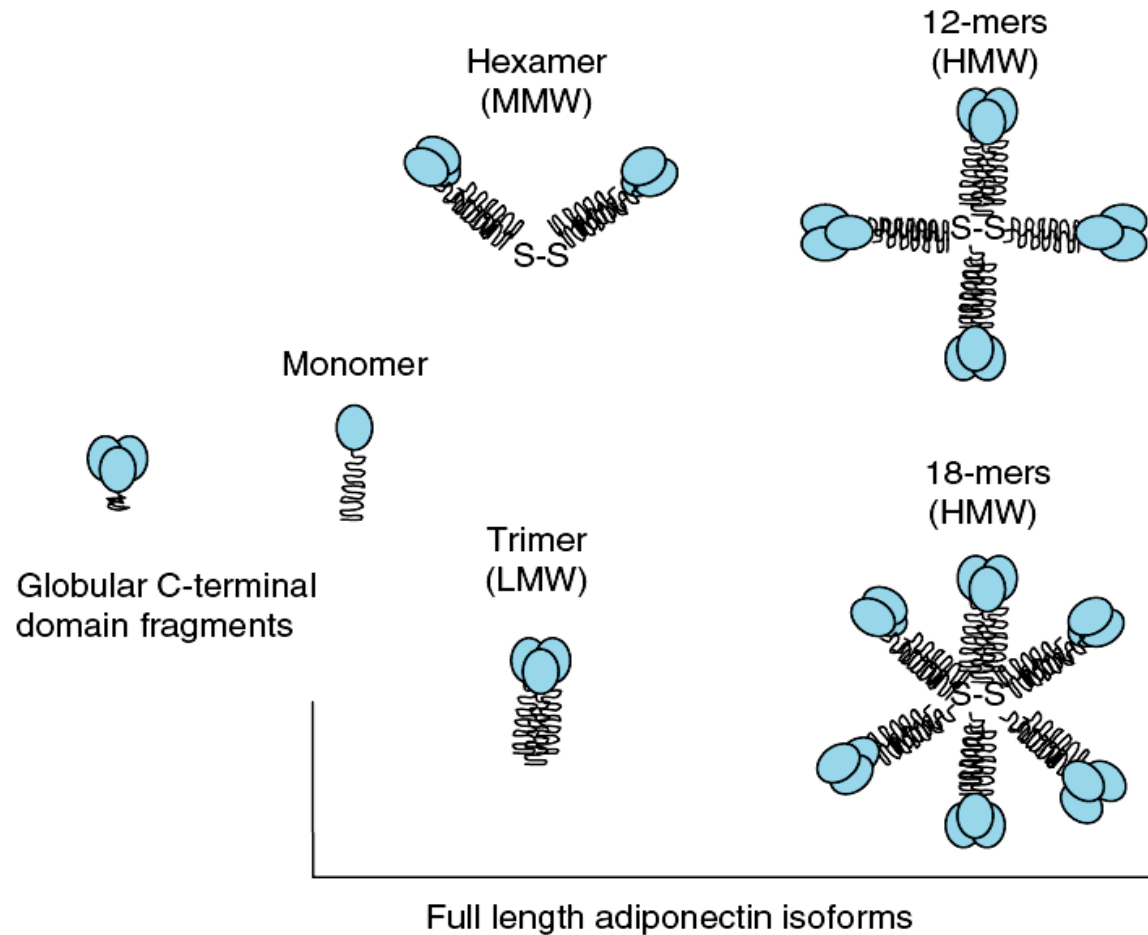


# Sympathetic nervous system (SNS) and oxidative stress-induced nitric oxide (NO) deficiency in the pathogenesis of leptin-induced hypertension



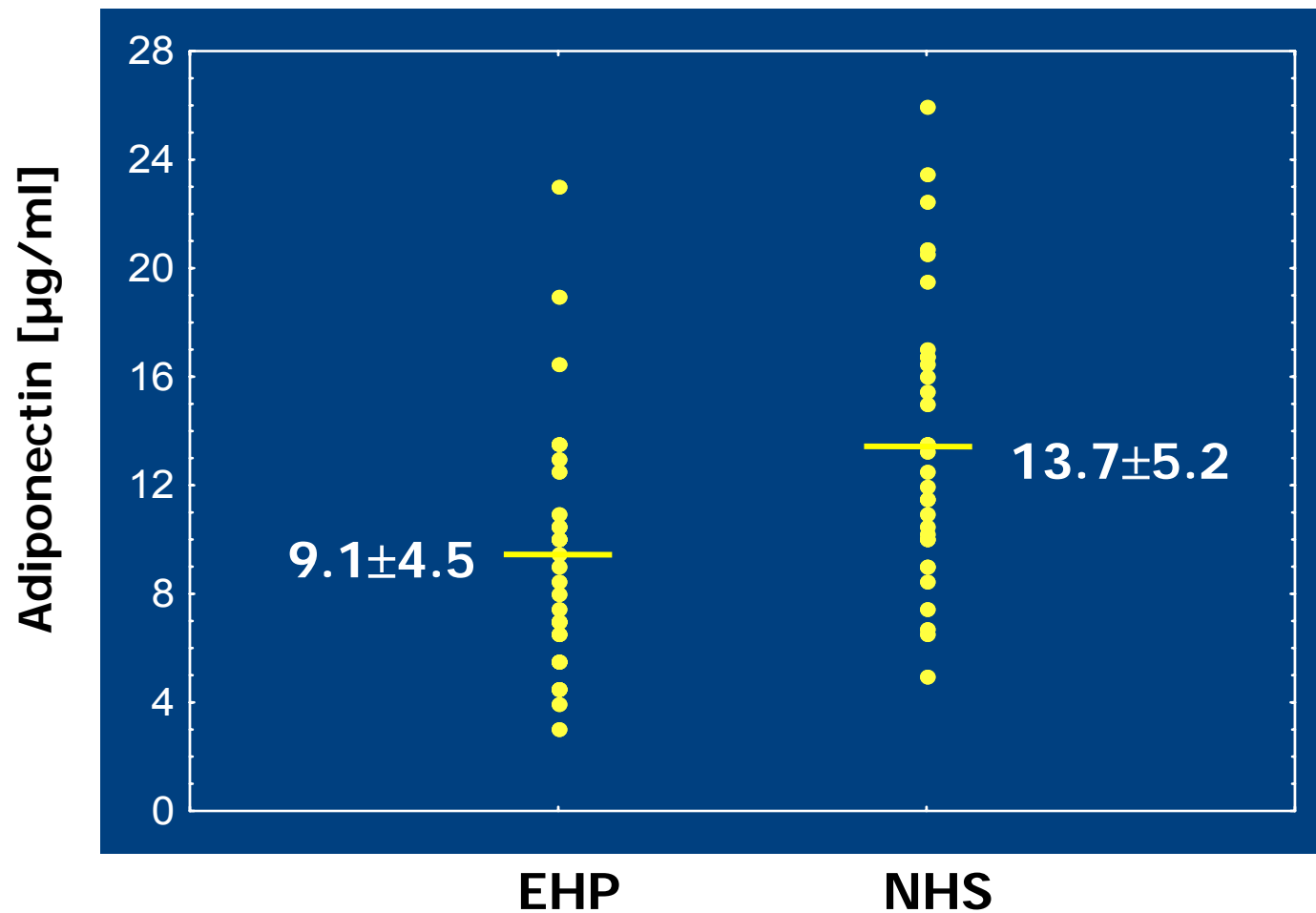
- Cardiovascular and reologic effects, sleep apnea
- Renal effects
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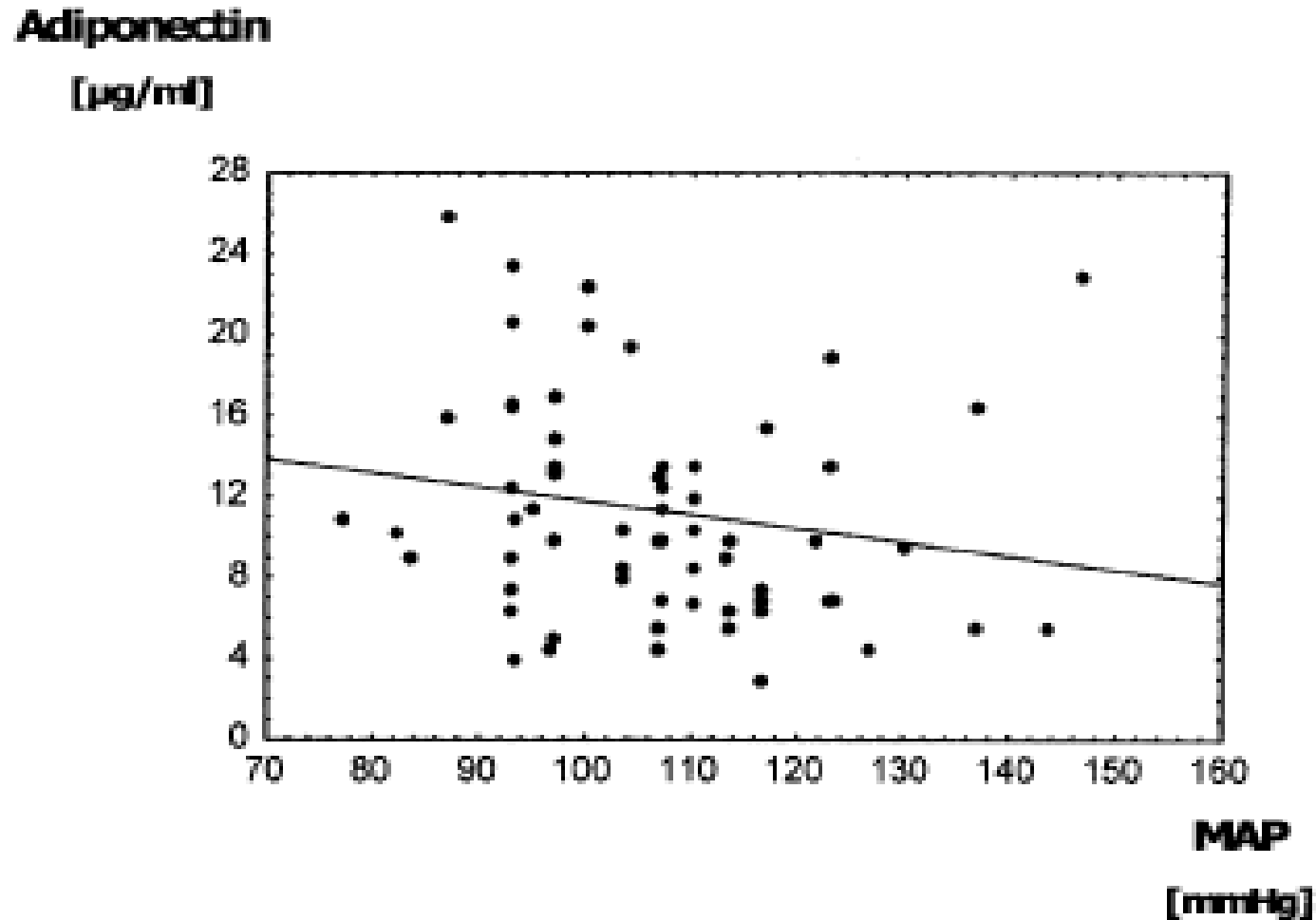


**Fig. 1.** Adiponectin is present as full-length molecules (almost all) or smaller globular C-terminal domain fragments. Within the circulation, adiponectin forms a wide range of multimers: from trimers (low molecular weight, LMW), hexamers (medium molecular weight, MMW) to 12-mers or 18-mers (high molecular weight, HMW). Different forms of adiponectin aforementioned, may potentially possess different physiological properties.

In patients with essential hypertension (EHP) plasma adiponectin concentration was significantly lower than in normotensive healthy subjects (NHS)

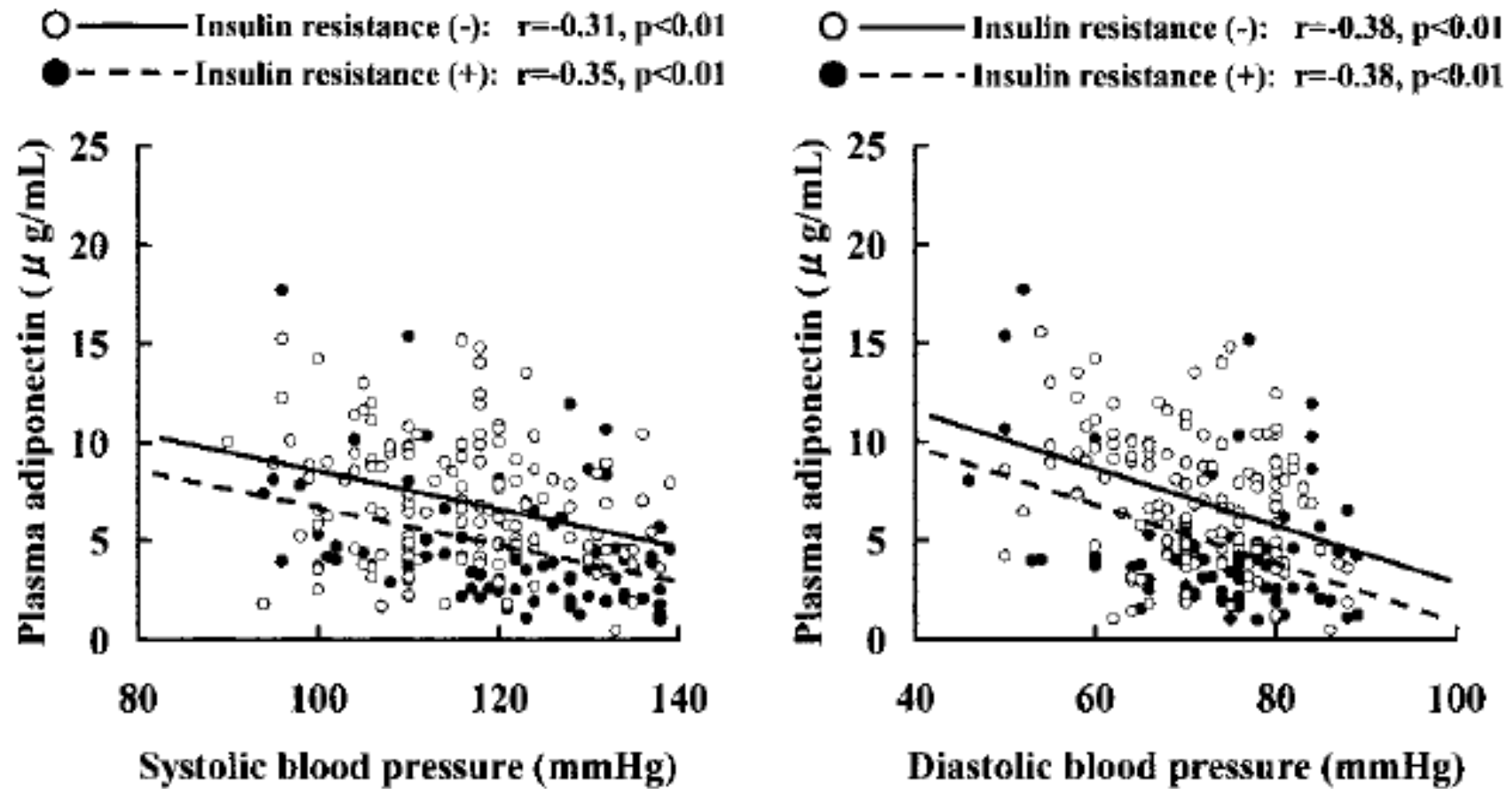


**In patients with essential hypertension blood pressure was inversely related to plasma adiponectin concentration**

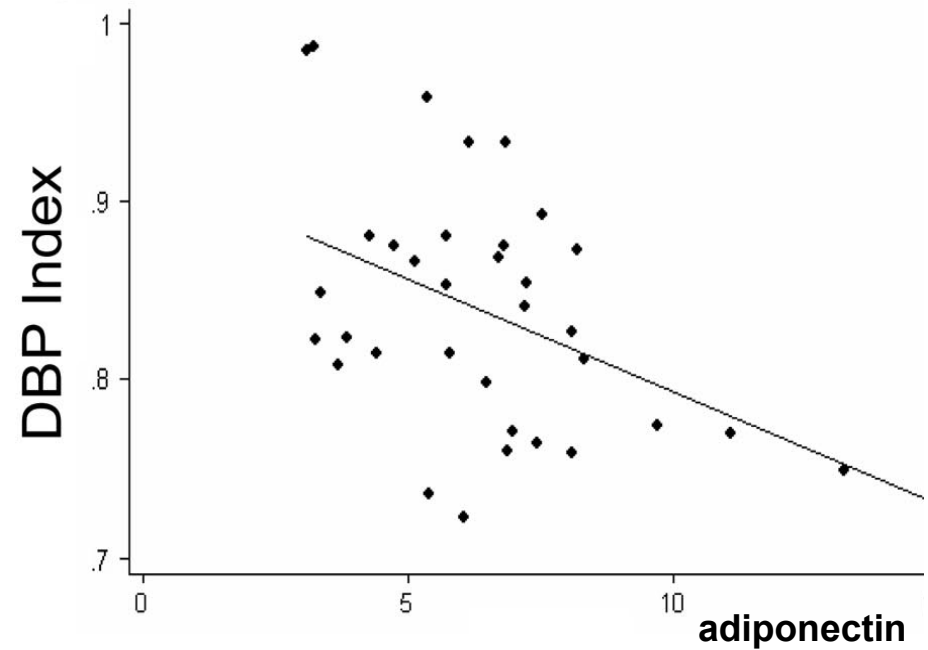
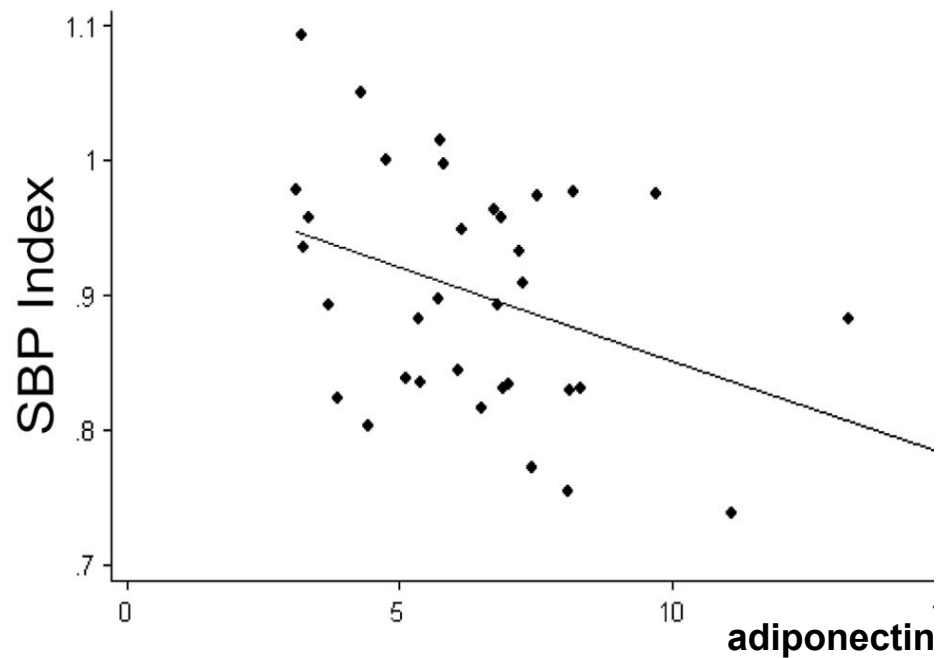


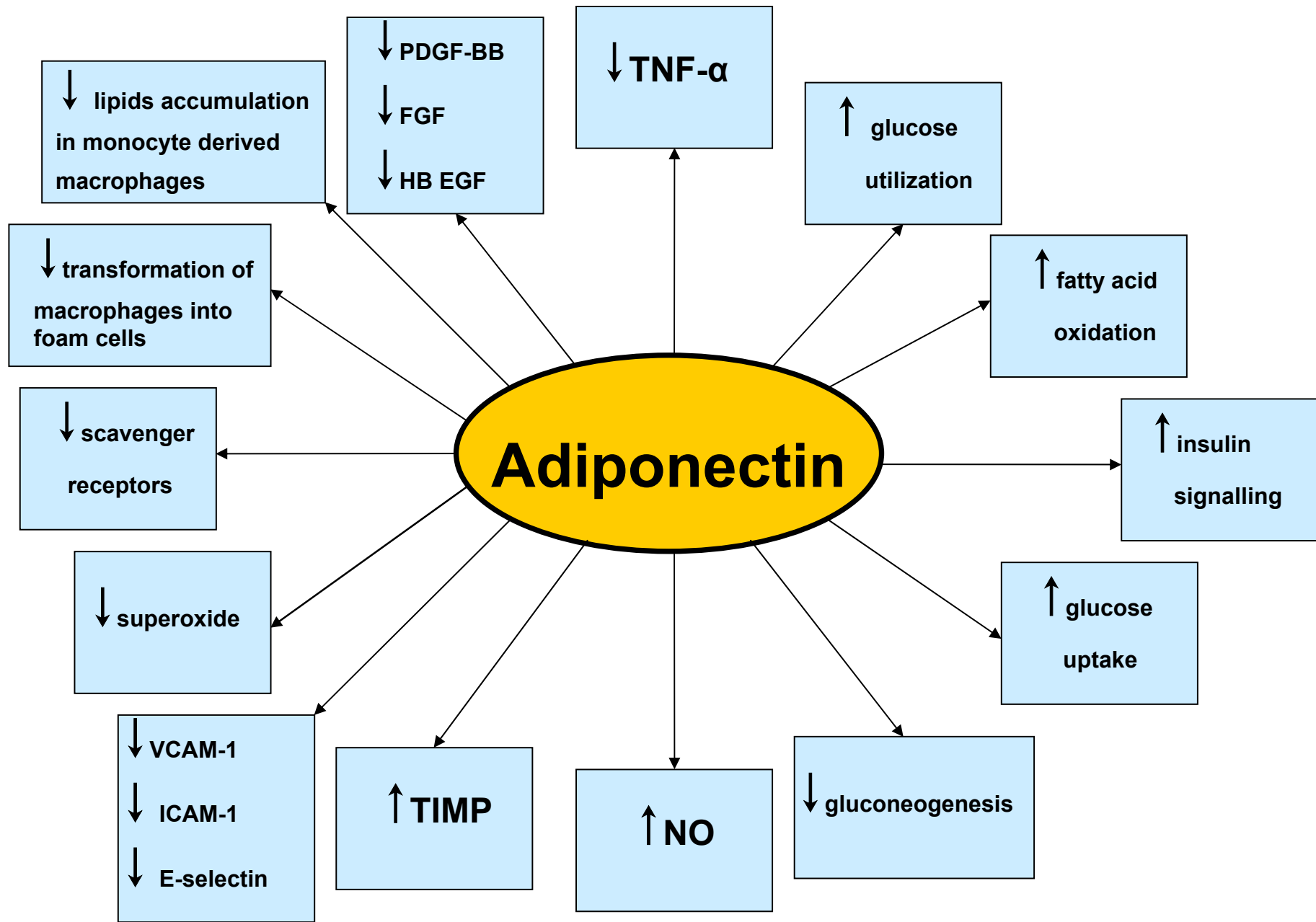
*Adamczak M., Więcek A., Funahashi T., Chudek J., Kokot F., Matsuzawa Y. Am J Hypertens 2003; 16: 72-75.*

# In healthy subjects blood pressure was inversely related to plasma adiponectin concentration



**In obese adolescents 24 hours ambulatory systolic and diastolic blood pressure indices were inversely related to plasma adiponectin concentration**

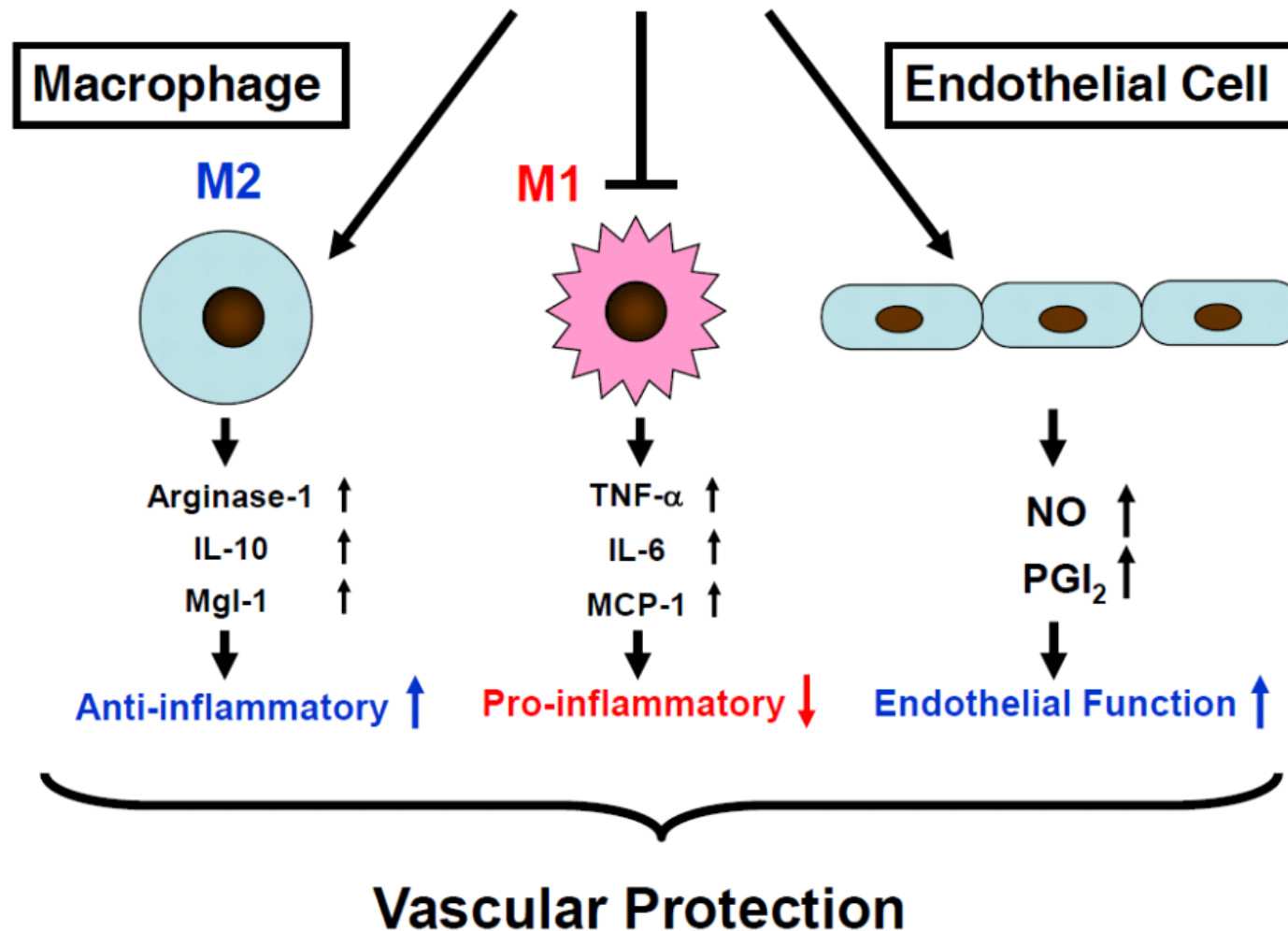




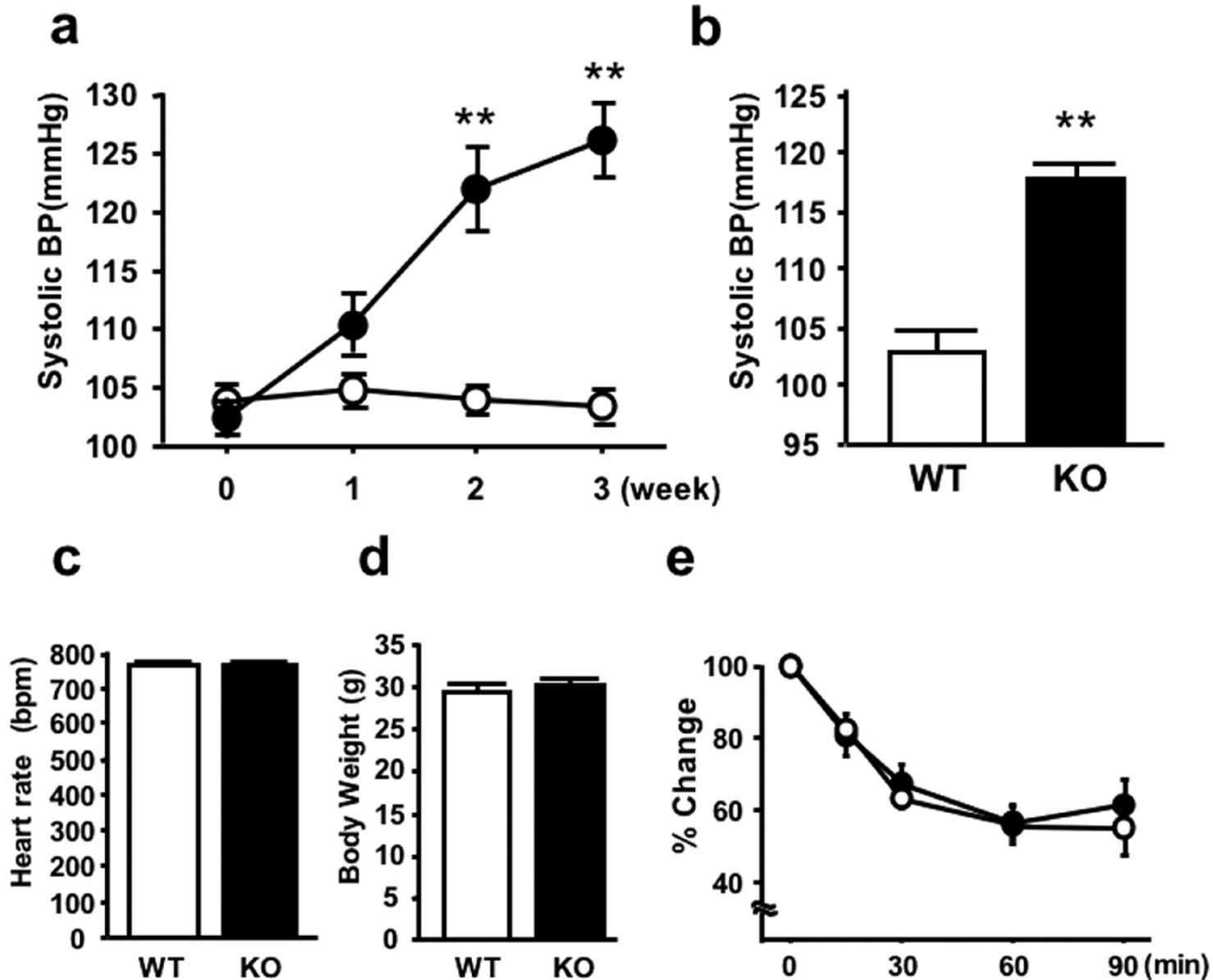
**anti-atherogenic actions**

**insulin-sensitizing actions**

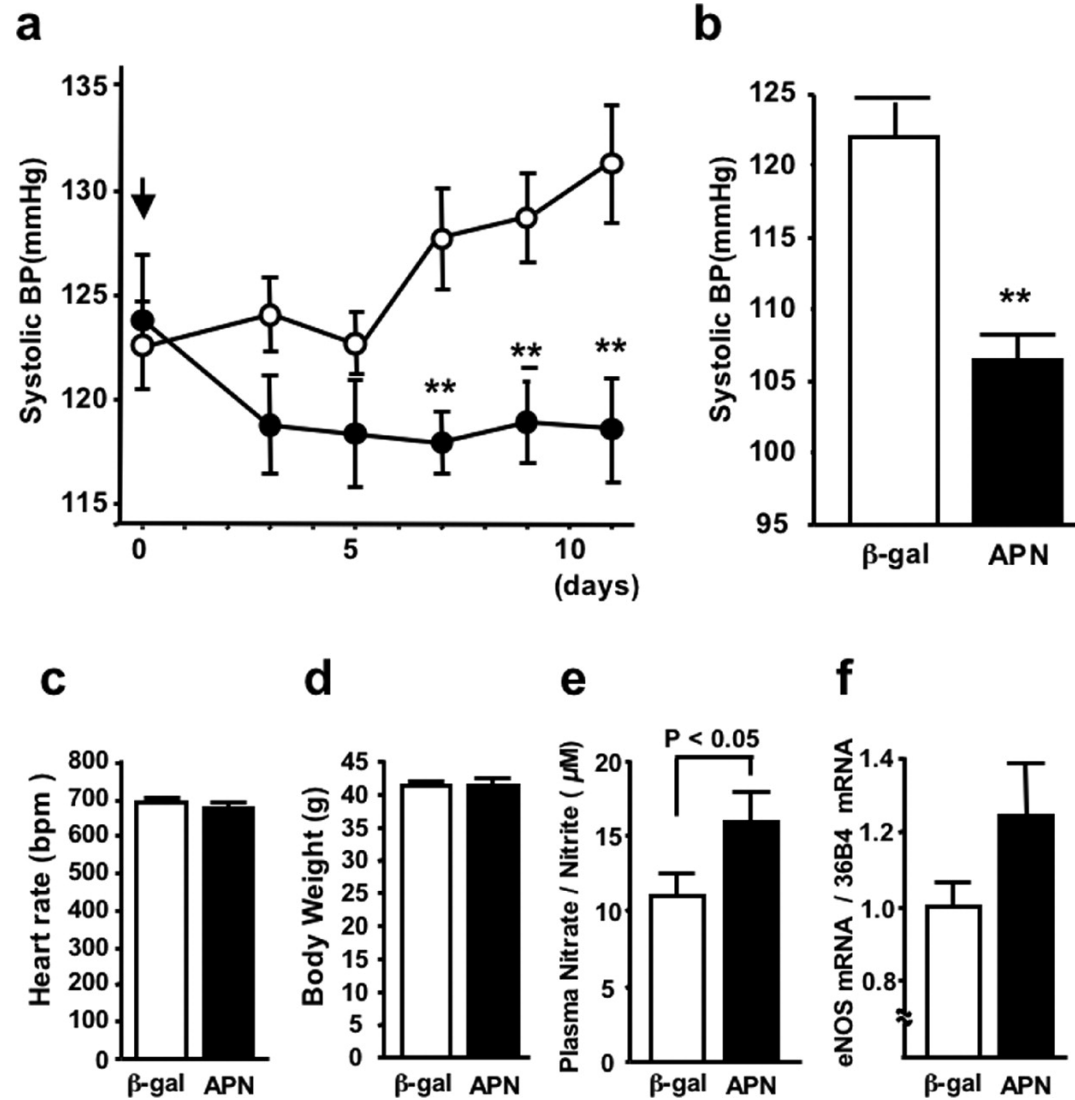
# Potential mechanism of vascular protection by Adiponectin



# Salt-induced hypertension in adiponectin KO mice



# Adiponectin supplementation ameliorates hypertension of genetically obese KKAY mice



# Clinical studies showed that:

- **in patients with essential hypertension plasma adiponectin concentration is decreased,**
- **high blood pressure values were related to low plasma adiponectin concentration,**
- **organ complications of essential hypertension (*left ventricular hypertrophy, diastolic left ventricular dysfunction, increased arterial stiffness, increased carotid artery intima-media thicknesses (cIMT), occurrence of higher grades of hypertensive retinopathy and albuminuria*) were related to low plasma adiponectin concentration.**

# Can hypoadiponectinemia predispose to hypertension?

**Decreased plasma adiponectin concentration in individuals with increased risk of hypertension:**

- **in young normotensive men with a family history of essential hypertension,**
- **in young men with high-normal blood pressure (SBP 130–139 or DBP 85–89 mmHg),**
- **in individuals with prehypertension (SBP 120–139 or DBP 80–89 mmHg).**

**Furuhashi M. et al. Hypertens Res 2005; 28: 141-146.**

**Papadopoulos D.P. et al. Blood Press 2008; 17: 50-54.**

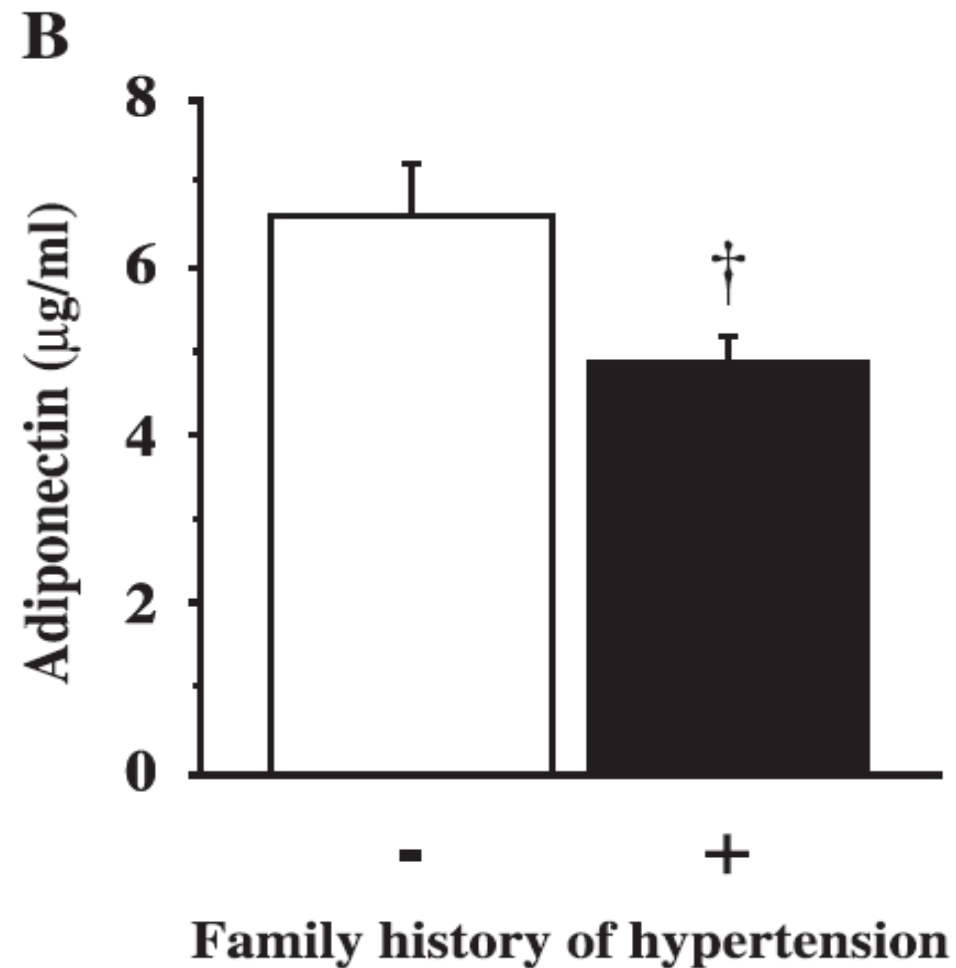
**Patel D.A. Met Clin Exp 2006; 55: 1551– 1557.**

**Kazumi T. et al. Diabetes Care 2002; 25: 971-976.**

**Papadopoulos D.P. et al. J Clin Hypertens (Greenwich) 2005; 7: 729-733.**

**Bo S. et al. J Hypertens 2009; 27: 102–108.**

Decreased plasma adiponectin concentration in young normotensive men with a family history of essential hypertension.



Furuhashi M. et al. Hypertens Res 2005; 28: 141-146.

# Plasma adiponectin concentrations decreased progressively with higher grades of hypertensive retinopathy

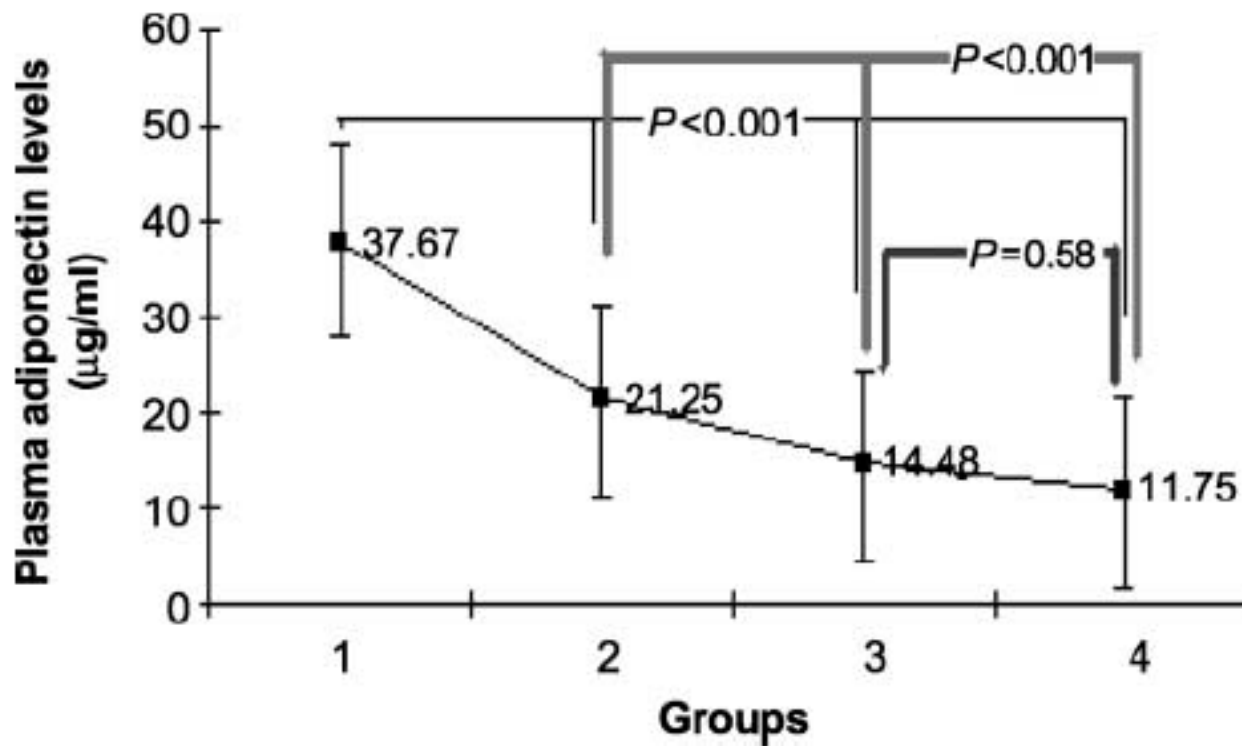


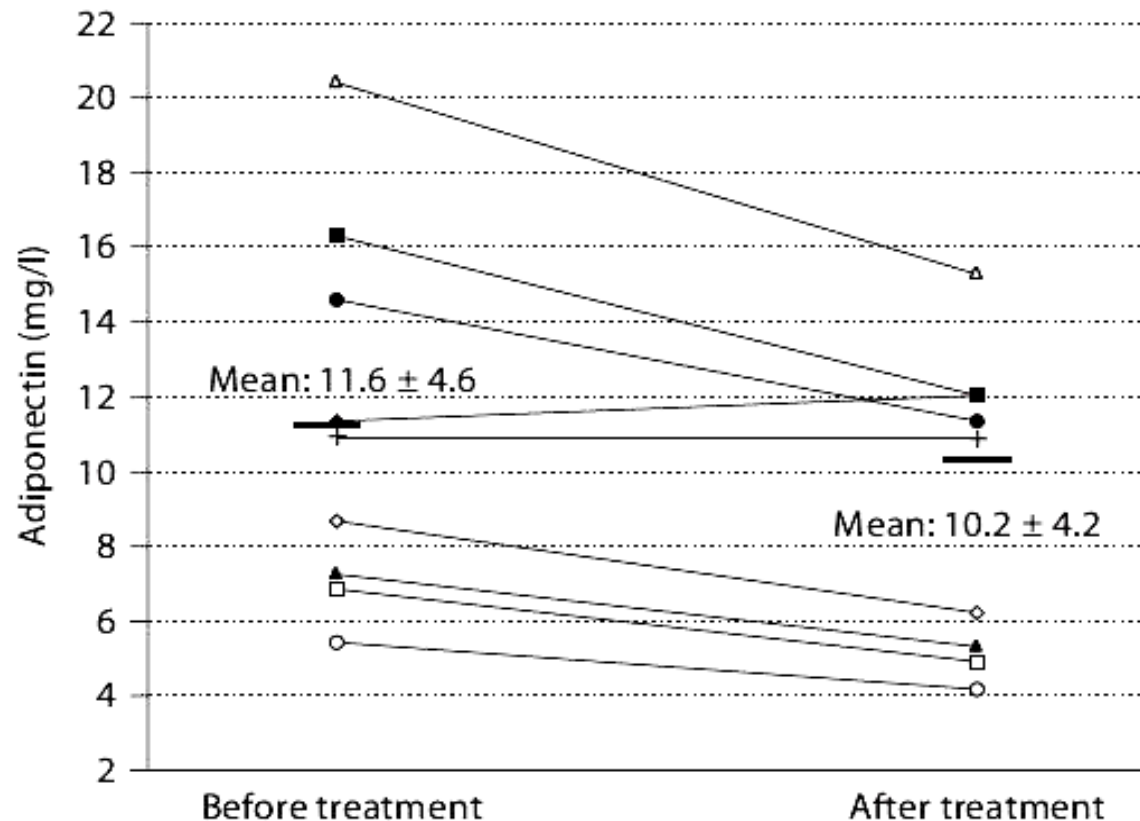
Figure 2 Plasma adiponectin levels of patients with hypertension by severity of hypertensive retinopathy. 1, control group; 2, grade 0; 3, grade 1; 4, grade 2.

# Obesity and hypertension – pathogenetic factors

- **Endothelial dysfunction**
- **Renin-angiotensin-aldosterone system activation**
- **Sympathetic nervous system activation**
- **Increased tubular sodium reabsorption leading to hypervolemia**
- **Insulin resistance/diabetes**
- **Glomerular hyperfiltration (↑ afferent arterioles blood flow)**
- **Kidney compression due to increased intrabdomen pressure**
- **Adipokines metabolism disturbances (among others hyperleptinemia and hypoadiponectinemia)**

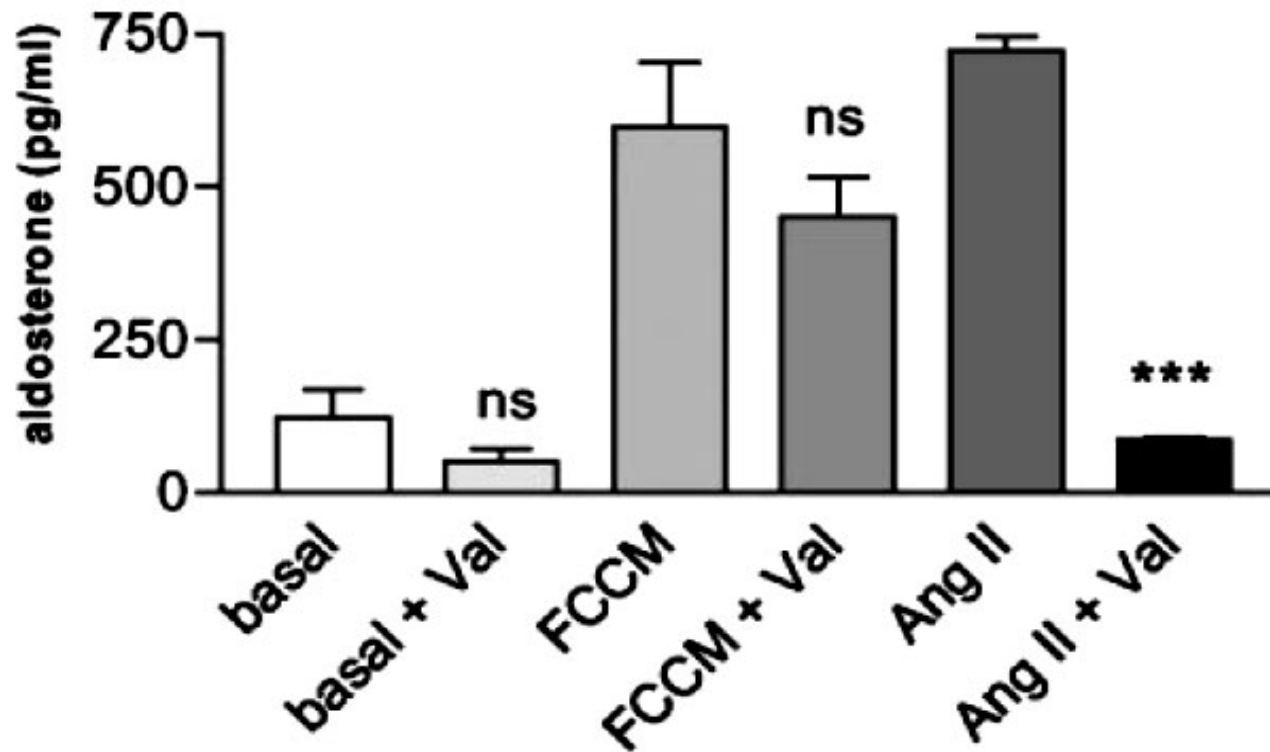
- Plasma Adiponectin concentration and mRNA expression are decreased in:
  - Obese
  - Diabetes mellitus
  - Hypertension
  - Coronary artery disease
  - Therapy (statins, indapamide)
- PPAR $\gamma$  activators, ACEi, ARBs, rilmenidine, ribonabant – increase adiponectin serum concentration and mRNA expression

# Plasma adiponectin concentration before and after indapamide therapy in hypertensive patients



Piecha G. et al., *Kidney Blood Press. Res.* 2007; 30: 187–194

FCCM =  
Fet Cell Conditioned Medium



**Fig. 3.** Angiotensin II ( $10^{-5}$  M) stimulated aldosterone secretion (AngII) is significantly inhibited (\*\*\*,  $P < 0.001$ ) by addition of the angiotensin type 1 receptor antagonist valsartan (Val) ( $10^{-5}$  M), whereas it had no significant (ns) effect on basal and FCCM-stimulated aldosterone secretion. FCCM contained 10% FBS. Mean  $\pm$  SEM,  $n = 3$  separate fat cell preparations, four wells per experiment.

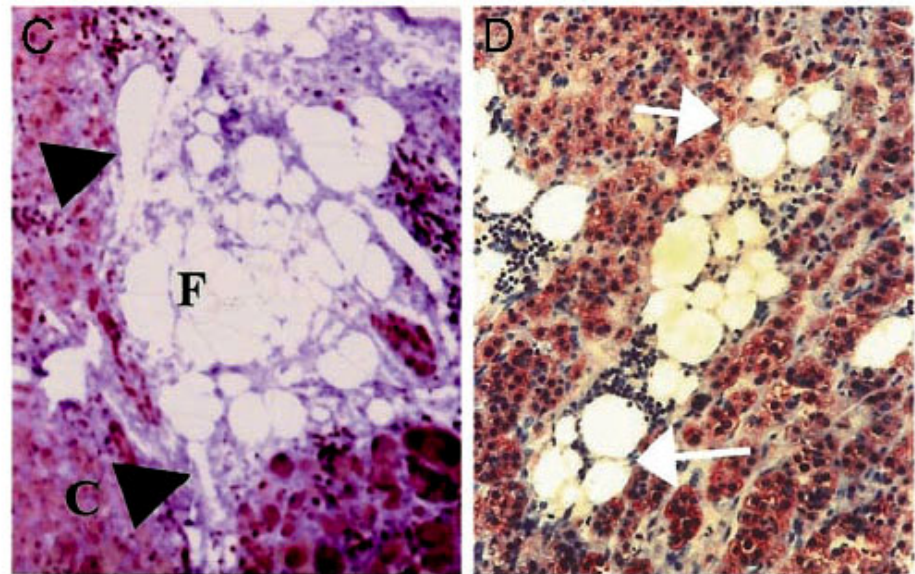
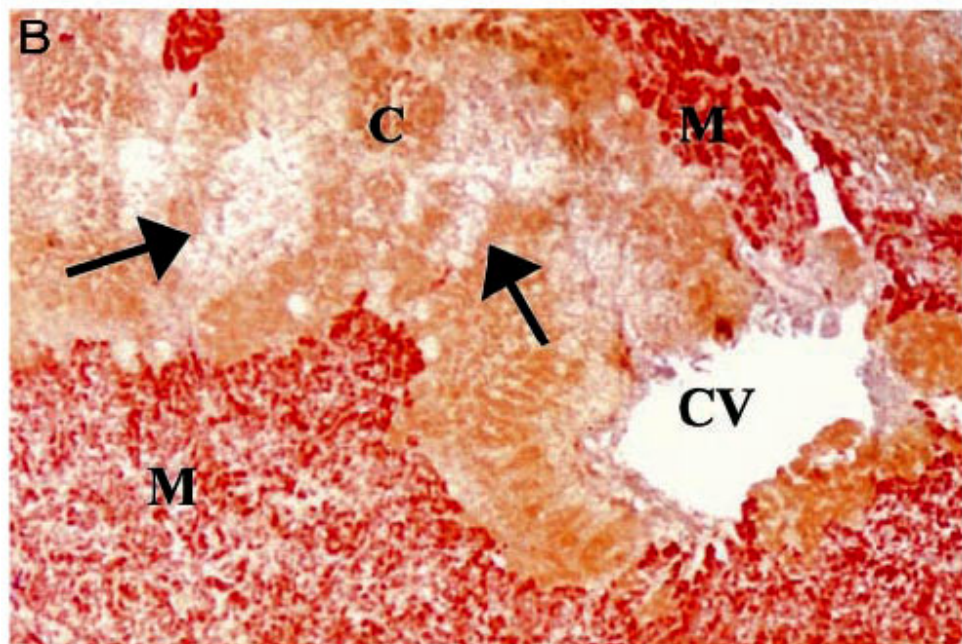
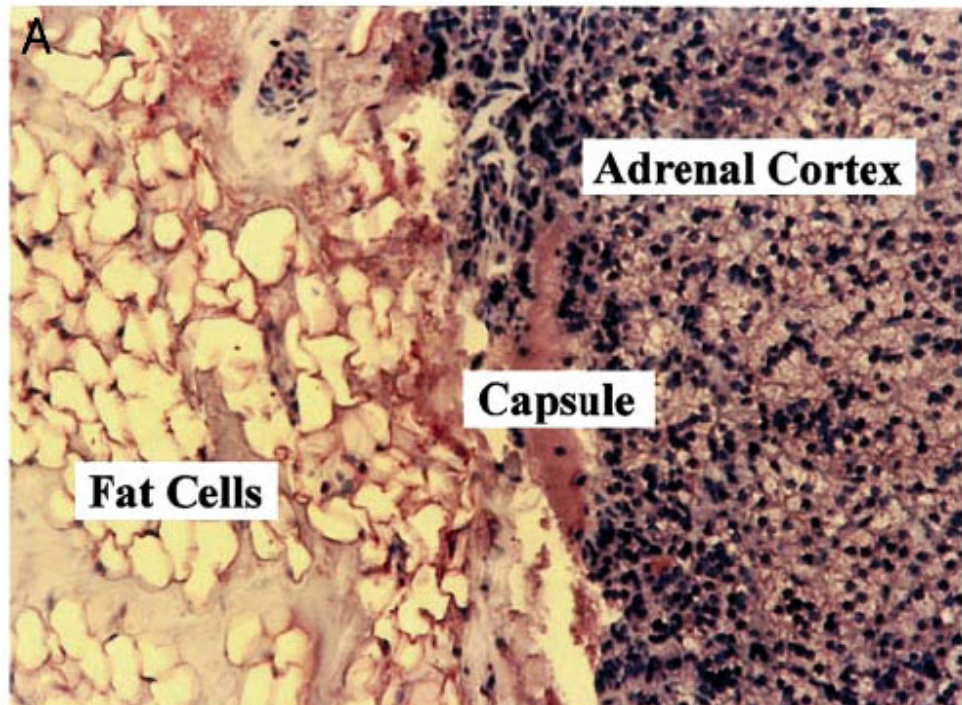
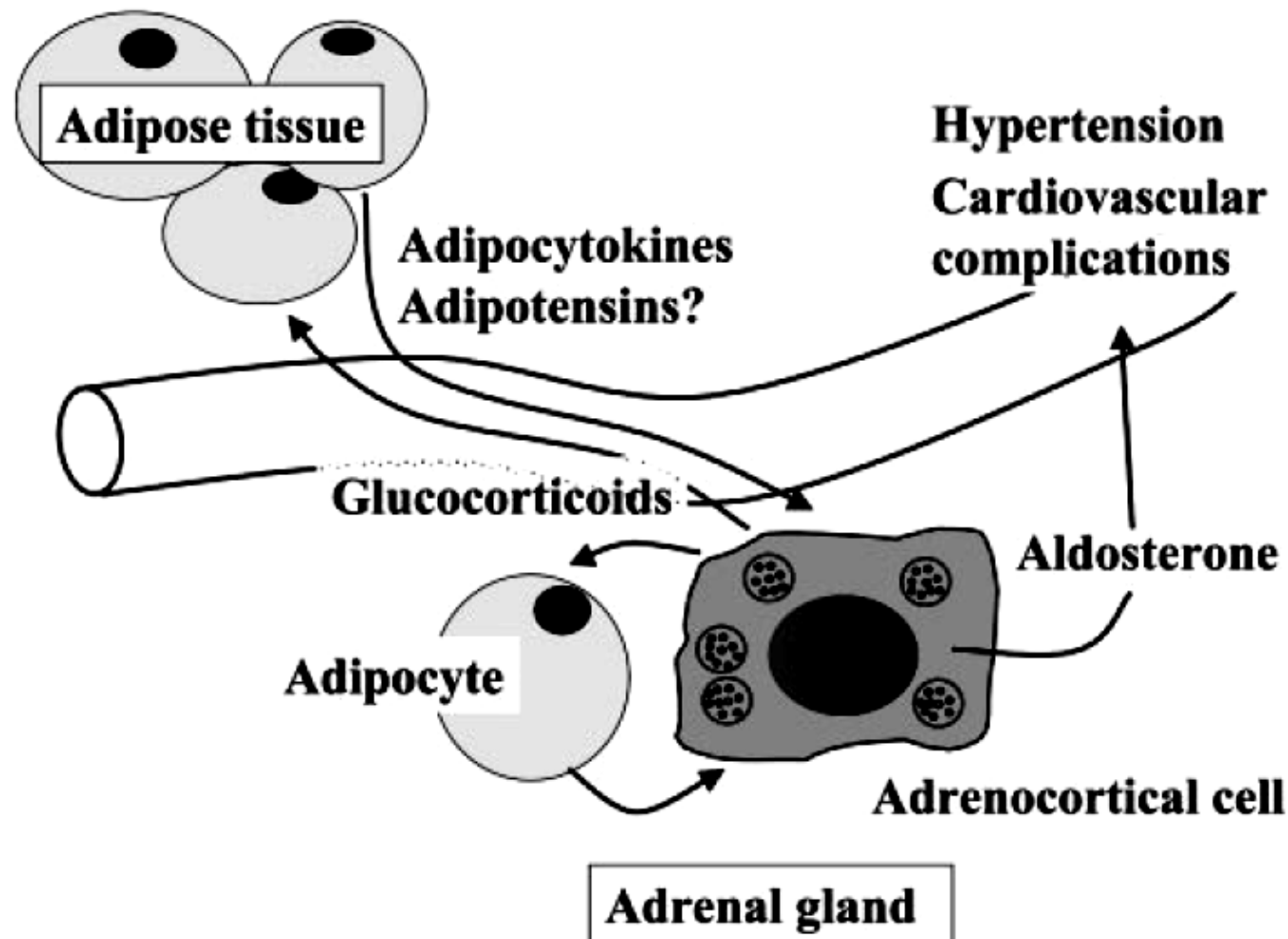


Fig. 5. Paraffin sections of normal human adrenal gland. (A) Human adrenals are embedded in periadrenal fat. (B–D) Adrenocortical cells are immunostained (brown) with an antibody against  $17\alpha$ -hydroxylase; in B, chromaffin cells are immunostained with an antibody against chromogranin A (red staining). (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.

# Factors involved in the pathogenesis of

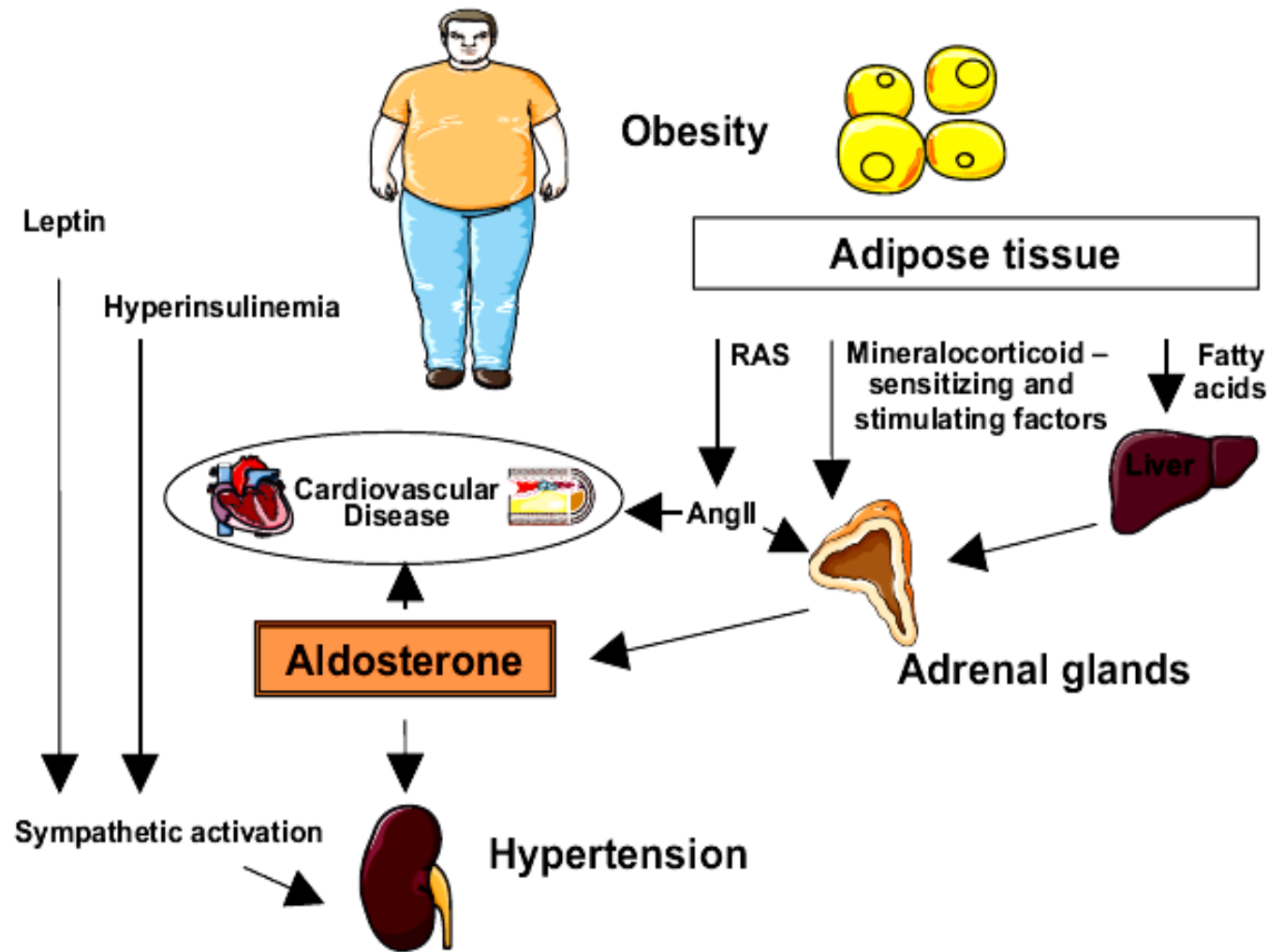
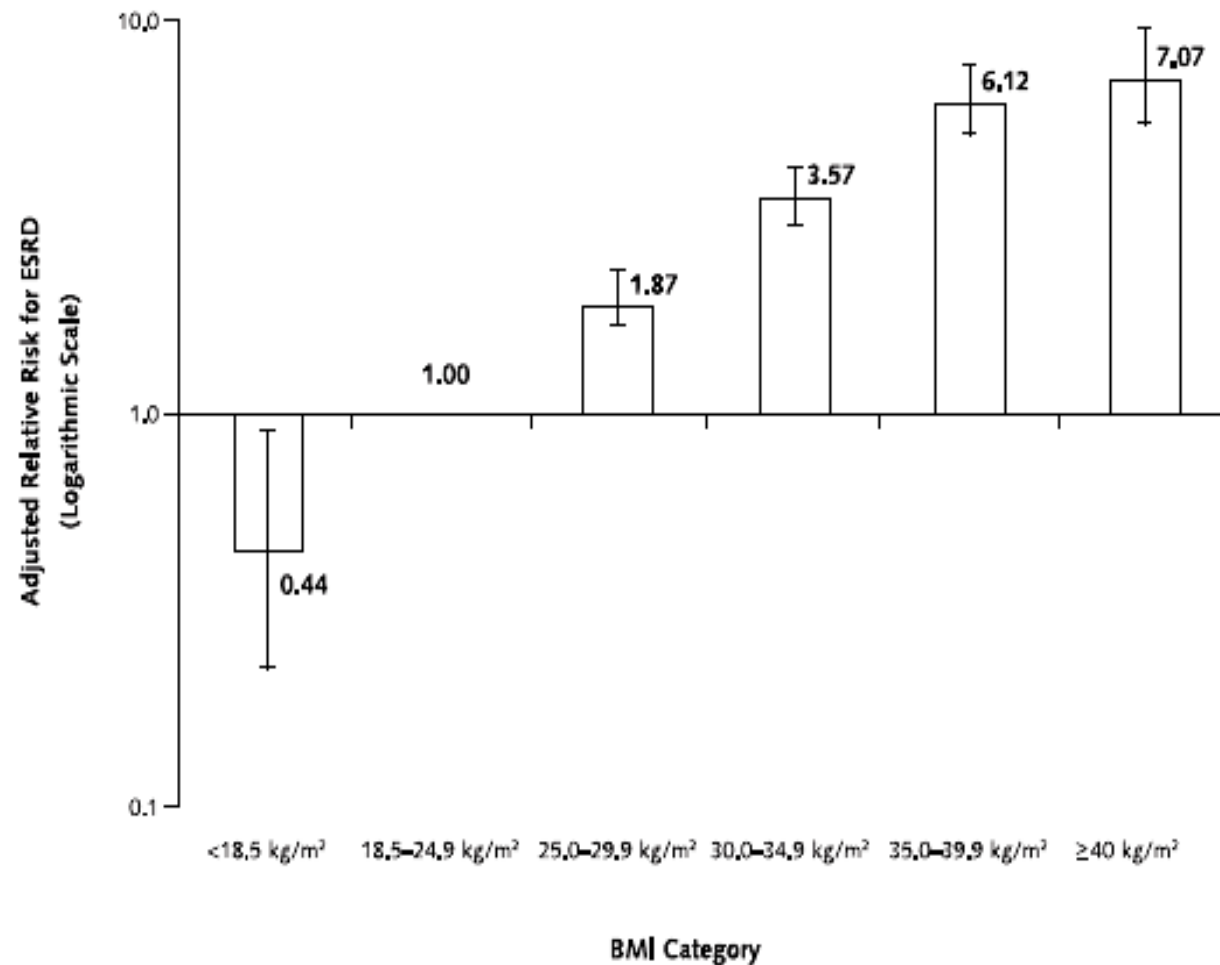


Figure. Adjusted relative risk for end-stage renal disease (ESRD) by body mass index (BMI).



Model adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Error bars represent 95% CIs.

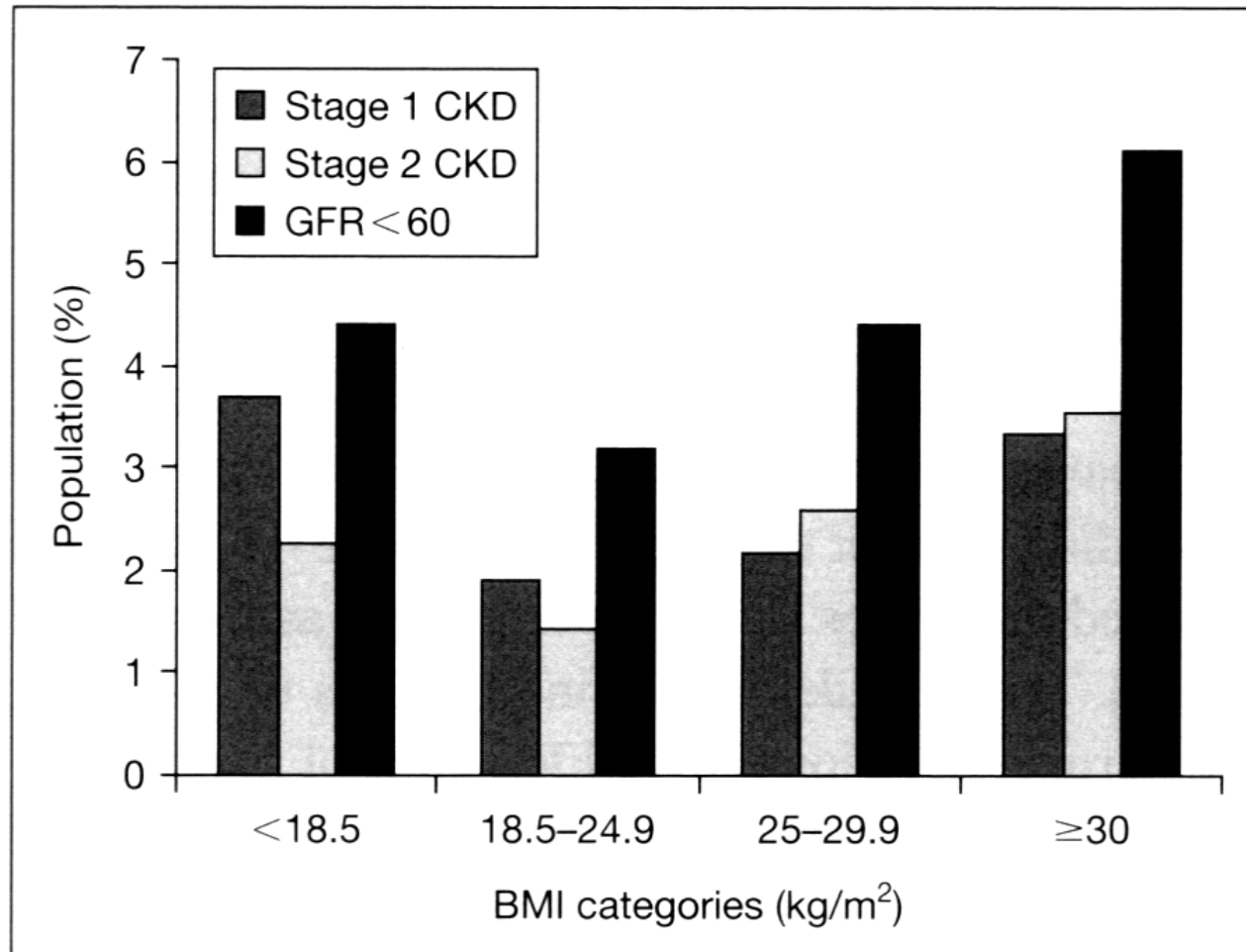
#### Implications

High BMI is a potentially modifiable risk factor for ESRD.

Hsu Ch., *Ann. Internal Med.*, 2006; 144: 21-28

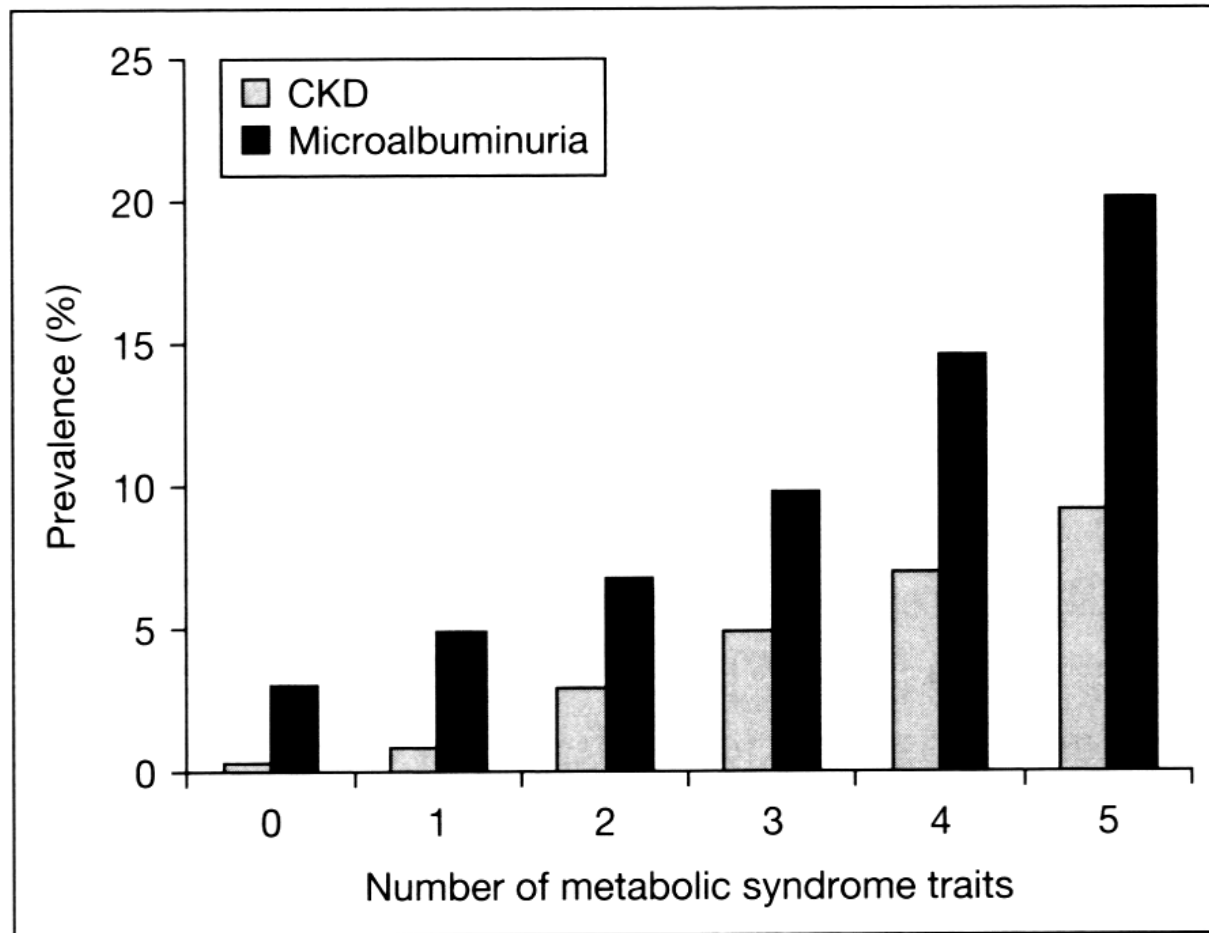
# Prevalence of CKD by BMI categories

National Health and Nutrition Examination Survey 1999-2000 (n=5897)

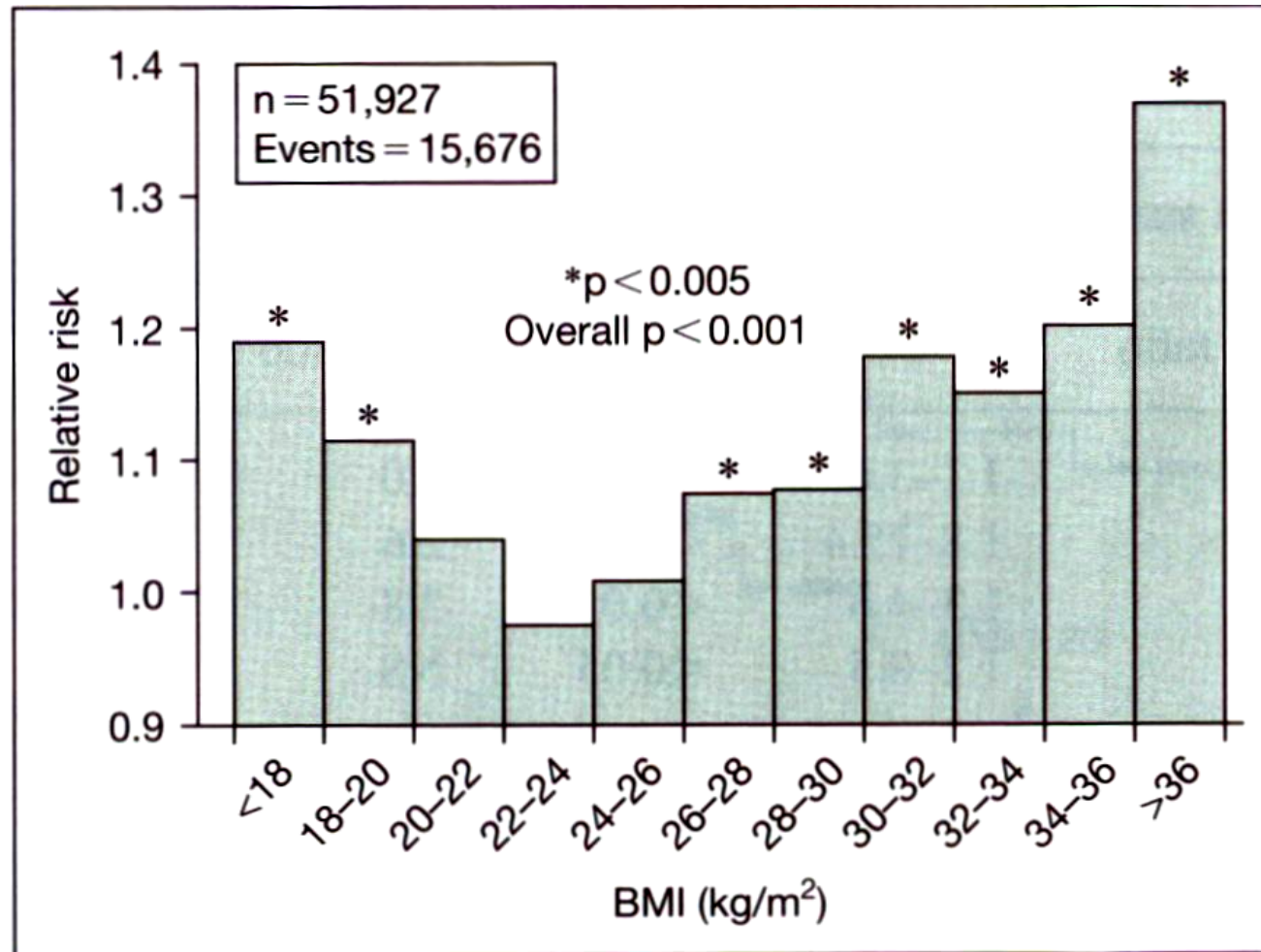


**Kramer H., Contrib. Nephrol., 2006, 151, 1-18**

# Prevalence of CKD (estimated GFR<60 ml/min/1,73) and microalbuminuria by number of metabolic syndrome traits in the non-diabetic U.S population



# Relative risk for graft loss by BMI



## Association between obesity and kidney disease: A systematic review and meta-analysis

Y Wang<sup>1</sup>, X Chen<sup>1</sup>, Y Song<sup>2</sup>, B Caballero<sup>1</sup> and LJ Cheskin<sup>1</sup>

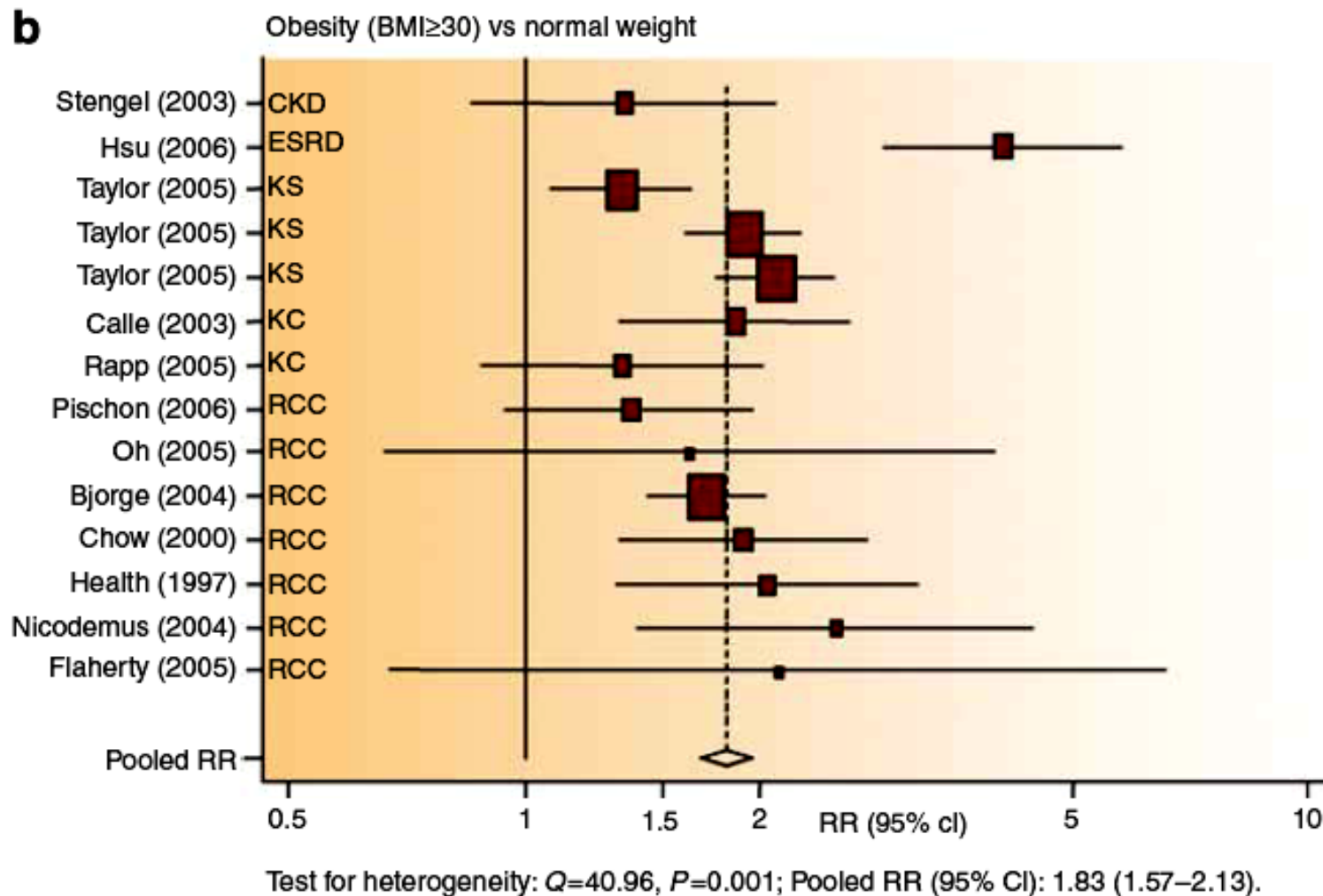
<sup>1</sup>Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA and <sup>2</sup>Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

This study aimed to comprehensively assess epidemiologic evidence on the relation between obesity and kidney disease (KD). From 247 retrieved articles via PubMed (1980–2006), 25 cohorts, 3 cross-sectional, and 19 case-control studies met inclusion criteria. Related data were extracted using a standardized protocol. We estimated the pooled relative risk (RR) and 95% confidence interval (95% CI) of KD for each body mass index (BMI) category compared with normal weight using meta-analysis models. Population attributable risk was also calculated. Compared with normal-weight individuals (18.5 < BMI < 25), overweight individuals (25 ≤ BMI < 30) had elevated risk for KD (RR = 1.40; 95% CI 1.30–1.50); obese individuals were at much higher risk (RR = 1.83 (1.57–2.13)). Obesity in women was associated with a higher risk than in men (RR = 1.92 (1.78–2.07) vs 1.49 (1.36–1.63); *P* < 0.001). Results from cohort studies in patient populations and cross-sectional and case-control studies all indicated a positive association between BMI and risks for KD outcomes. We estimated that 24.2% and 33.9% of KD cases among US men and women, respectively, and in industrialized countries, 13.8% in men and 24.9% in women, could be related to overweight and obesity. Obesity increases the risk for KD in the general population, and the association appears to be stronger in women than in men. Obesity adversely affects the progress of KD among patients with kidney-related diseases.

Obesity is known to increase the risk of a number of chronic diseases.<sup>1–3</sup> The growing worldwide obesity epidemic has become a public health crisis, affecting many countries. In the United States, obesity is now the second leading cause of preventable disease and death, surpassed only by smoking. There has been increasing interest on the role of the obesity epidemic on risk of kidney disease (KD)<sup>4–6</sup> in part because of the concurrent dramatic rise in the prevalence of end-stage renal disease (ESRD),<sup>7</sup> which has more than doubled in the past decade.<sup>8</sup> The number of patients living with ESRD is projected to reach 650 000 by 2010 in the United States, accounting for \$28 billion in medical care expenditures.<sup>9</sup>

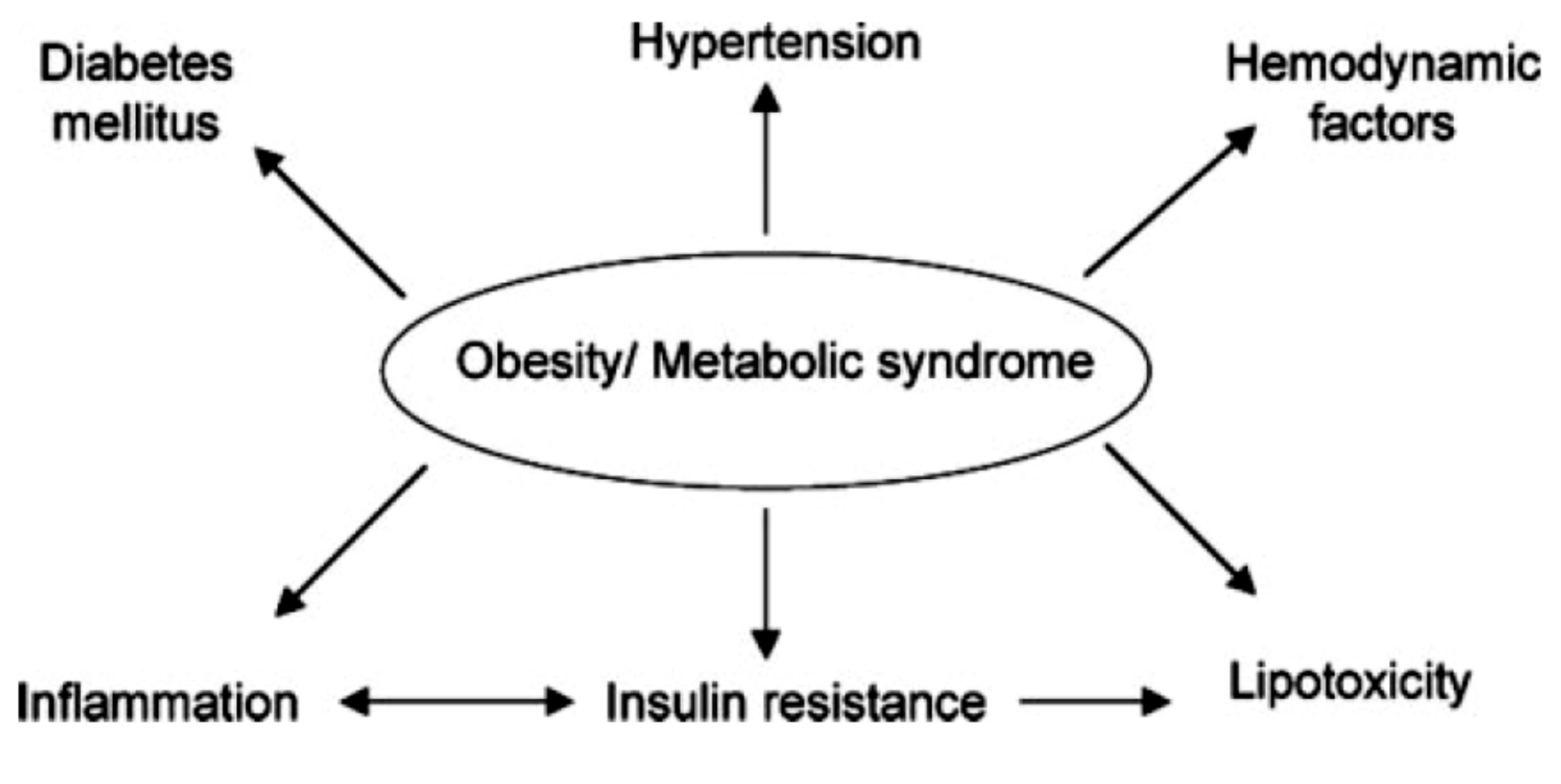
Interventions to prevent KD and its progression to ESRD have the potential to save many lives as well as decrease health-care costs.<sup>10</sup> Identifying modifiable risk factors for KD is critical in order to develop effective, population-based strategies.<sup>11–13</sup> As obesity is closely associated with the two most common causes of ESRD, namely type II diabetes and hypertension, it may increase the risk of ESRD.<sup>14–17</sup> Available data suggest that the incidence of some KD outcomes vary greatly across different regions of the world that have different prevalence of obesity, suggesting that obesity may be an important risk factor for KD.<sup>18–22</sup> For example, the incidence of renal cell cancer (RCC) varies more than 10-fold in different regions of the world. It is the highest in North America, and lowest in Asia.<sup>23</sup> Two major obstacles to prospectively studying risk

# Relative risk and 95% CI for the association between obesity and CKD based on cohort studies in the general populations



**Figure 1 | Pooled random-effects estimate of RR and 95% CI for the association between obesity and KD based on cohort studies in the general populations. (a) Overweight ( $25 \leq \text{BMI} < 30$ ) vs normal weight. Test for heterogeneity:  $Q=37.11$ ,  $P=0.003$ ; pooled RR (95% CI): 1.40 (1.30-1.50). (b) Obesity ( $\text{BMI} \geq 30$ ) vs normal weight. Test for heterogeneity:  $Q=40.96$ ,  $P<0.001$ ; pooled RR (95% CI): 1.83 (1.57-2.13).**

# Potential mechanisms of renal injury in patients with obesity and obesity initiated metabolic syndrome

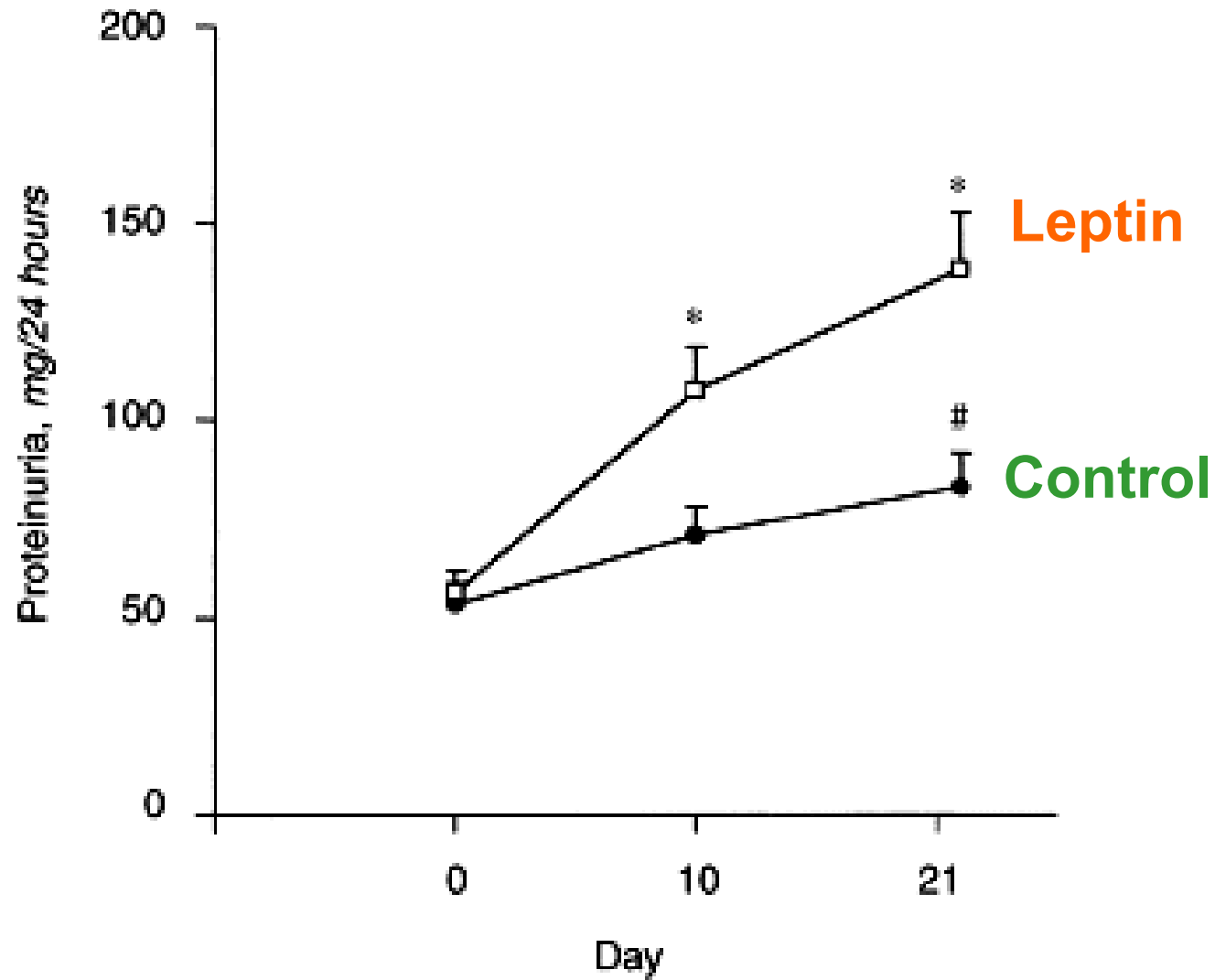


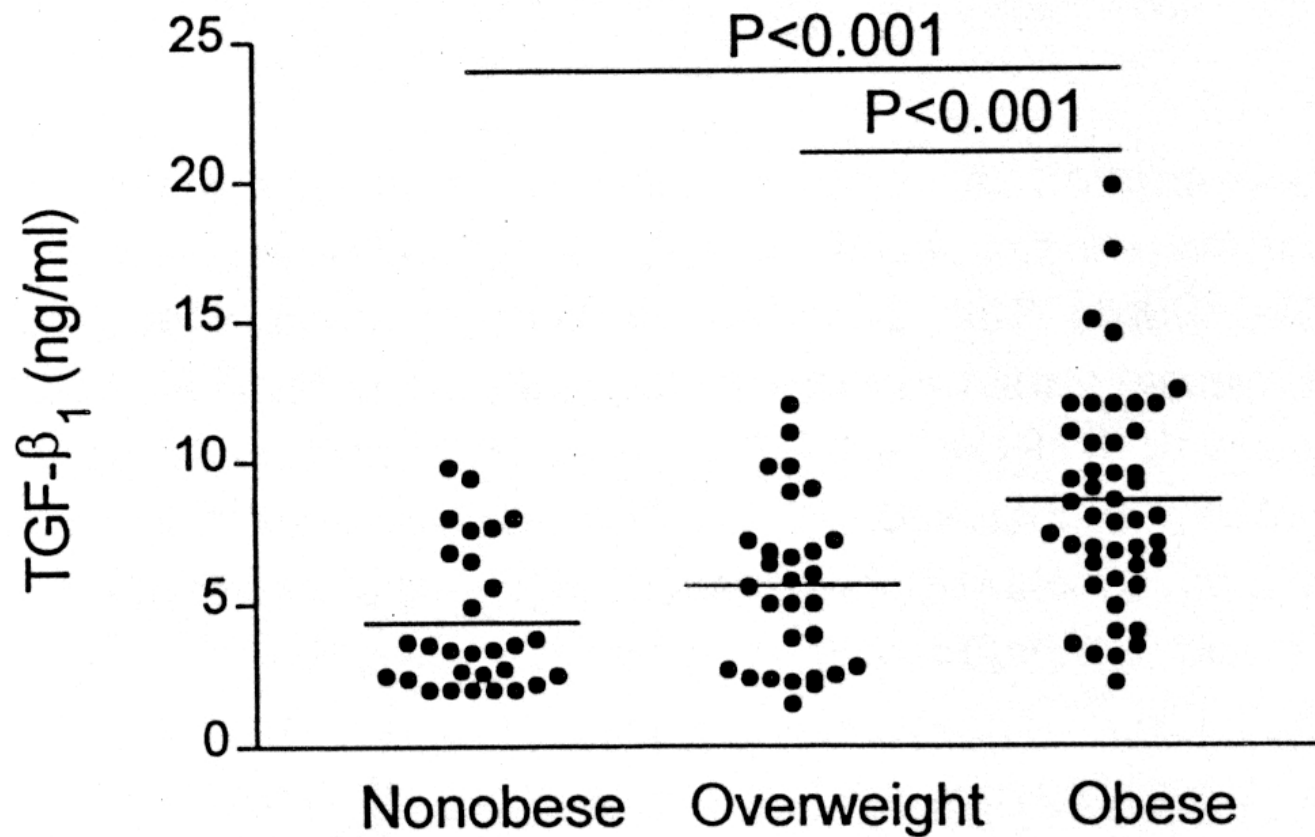
## A role for leptin in

- Leptin ~~glomerulosclerosis?~~ glomerulosclerosis and 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., *Kidney Int.* 1999, 56, 860-872**

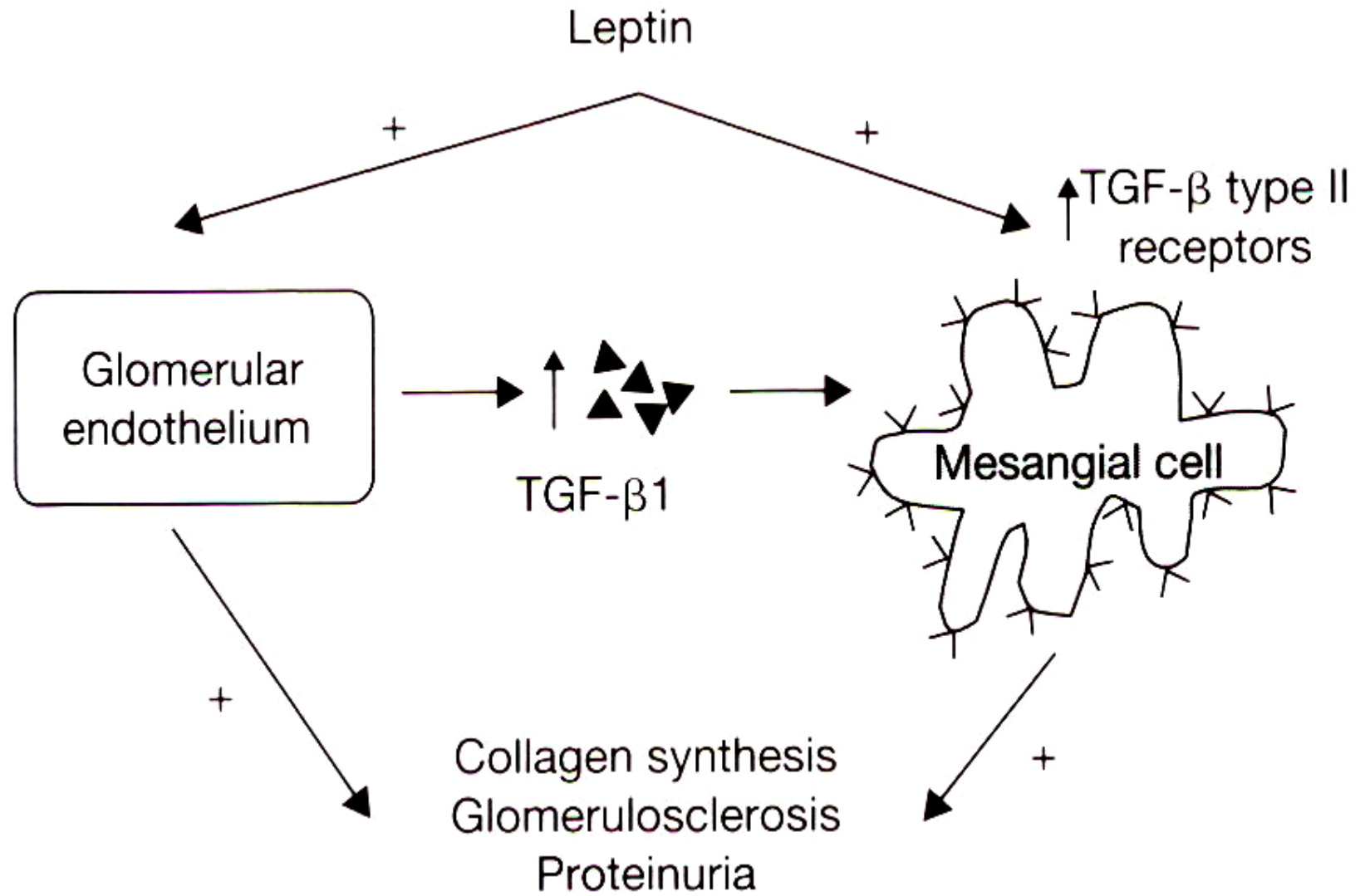
## Development of proteinuria during three weeks of leptin infusion



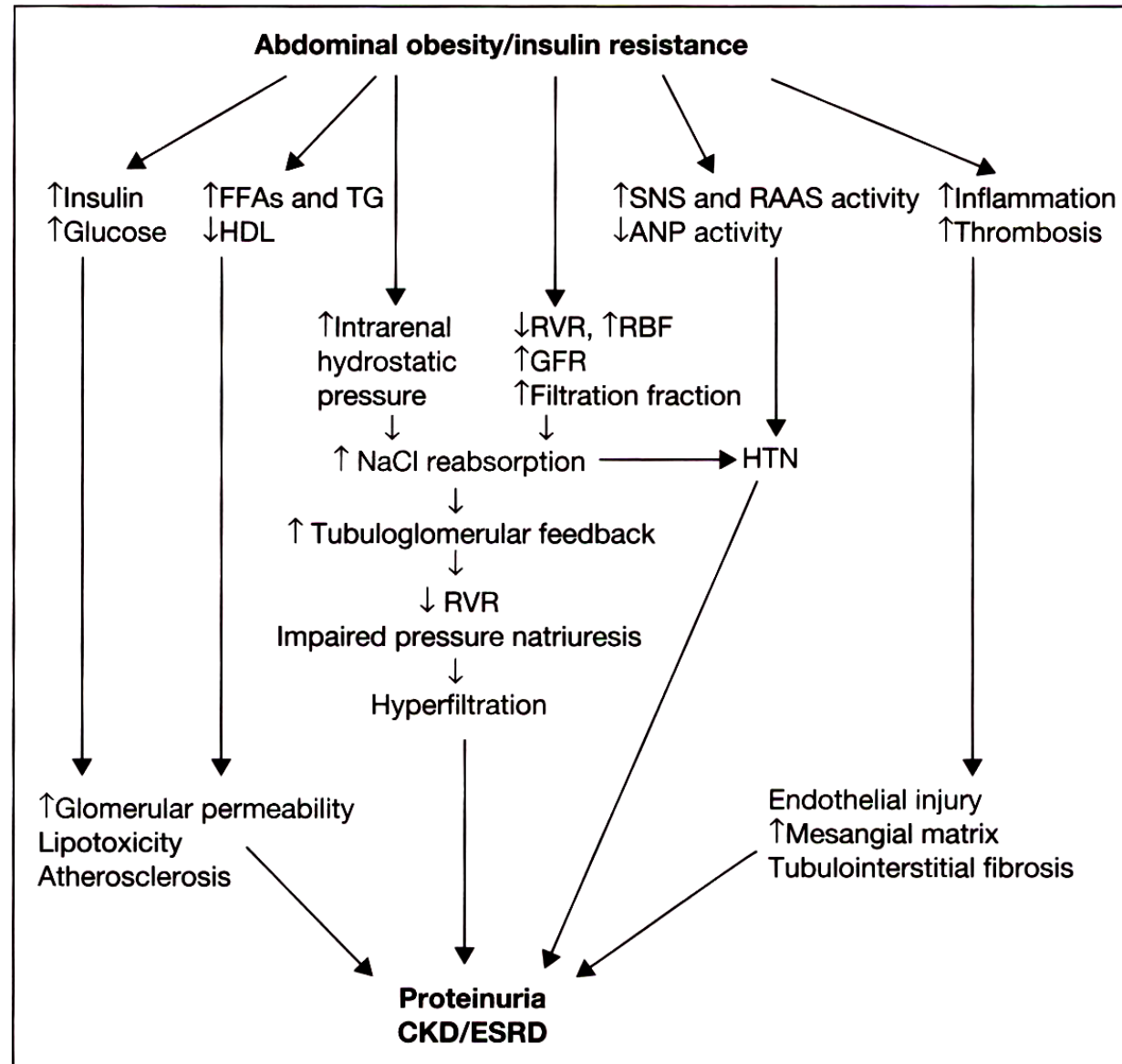


**FIG. 1.** Scatterplot of TGF-β<sub>1</sub> plasma levels in nonobese ( $n = 29$ ), overweight ( $n = 29$ ), and obese ( $n = 46$ ) hypertensive patients. TGF-β<sub>1</sub> = transforming growth factor-β<sub>1</sub>.

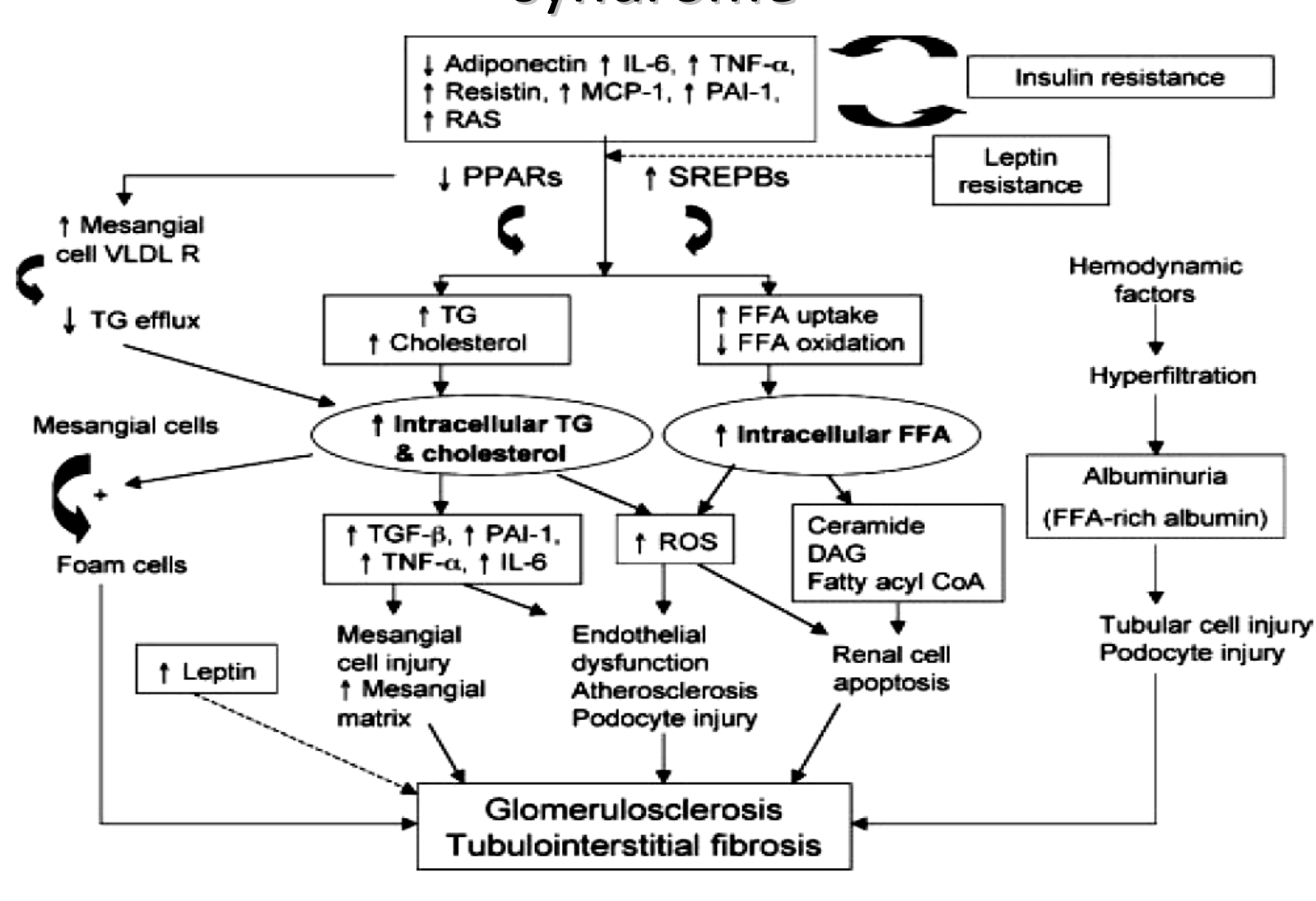
# Leptin and renal fibrosis



# Mechanism of kidney injury caused by obesity



# Potential mechanisms of renal dysfunction in obesity and obesity initiated metabolic syndrome



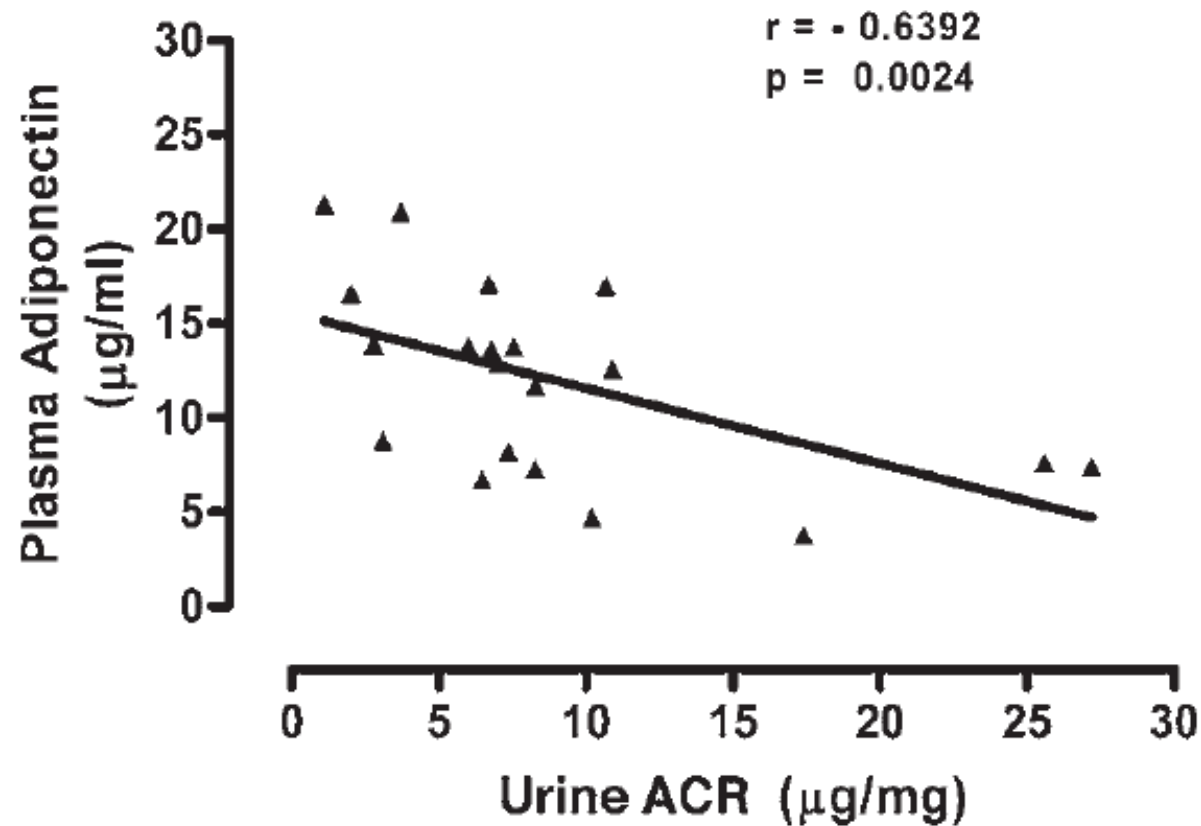
# **Albuminuria is related to the decreased plasma adiponectin concentration in patients with essential hypertension and in type 2 DM**

**Tsioufis C. et al. Am J Cardiol. 2005; 96: 946-951.**

**Barlovic D.P. et al. Cytokine. 2009; 46: 142-145.**

**Wakabayashi S. et al. Diabetes Care 2004; 27: 2392-2397.**

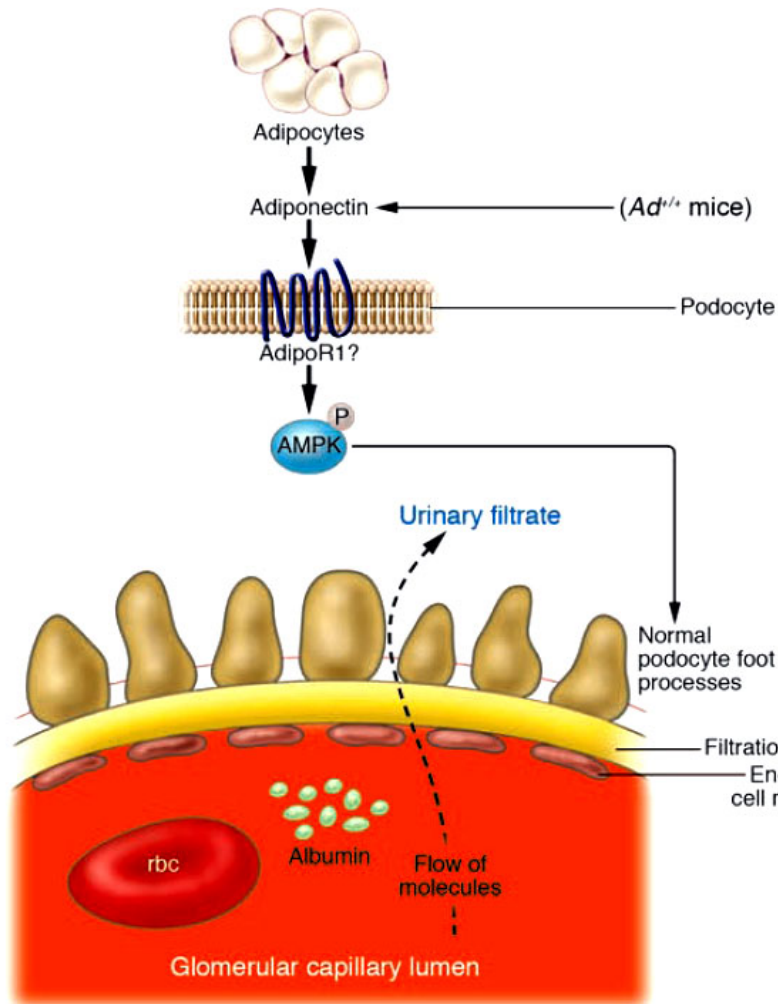
# Negative correlation between albuminuria and plasma adiponectin levels in obese adults African Americans



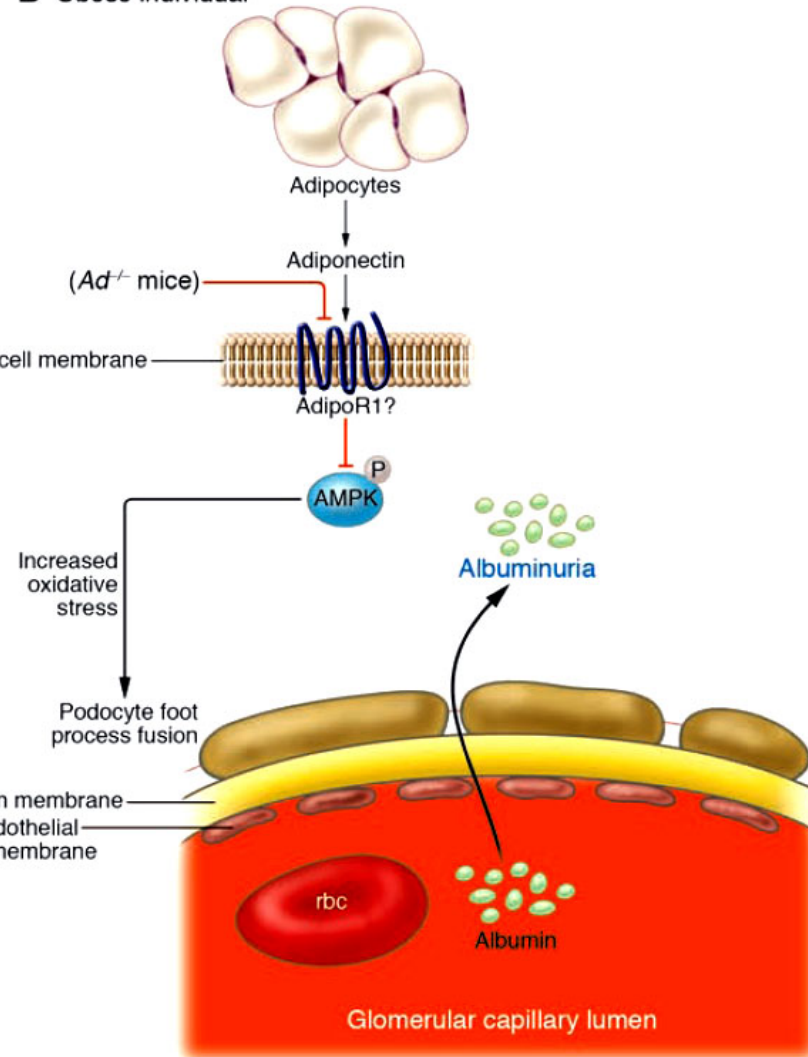
Sharama K J. Clin. Invest. 118:1645–1656 (2008)

# Effects of adiponectin on podocytes

**A** Lean individual

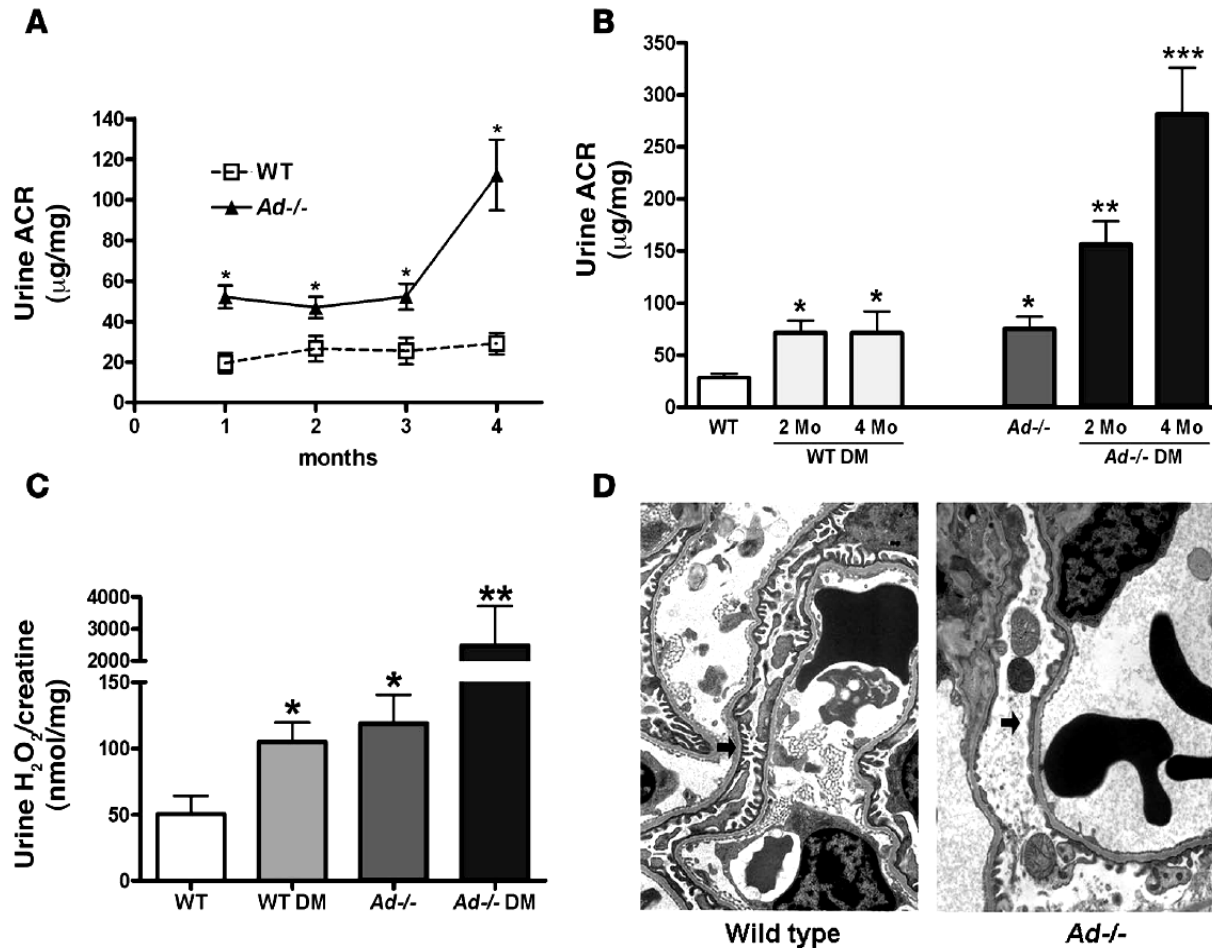


**B** Obese individual



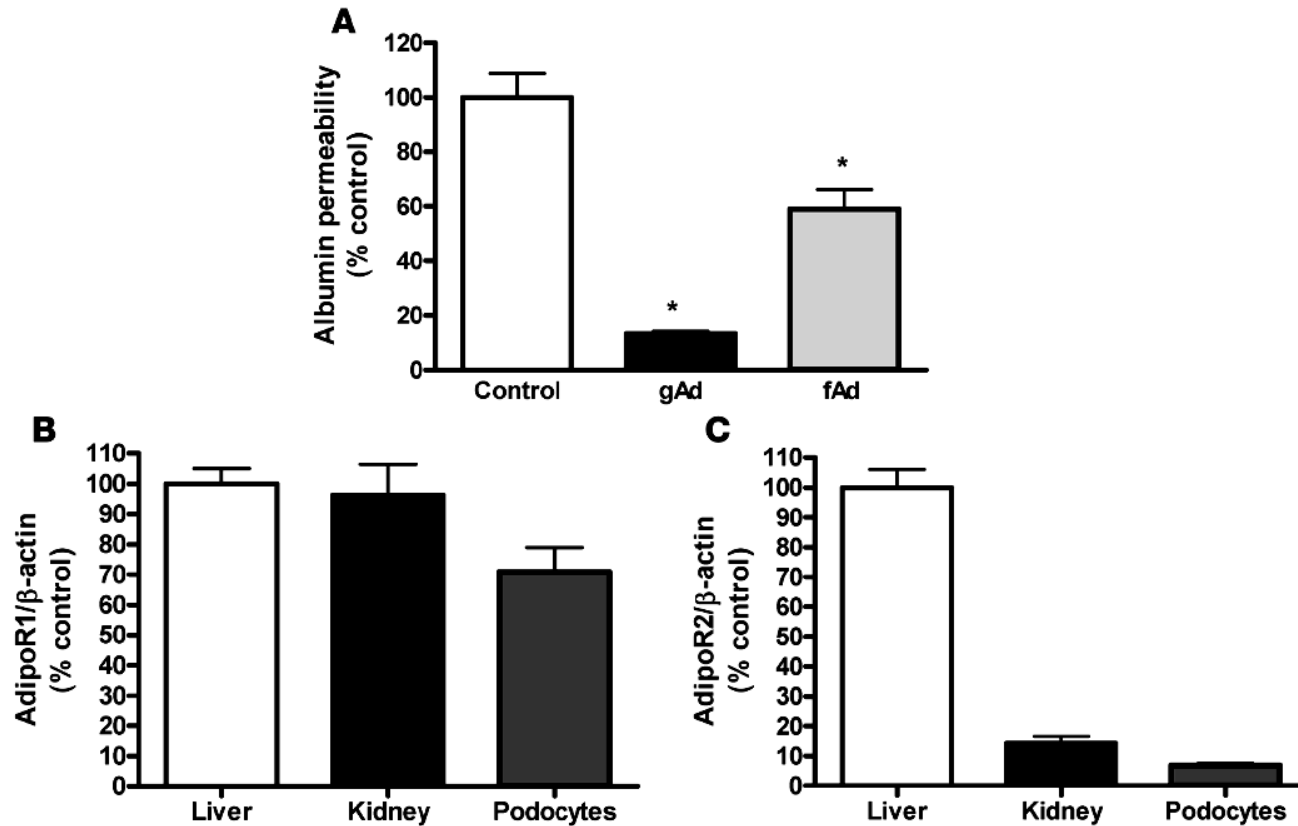
Ahima R. J. Clin. Invest. 118:1619–1622 (2008)

# 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



# Clinical significance of adipokines in chronic kidney disease

Adipokines	Biological significance	Clinical significance in CKD
Leptin	<ul style="list-style-type: none"> <li>Reflects the content of body fat</li> <li>Control food intake</li> <li>Appetite</li> <li>Energy expenditure</li> <li>Bone turn-over regulation</li> <li>Pro-inflammatory adipokine</li> </ul>	<ul style="list-style-type: none"> <li>Markedly elevated serum level</li> <li>Clinical marker of body fat content in dialysis</li> <li>Absence of relationship between leptin and anorexia in dialysis</li> <li>Low bone turnover in dialysis</li> <li>Influence EPO sensitivity in ESRD</li> <li>Associated to inflammation, atherogenic lipid profile and insulin resistance in CKD</li> <li>Low leptin is an independent risk factor for mortality in HD</li> </ul>
Adiponectin	<ul style="list-style-type: none"> <li>Increases insulin sensitivity</li> <li>Anti-inflammatory and anti-atherogenic adipokine</li> <li>Bone turnover regulation</li> </ul>	<ul style="list-style-type: none"> <li>Elevated serum level</li> <li>Inversely associated with metabolic risk factors in uraemia</li> <li>Inversely associated with CV events in HD</li> <li>Improved survival and better outcome in dialysis patients</li> </ul>
Visfatin	<ul style="list-style-type: none"> <li>Energetic metabolism</li> <li>Immunity</li> <li>Mimics insulin action</li> <li>Pro-inflammatory adipokine</li> <li>Induces IL-6 expression</li> </ul>	<ul style="list-style-type: none"> <li>Elevated serum level</li> <li>Anorexigenic</li> <li>Decreased circulating levels of amino acids and triacylglycerols</li> <li>Mortality predictor in CKD?</li> </ul>
TNF- $\alpha$	<ul style="list-style-type: none"> <li>Pro-inflammatory adipokine</li> <li>Implicated in pathogenesis of obesity and insulin resistance</li> <li>Correlates with BMI and body fat and hyperinsulinaemia</li> </ul>	<ul style="list-style-type: none"> <li>Elevated serum level</li> <li>Enhance gene expression of TNF-<math>\alpha</math> in circulating blood cells in uraemia</li> <li>Elevated TNF-<math>\alpha</math> associated to: Increased mortality in HD</li> <li>Anorexia and a poor nutritional status in PD</li> </ul>
IL-6	<ul style="list-style-type: none"> <li>Pro-inflammatory adipokine</li> <li>Hyperglycaemia and hyperinsulinaemia</li> <li>Insulin resistance</li> <li>Correlates positively with human obesity and insulin resistance</li> <li>Predictive of type 2 diabetes</li> <li>Associated with the appearance of coronary heart disease events, congestive heart failure events and stroke events</li> </ul>	<ul style="list-style-type: none"> <li>Elevated serum levels</li> <li>Reliable predictor of mortality</li> <li>Better mortality predictor than TNF-<math>\alpha</math> in CKD and HD</li> </ul>
Resistin	<ul style="list-style-type: none"> <li>Regulation of metabolism</li> <li>Inhibition of adipogenesis and inflammation</li> </ul>	<ul style="list-style-type: none"> <li>Elevated serum levels</li> <li>Similar levels in both HD and PD</li> <li>Associated to heart disease in dialysis?</li> </ul>

EPO, epoetin; ESRD, end-stage renal disease; CKD, chronic kidney disease; CV, cardiovascular; IL-6, interleukin-6; BMI, body mass index; TNF- $\alpha$ , tumour necrosis factor-alpha; HD, haemodialysis; PD, peritoneal dialysis.

**Katowice**

***Thank you for your attention !***

