

OBESITA', MIA SYNDROME E MALATTIA RENALE CRONICA

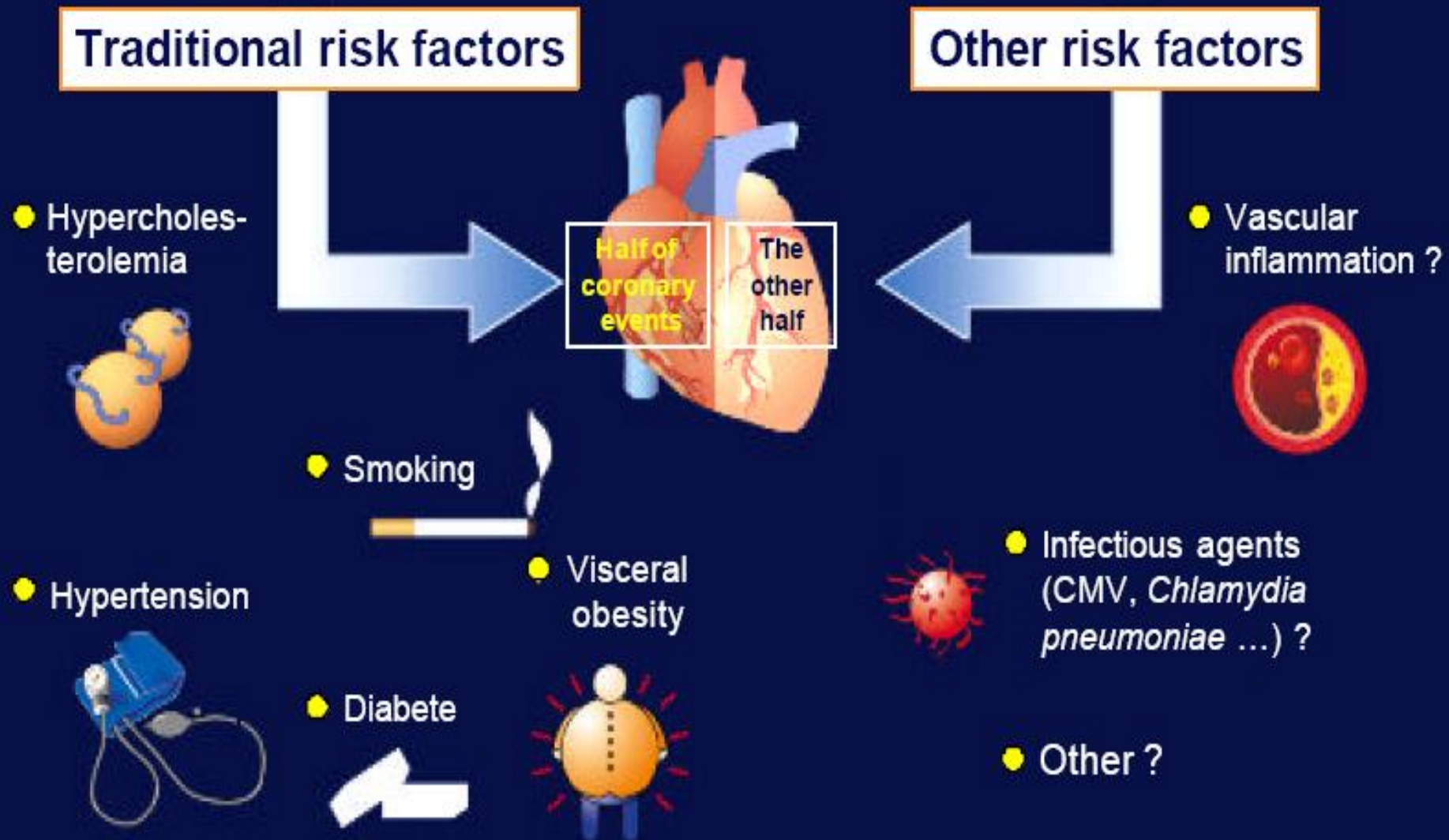
Prof. Vincenzo Panichi



Obesity and the Kidney - Talk Outline

- Pathogenesis
- Clinical consequences
- Reverse Epidemiology of Obesity in Hemodialysis Patients (Obesity Paradox)

Coronary disease : lipid and non lipid risk factors



Risk Factors for CVD in CKD Patients

TRADITIONAL

Age

Gender

Family history

Homocysteine

Smoking

Obesity

Hypertension

Dyslipidemia

NON TRADITIONAL

Volume overload

Anemia

Ca-PO₄ abnormalities, PTH

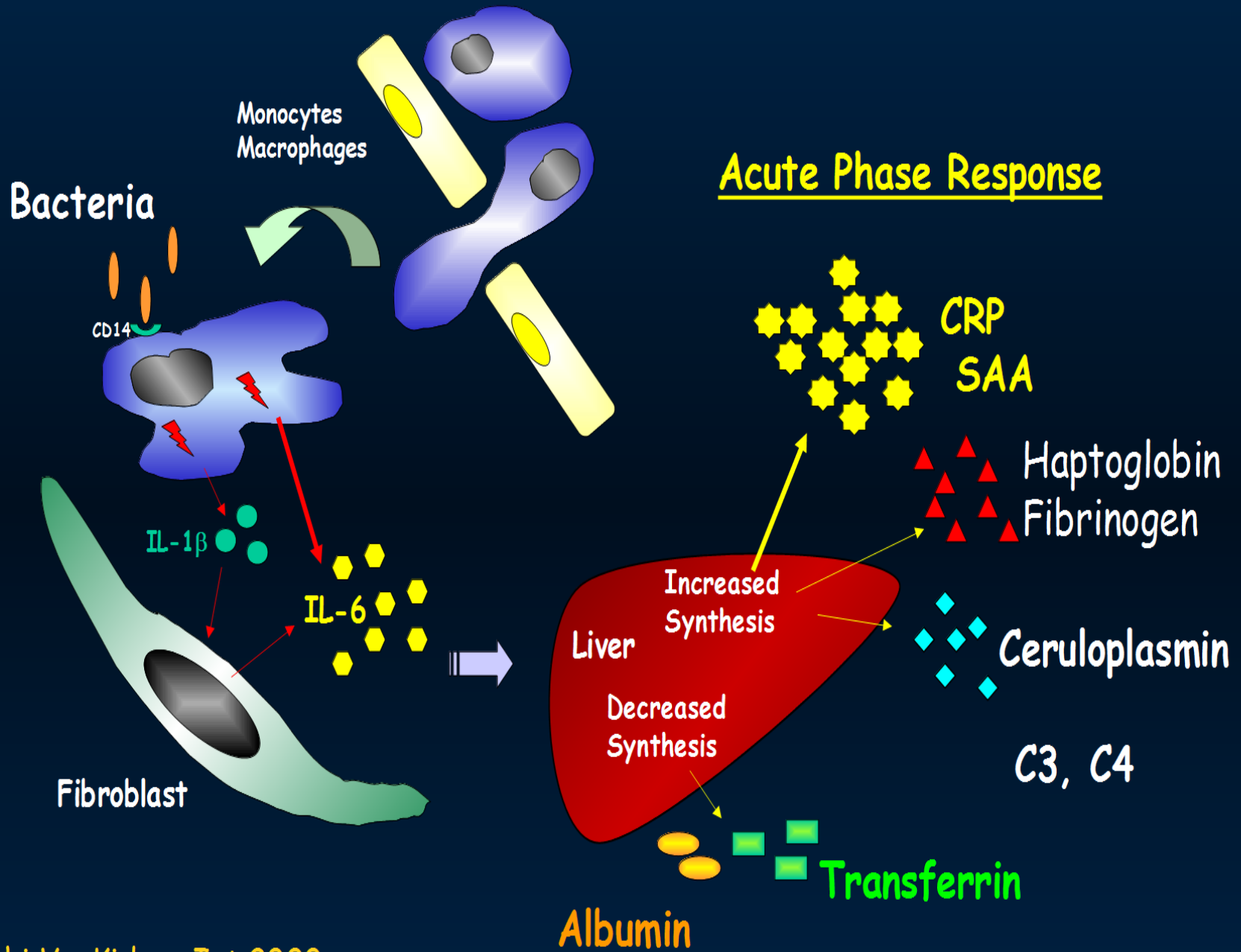
Asymmetric dimethylarginine

Oxidative stress

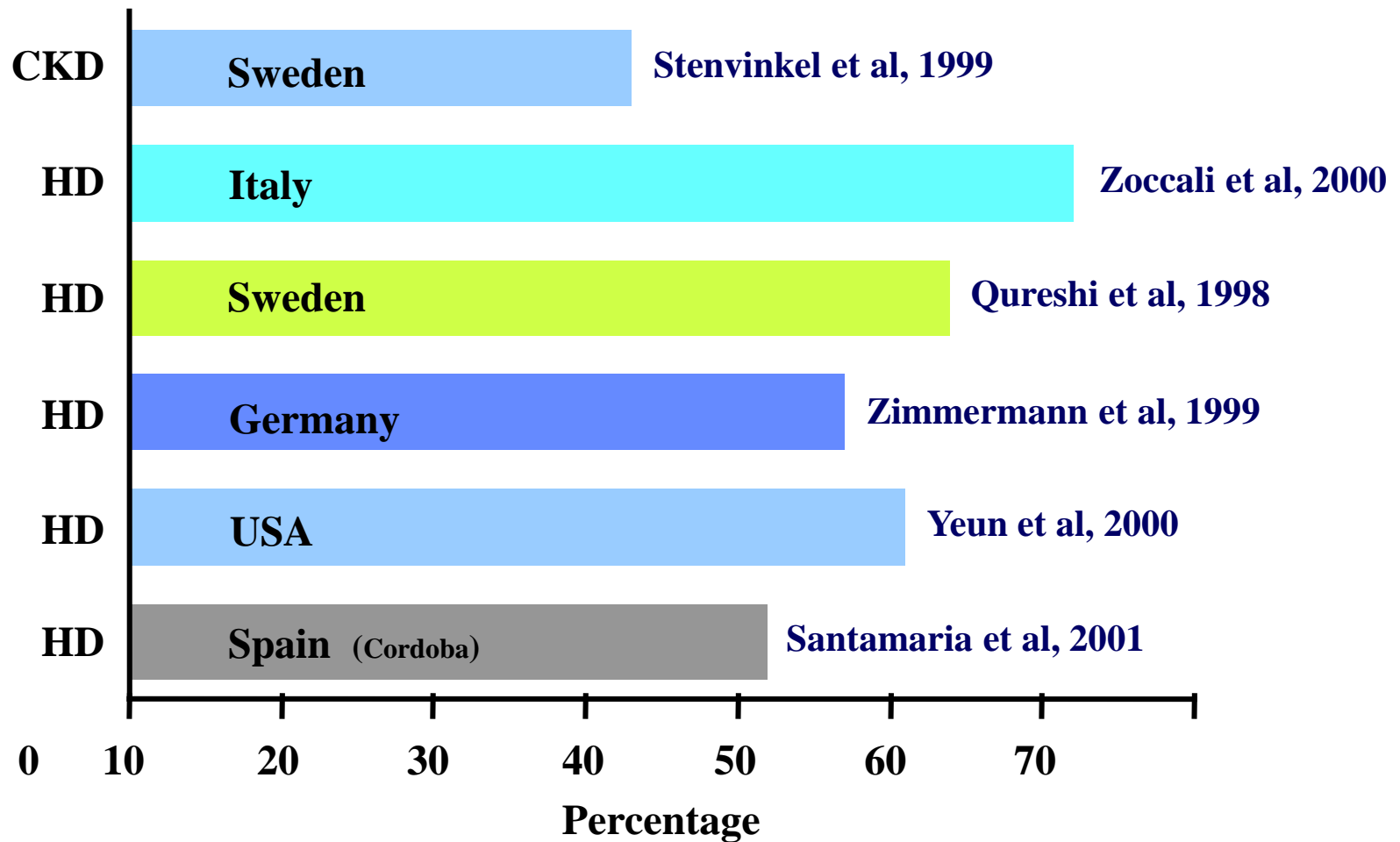
Hypermetabolism

Advanced glycation end products

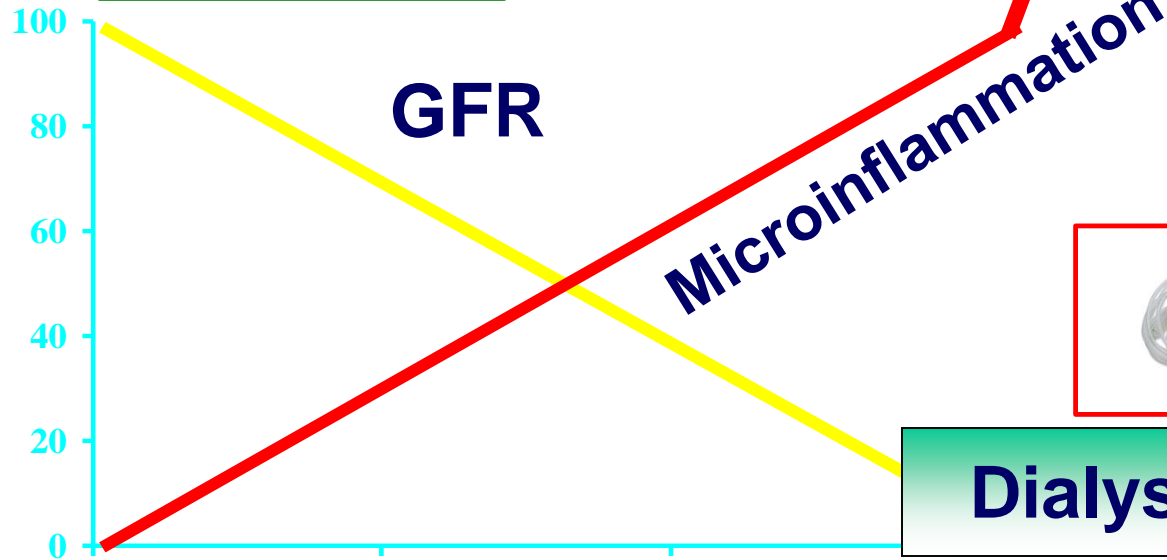
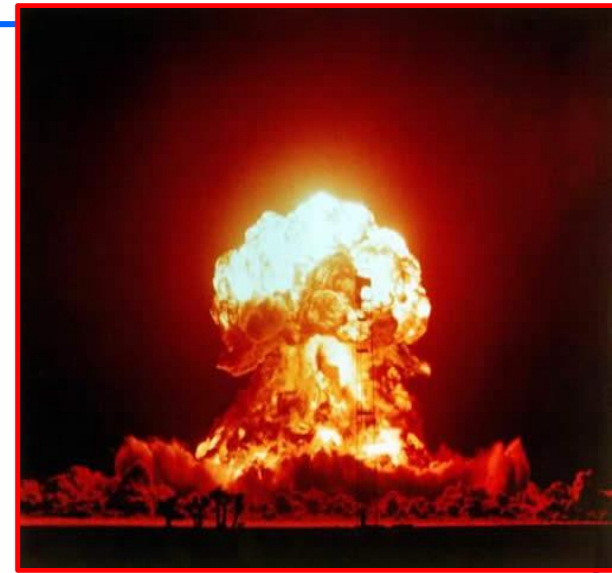
Chronic inflammation



Inflammation is common in CKD and HD patients

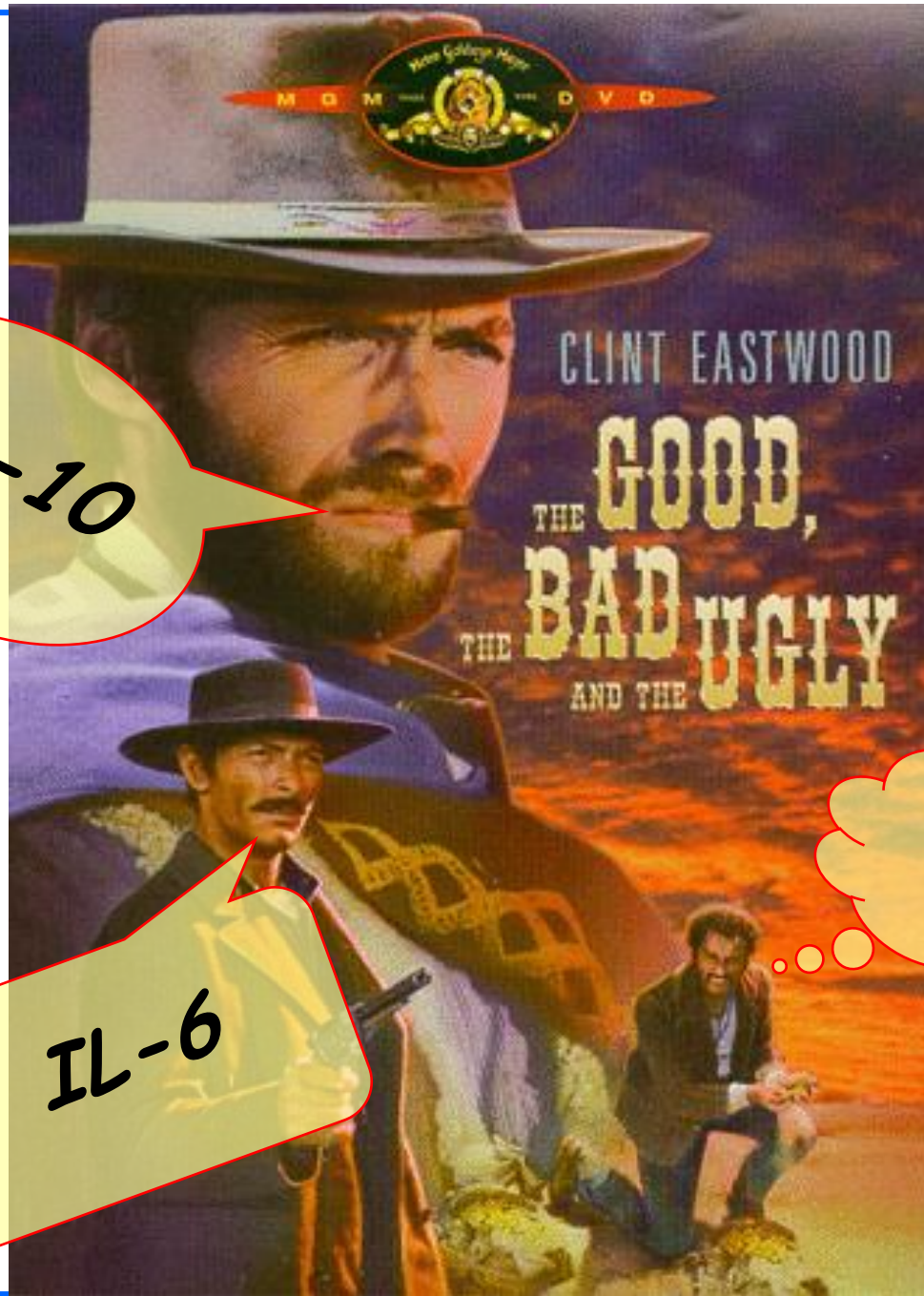


Microinflammation in uremia and in dialysis



Dialysis



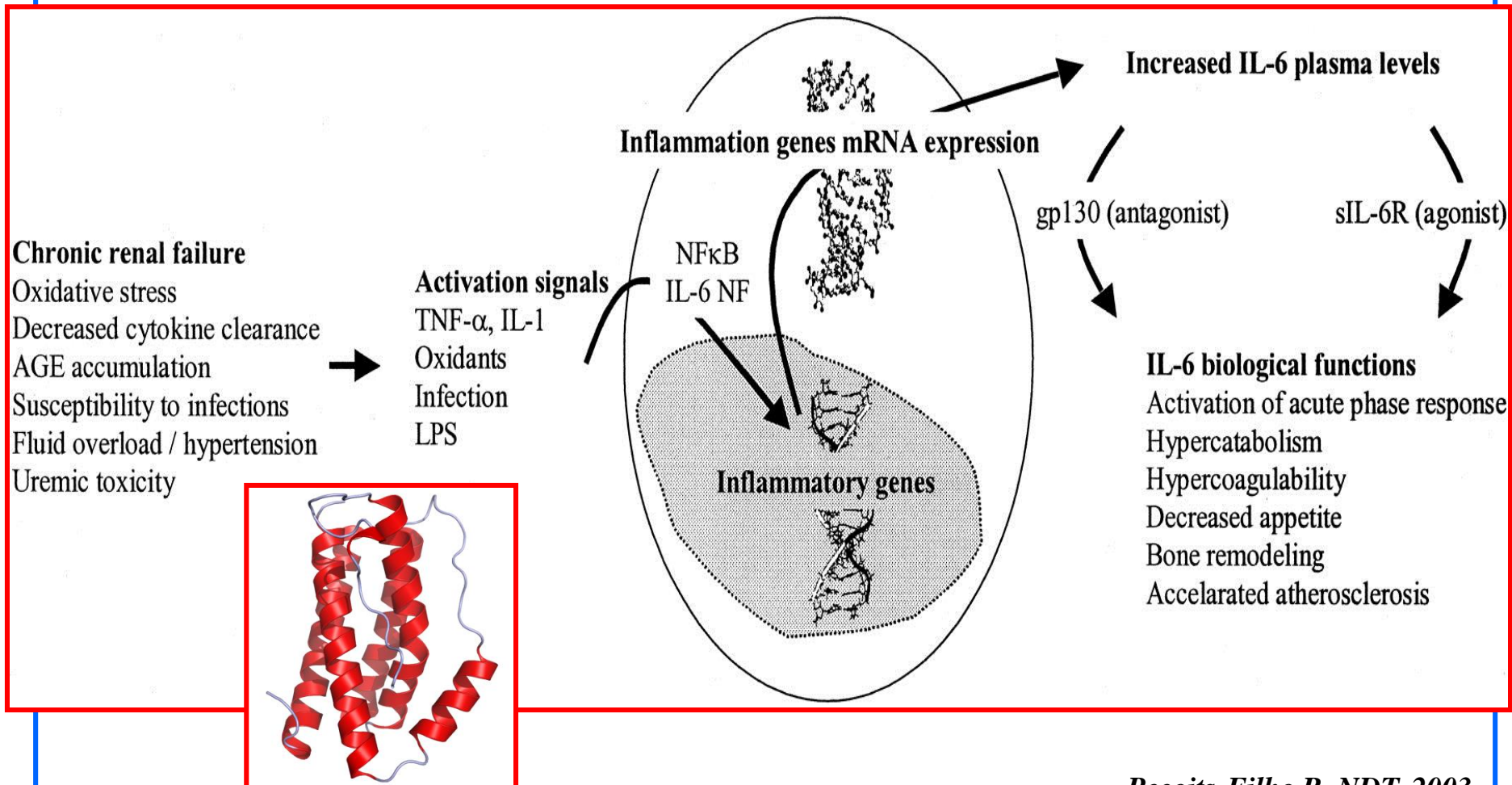


IL-10

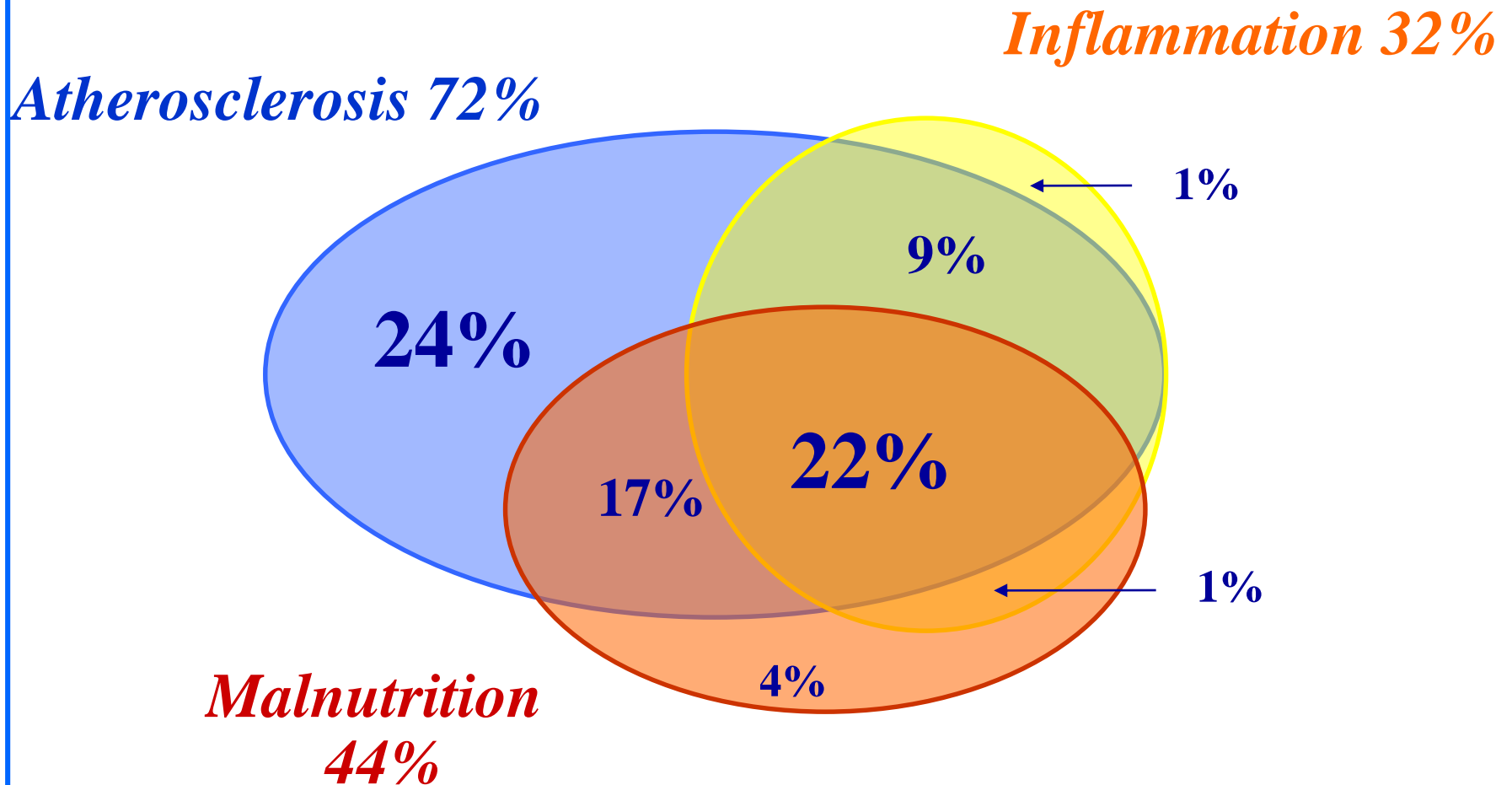
IL-6

IL-8

Update on interleukin-6 and its role in chronic renal failure



ASSOCIATION BETWEEN MALNUTRITION, INFIAMMATION AND ATHEROSCLEROSIS (MIA)





Obesity and the Kidney - Talk Outline

- Pathogenesis



Obesity

Obesity is defined as an accumulation of adipose tissue that is of sufficient magnitude to impair health.

Excess weight is best assessed by the body mass index or **BMI**.

Normal BMI range is **18.5** to **25** kg/m².

Individuals with BMI above **30** kg/m² are classified as **Obese**; those with BMI between **25** to **30** kg/m² are considered **Overweight**.

The term obesity will be applied to both the truly obese and the overweight.

Risks of Obesity Throughout the Course of Kidney Disease



The number of patients starting dialysis with a BMI greater than 35 has increased **64%** over the past decade.



If this continues, it is predicted that **20%** of all patients will initiate dialysis in this already obese state.



Intervention and attempts to prevent obesity before ESRD is beneficial.

Obesity and Kidney Disease

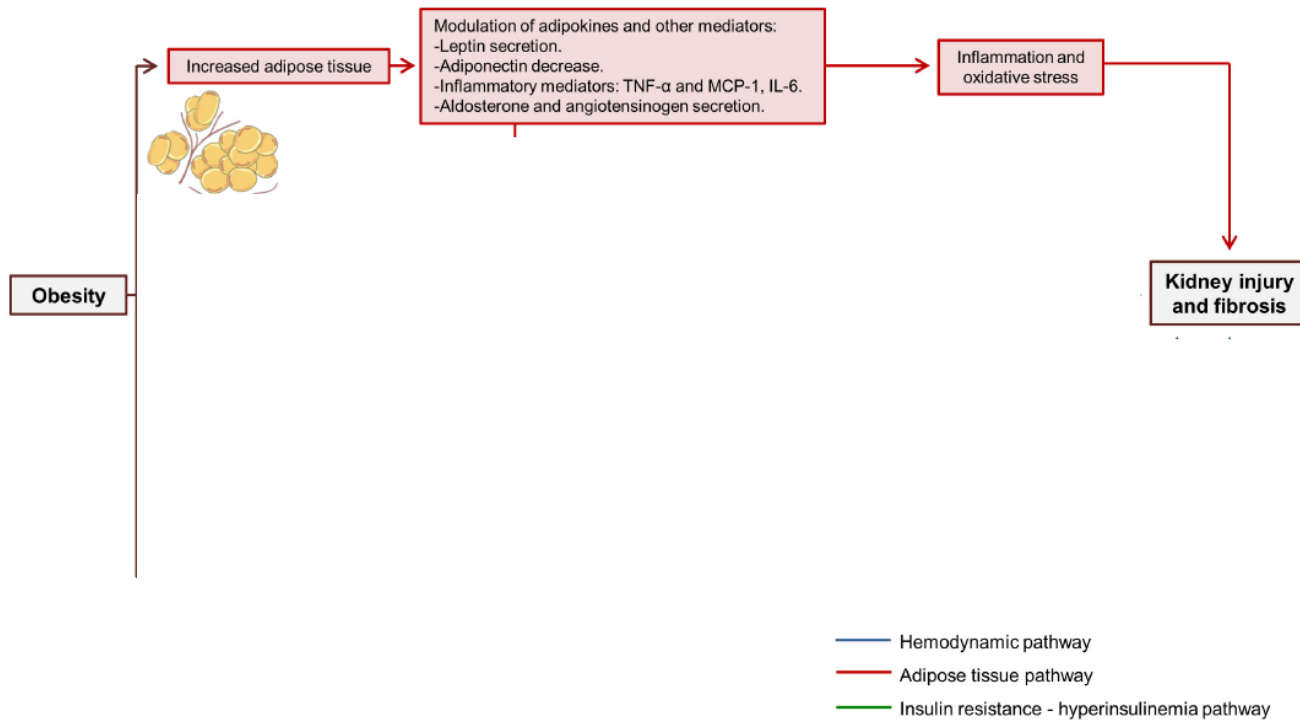
1. **Obesity** is associated with renal hemodynamic changes known to cause **CKD**.

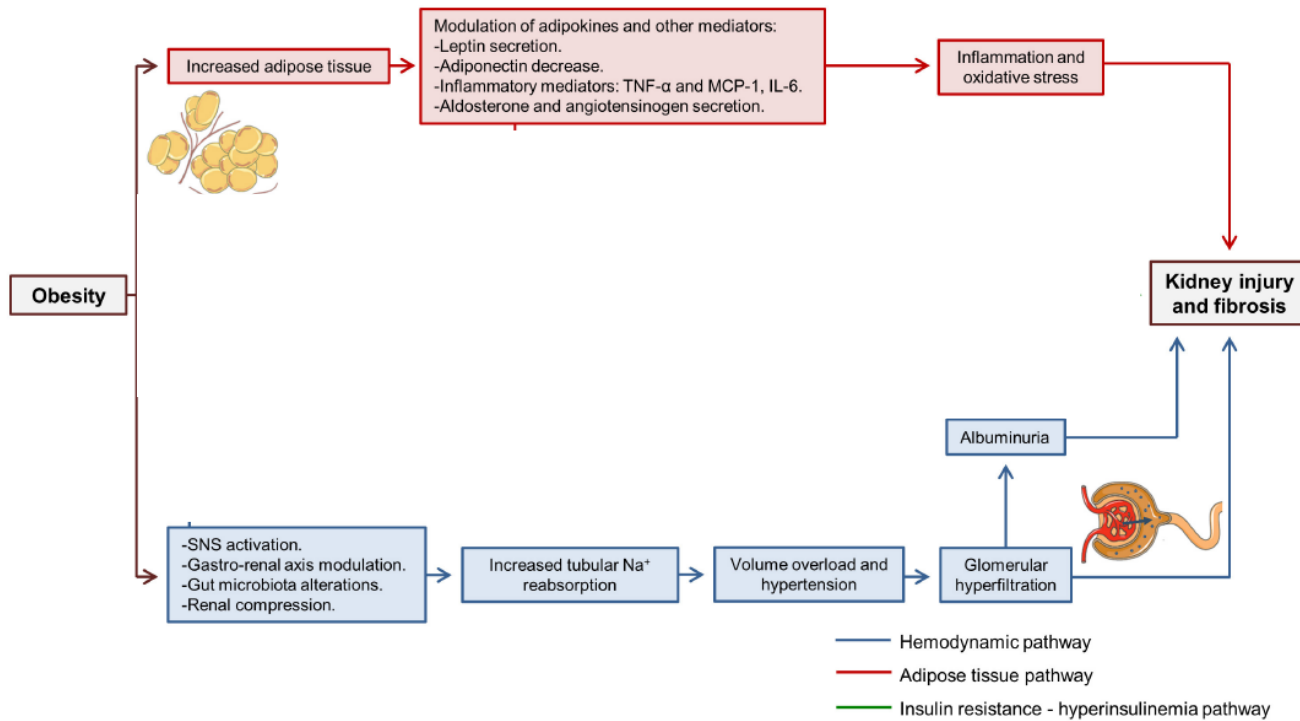
2. Adipose tissue possesses inflammatory and hormonal mediators of kidney injury.

3. Population studies have shown an association of **Obesity with CKD**.

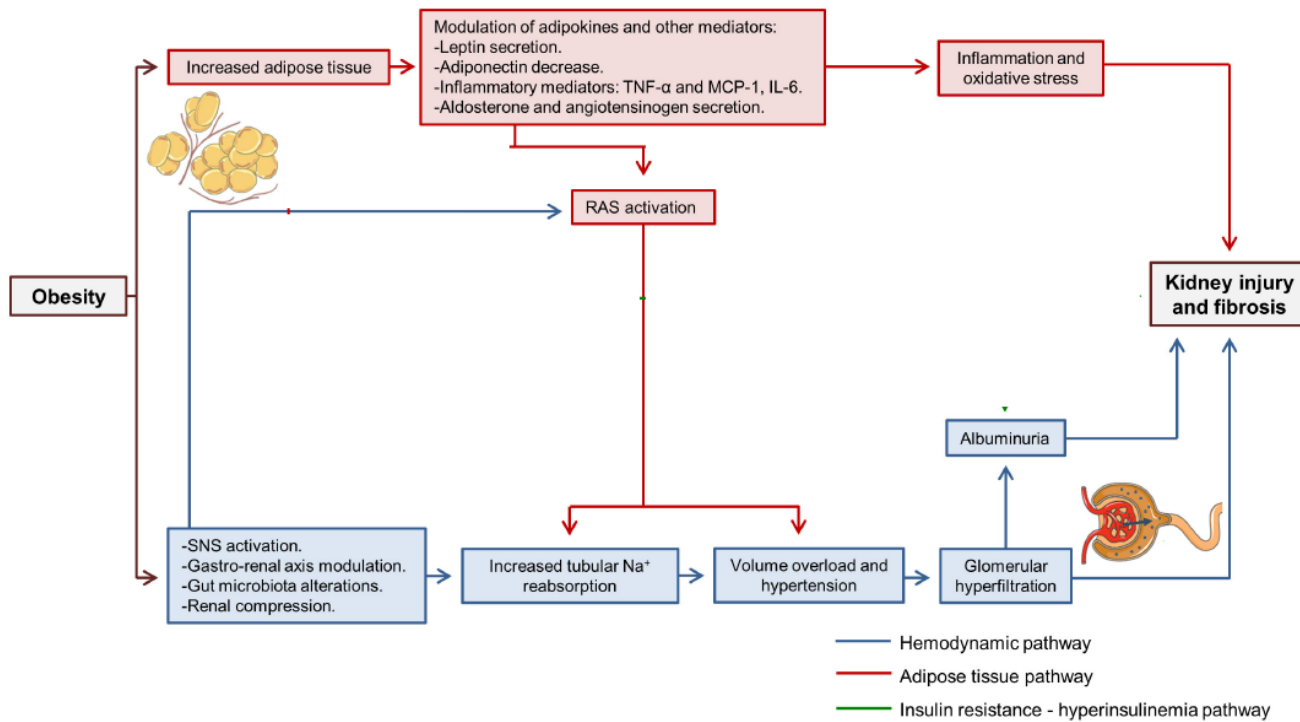
4. CKD patients who are obese progress to **ESRD** more rapidly.

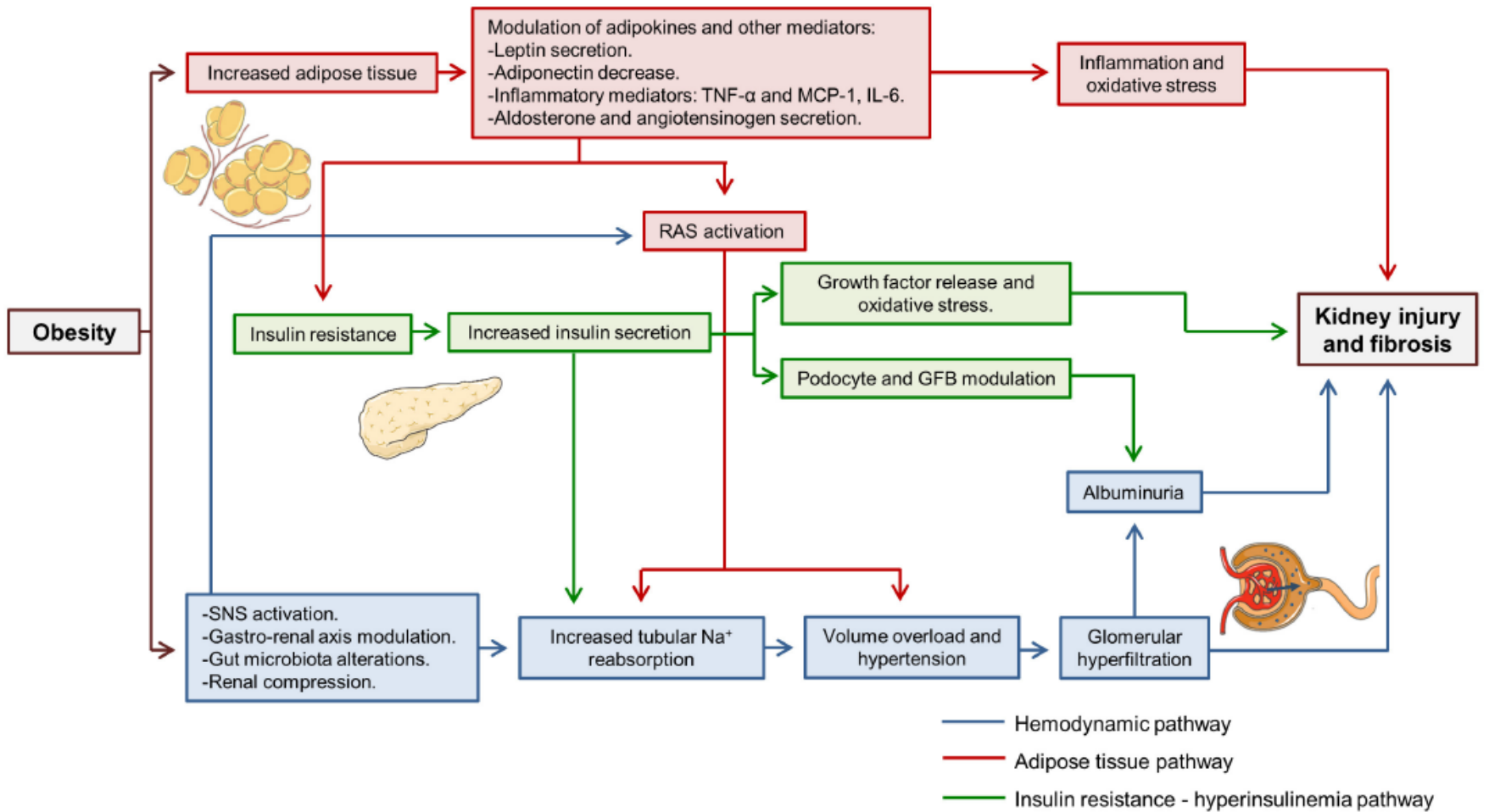
5. Obesity is associated with known risk factors for CKD – **metabolic syndrome, DM, HTN, and sleep apnea**.





Front Med (Lausanne). 2021 Apr 13;8:655871.





Front Med (Lausanne). 2021 Apr 13;8:655871.

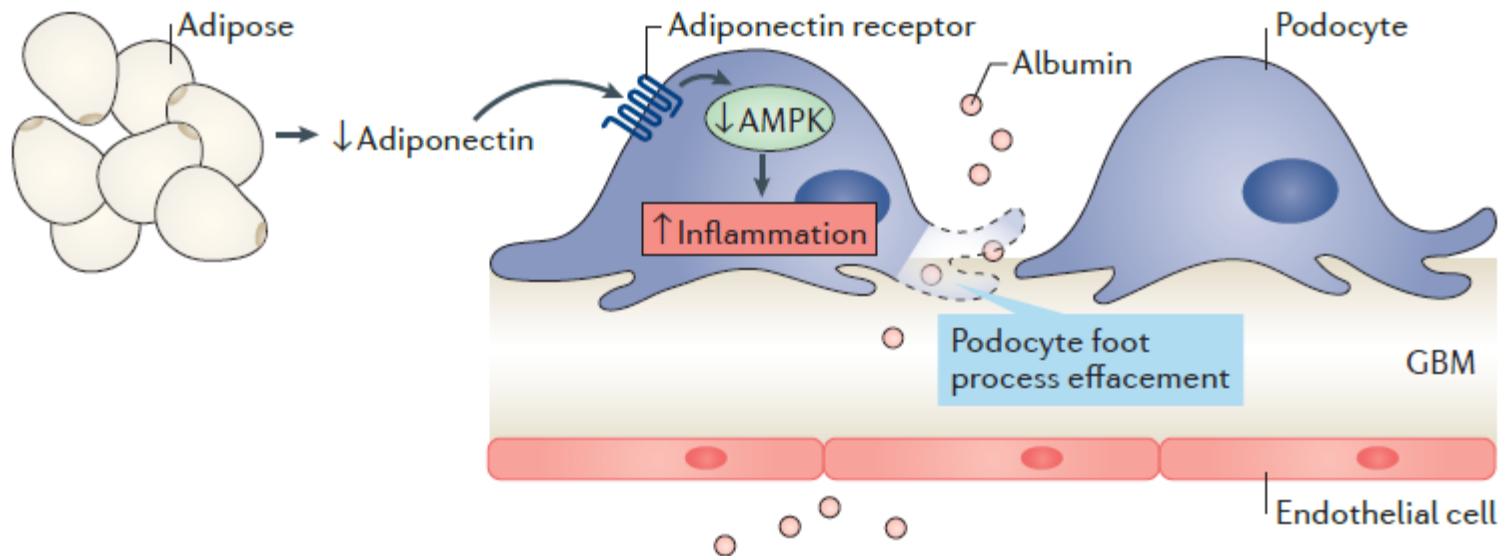


Figure 6 | **Effects of adiponectin on podocyte function.** Increased adipose mass leads to decreased levels of adiponectin and reduced activation of the adiponectin receptor on podocytes, reduced AMPK activation and increased inflammation. In mice, lack of adiponectin leads to foot process effacement and albuminuria. The early onset of albuminuria in patients with obesity and hypertension might also be associated with reduced adiponectin levels.

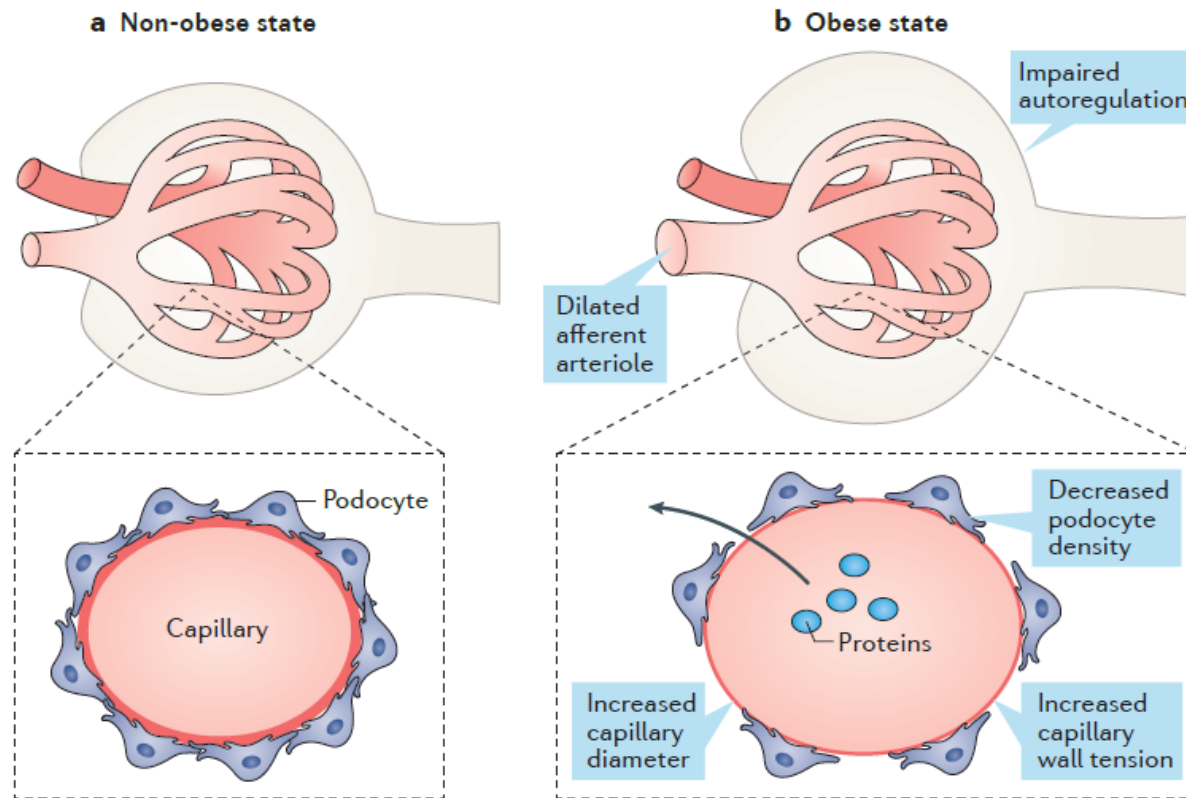


Figure 1 | **Mechanisms of kidney injury in the setting of obesity.** Obesity, especially morbid obesity, can induce afferent vasodilation in order to augment glomerular filtration rate. Glomerular autoregulation might be impaired and elevated systemic blood pressures could then be transmitted to the glomerular capillaries leading to barotrauma. Glomerular capillary dilation might heighten susceptibility to barotrauma, and the need for podocytes to cover a larger surface area could lead to proteinuria.

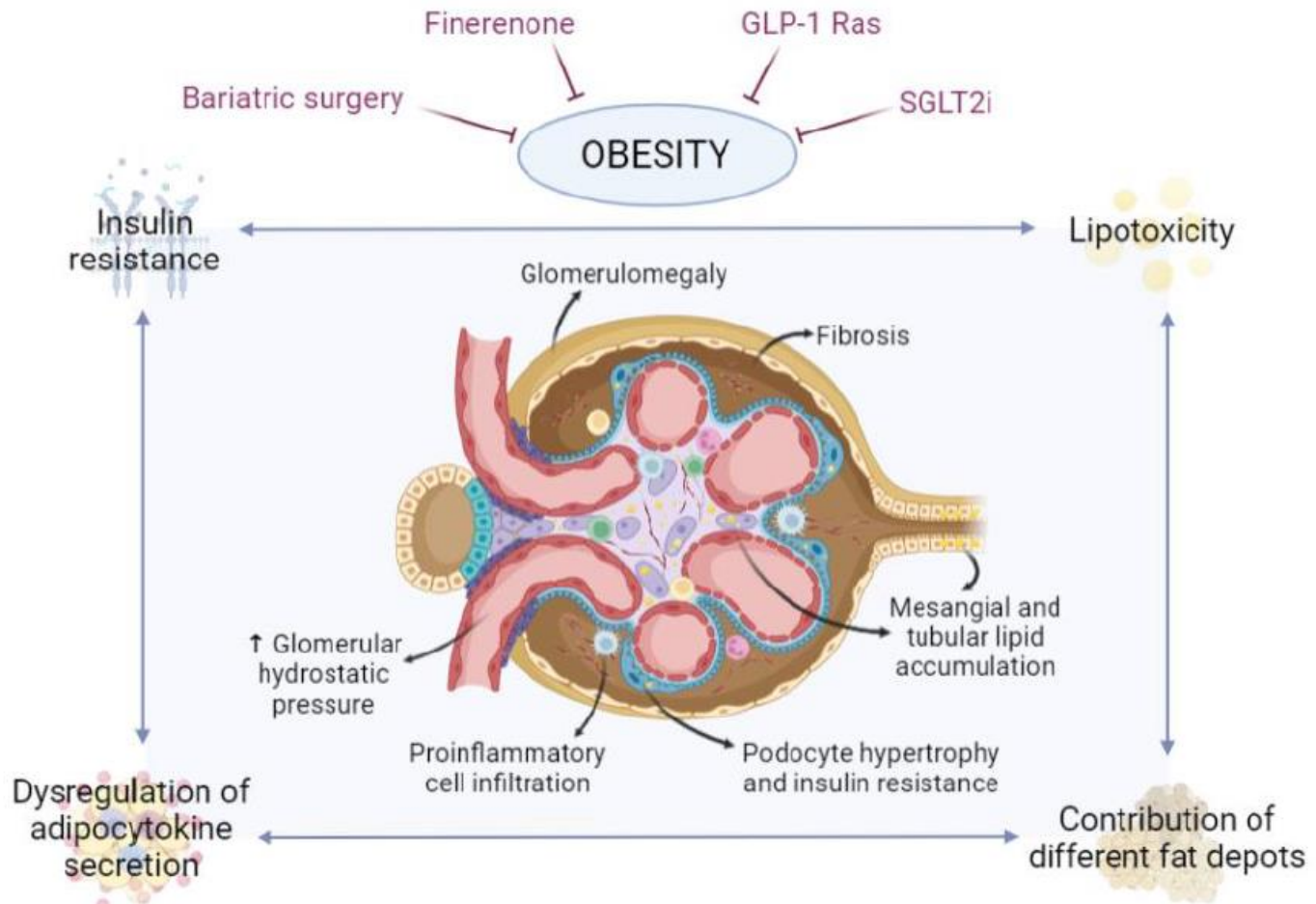


TABLE 1 Clinical consequences of obesity in the kidney.

<ul style="list-style-type: none">• Fatty kidney
<ul style="list-style-type: none">• Salt-sensitivity
<ul style="list-style-type: none">• Albuminuria and proteinuria (sub-nephrotic levels)
<ul style="list-style-type: none">• Hyperfiltration and progressive chronic kidney disease
<ul style="list-style-type: none">• Increase in the risk of progression of non-obese-related nephropathies
<ul style="list-style-type: none">• Indirect effects mediated by sleep-apnea and nocturnal hypoxemia and non-alcoholic fatty liver disease
<ul style="list-style-type: none">• Nephrolithiasis

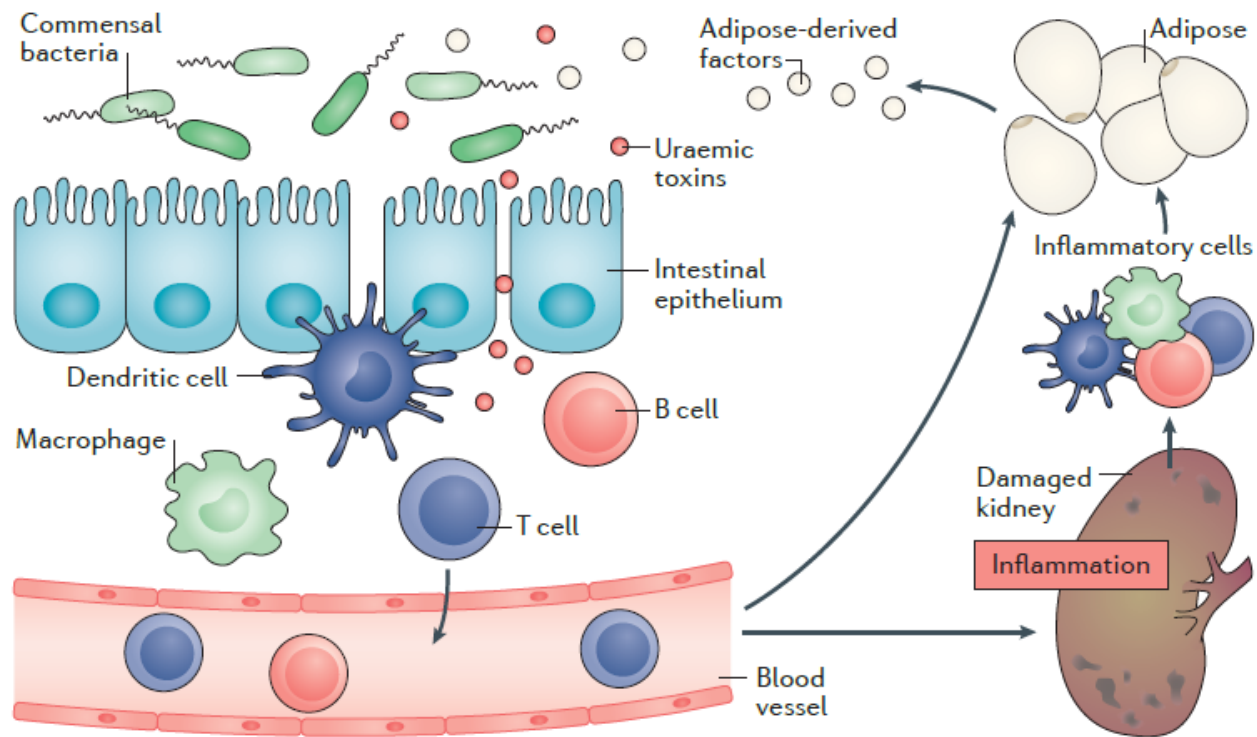
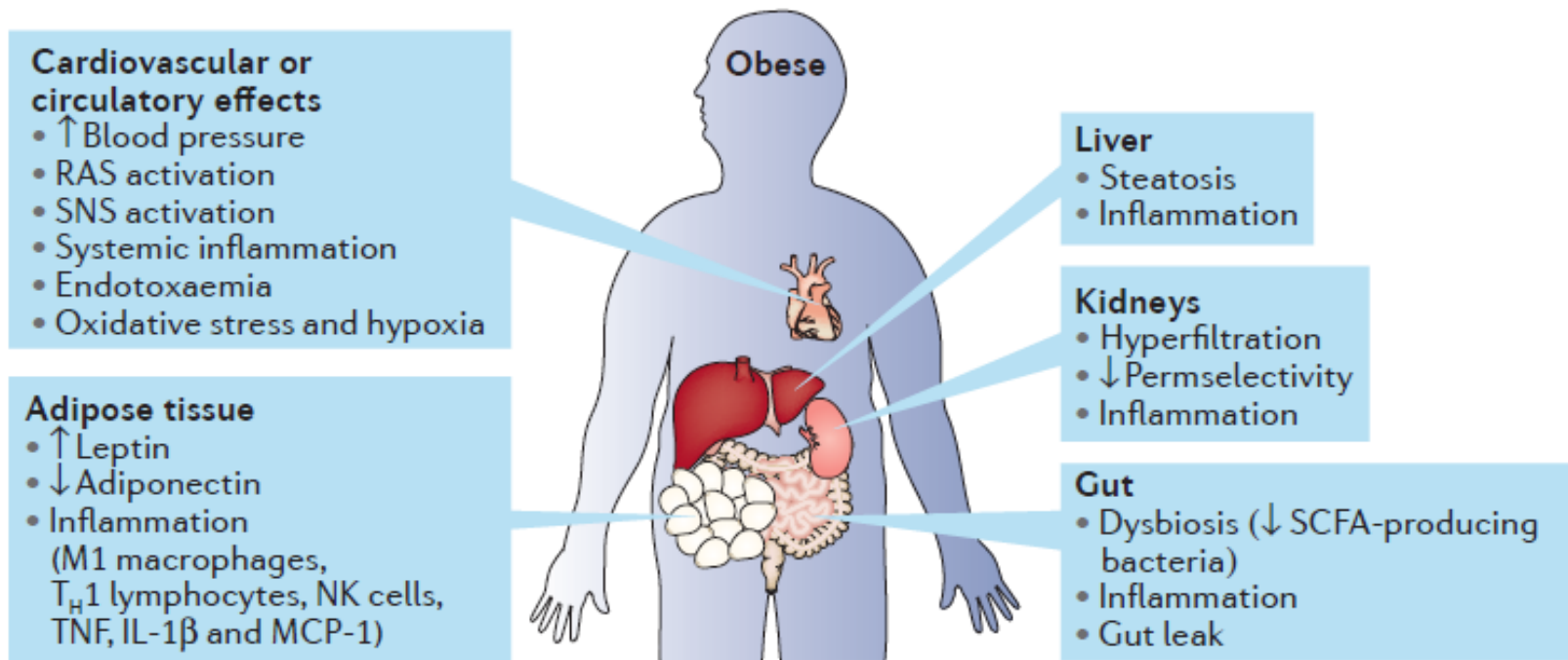
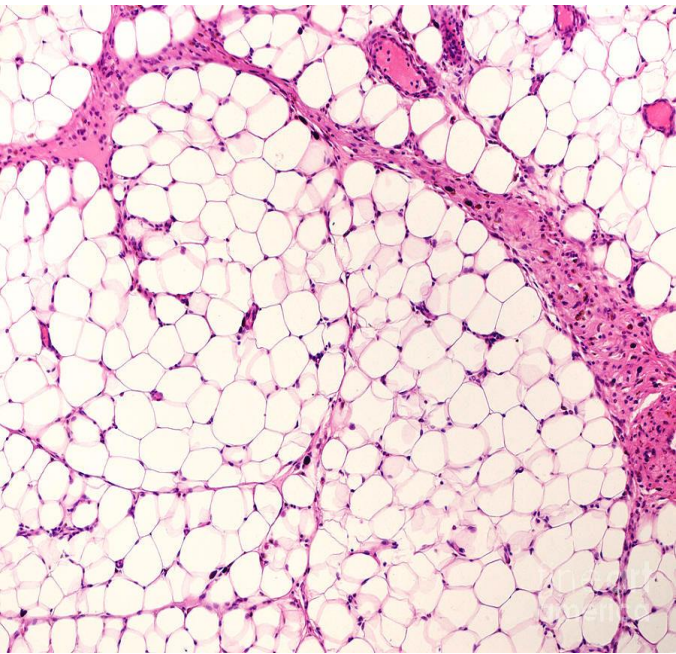


Figure 4 | **Interactions between adipose, the microbiome and kidney.** Alterations in microbiota in the presence of increased adiposity and renal dysfunction, arising from the effects of adipose-derived factors and uraemic toxins, respectively, could disrupt intestinal homeostasis, leading to leakage of inflammatory factors from the gut and amplification of inflammatory responses. Conversely inflammation within the damaged kidney could directly induce the migration and activation of immune cells into adipose tissue, further inducing inflammation and the release of adipose-derived factors.



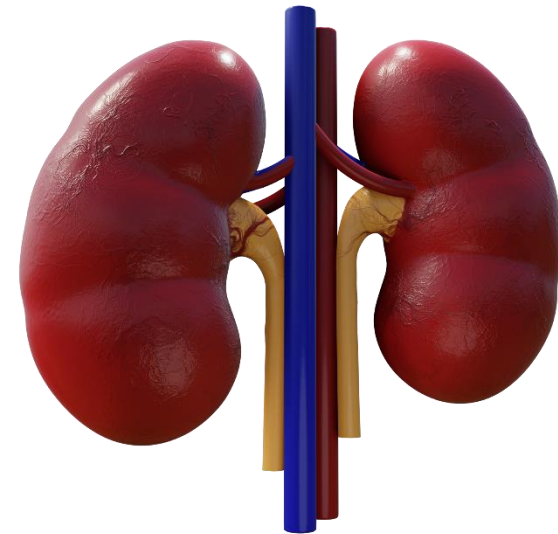
Impact of obesity on the kidney

White adipose tissue



- Microalbuminuria/proteinuria
- Glomerulopathy
- Inflammatory cytokines
- Increased renal plasma flow
- Enhances progression of other renal diseases
- Diabetic nephropathy
- Reduced kidney graft survival

Kidney



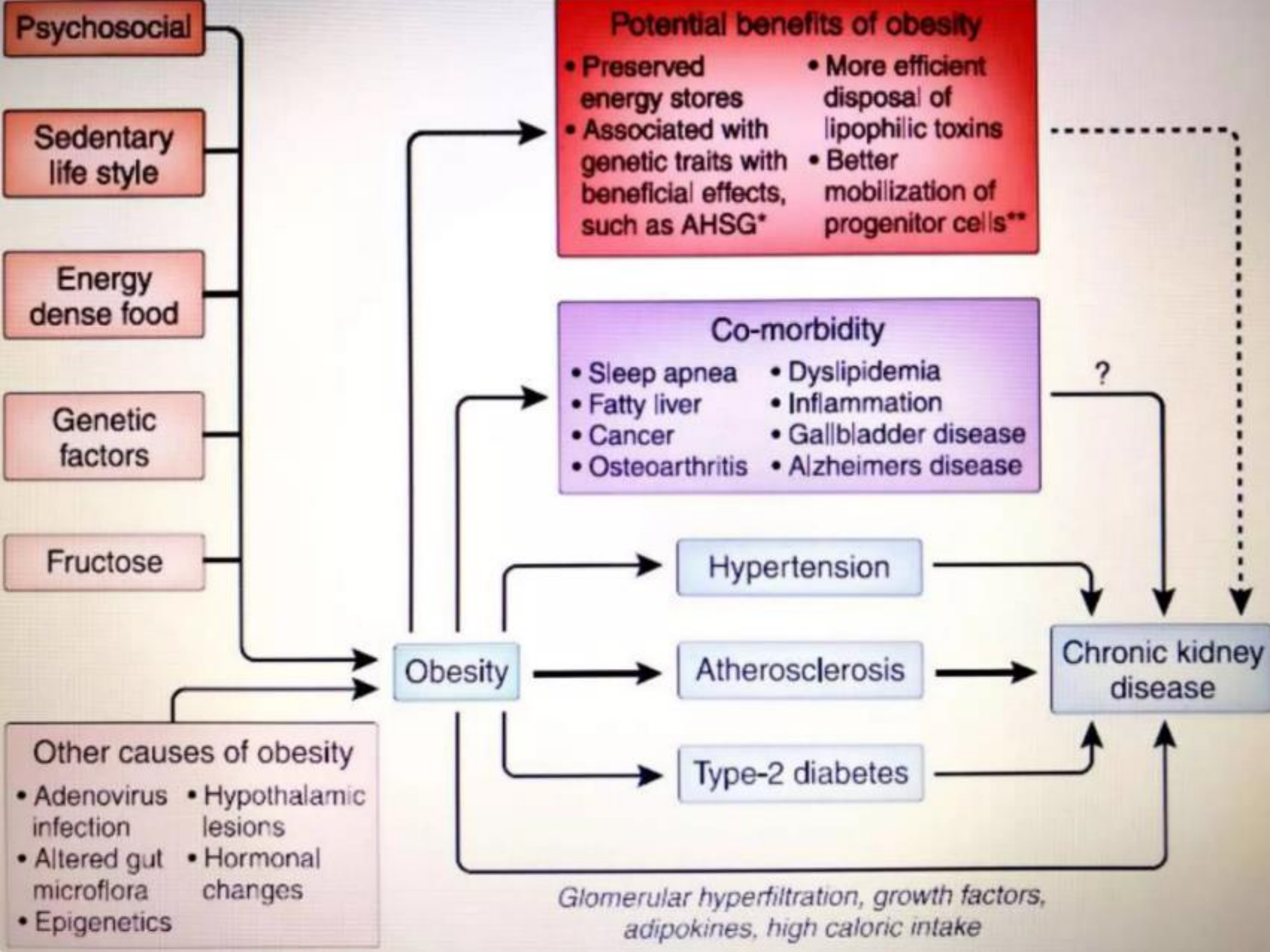
CKD Associated with Decreased Muscle Mass

- In a patient with CKD, BMI is affected by fat or muscle mass and fluid status.

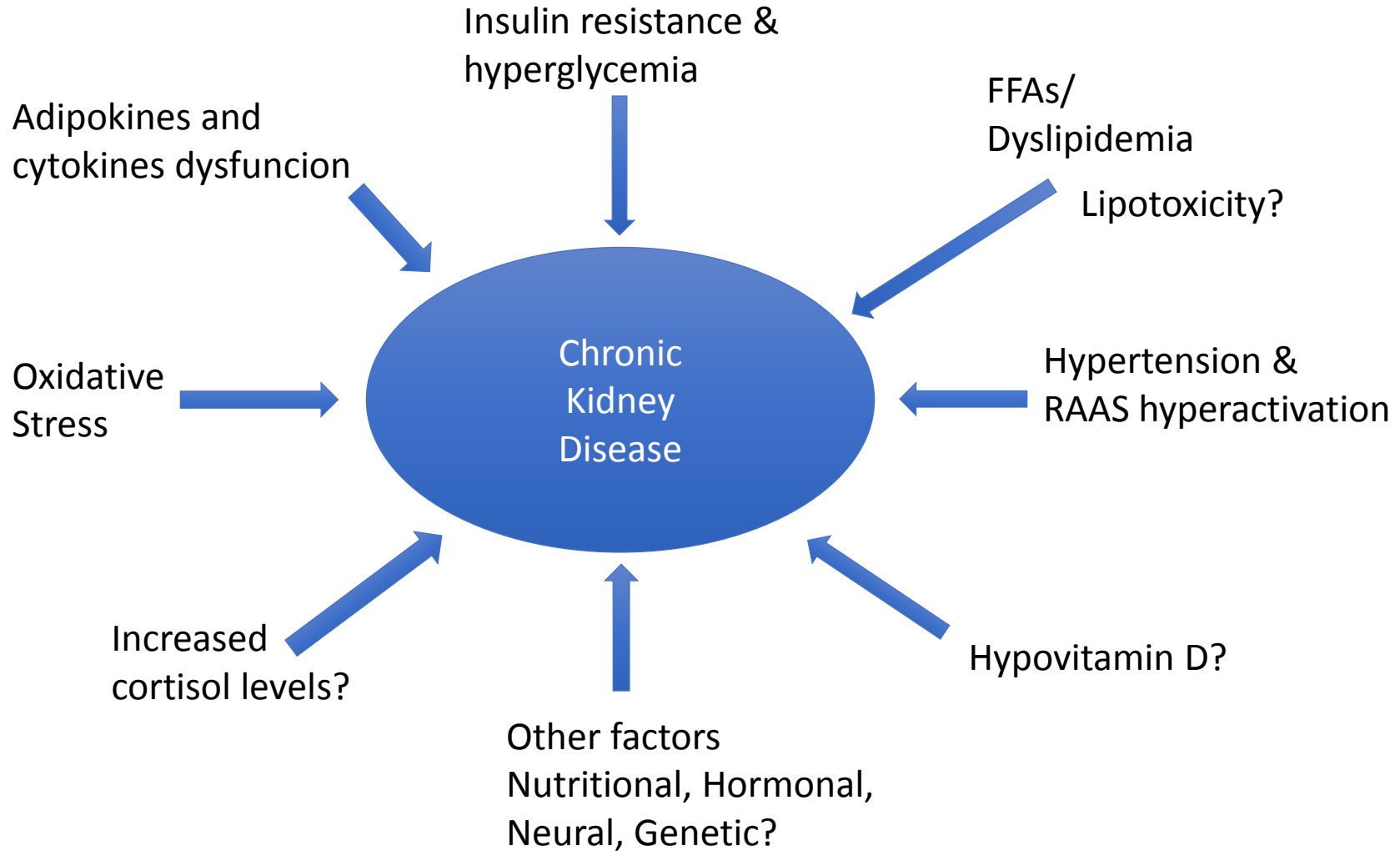
- Therefore, in a patient with CKD, lower BMI may reflect decreased fat (mostly subcutaneous) or decreased muscle mass.

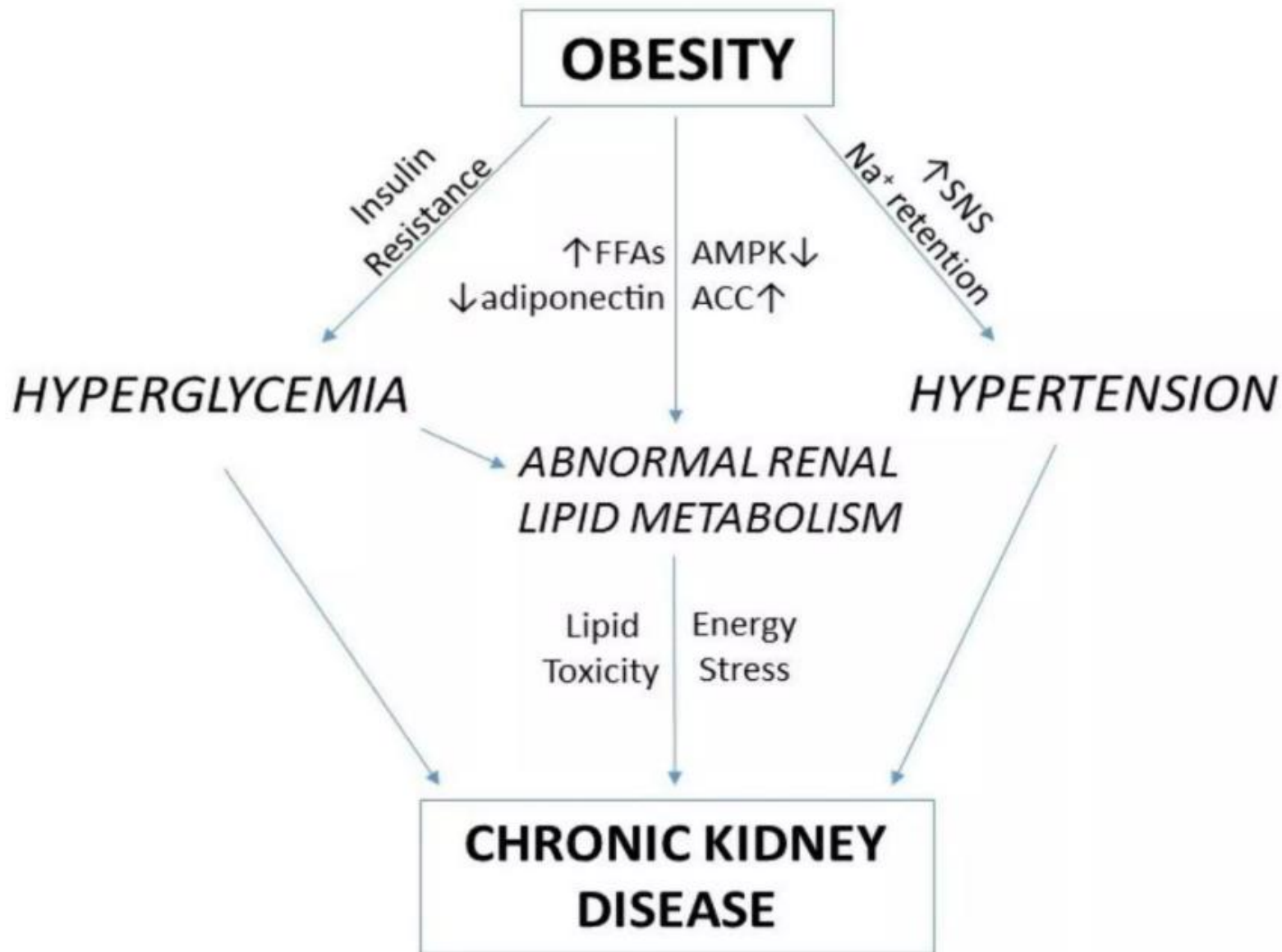
- The ultimate effect of BMI on outcomes will depend on the relative contributions of each as well as the amount of visceral fat.

- Therefore, BMI might not be the ideal anthropometric measurement for assessing obesity in patients with CKD.



Obesity & Obesity related factors

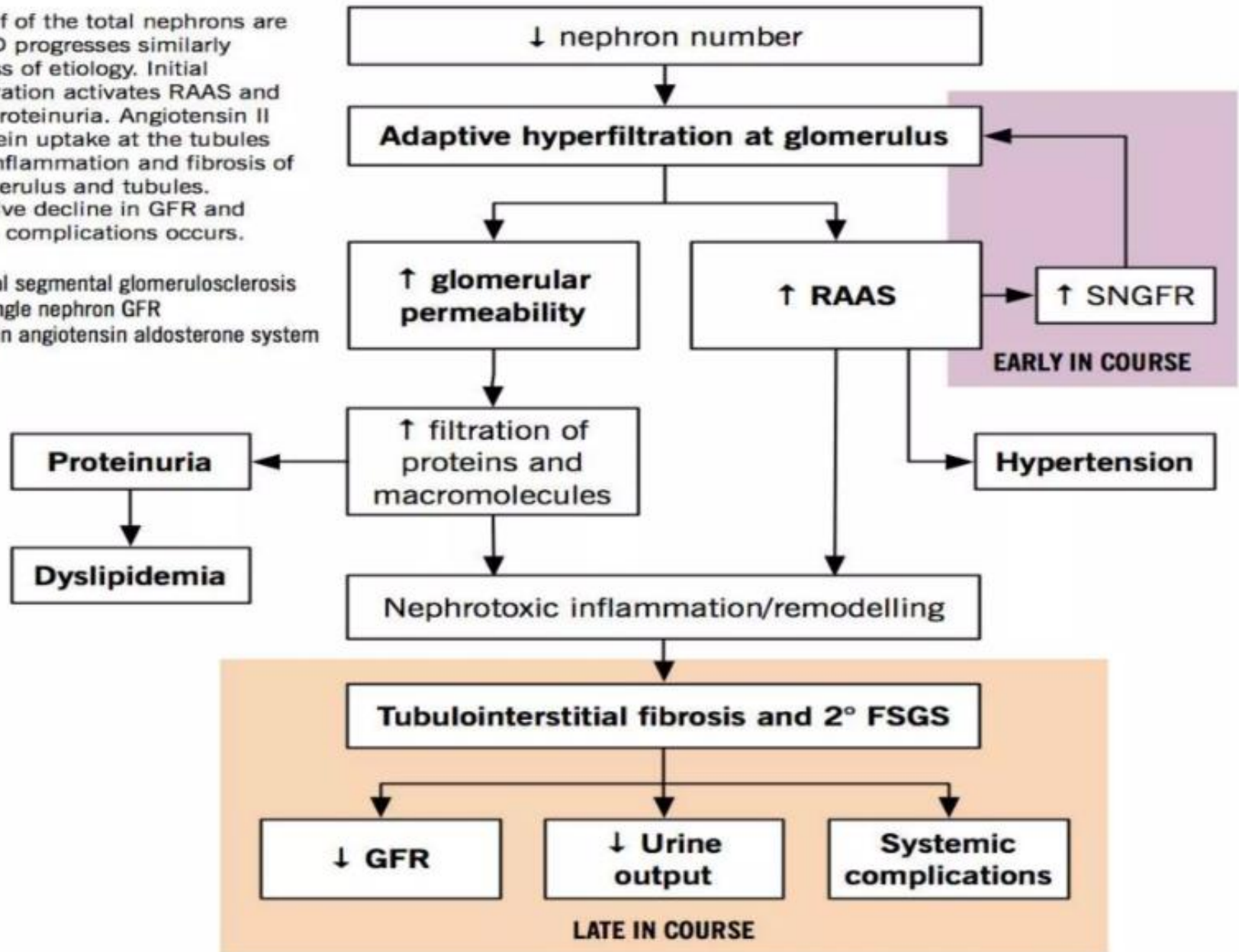




Pathogenesis of chronic kidney disease

Once half of the total nephrons are lost, CKD progresses similarly regardless of etiology. Initial hyperfiltration activates RAAS and causes proteinuria. Angiotensin II and protein uptake at the tubules causes inflammation and fibrosis of the glomerulus and tubules. Progressive decline in GFR and systemic complications occurs.

FSGS Focal segmental glomerulosclerosis
SNGFR Single nephron GFR
RAAS Renin angiotensin aldosterone system





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- Reverse Epidemiology of Obesity in Hemodialysis Patients (Obesity Paradox)



Obesity and the Kidney - Talk Outline

- Clinical consequences

Obesity-associated structural lesions and functional disorders

Renal dysfunction

Laboratory

Albuminuria

Proteinuria

Sub-nephrotic syndrome

GFR decline (CKD and ESRD)

Pathology

Fatty kidney

Glomerulomegaly

Glomerulosclerosis

FSGS

Renal replacement therapy

Hemodialysis

Dialysis time required

Vascular Access

Catheter functionality

Proximal calciphylaxis

Peritoneal

Catheter malfunction

Exit site infection

Kidney transplantation

Graft recipients

Delayed graft function

Risk of rejection

Wound infection

Donors

Delayed graft function

Risk of CKD and ESRD

Obesity and Its Impact on Kidney Stone Formation

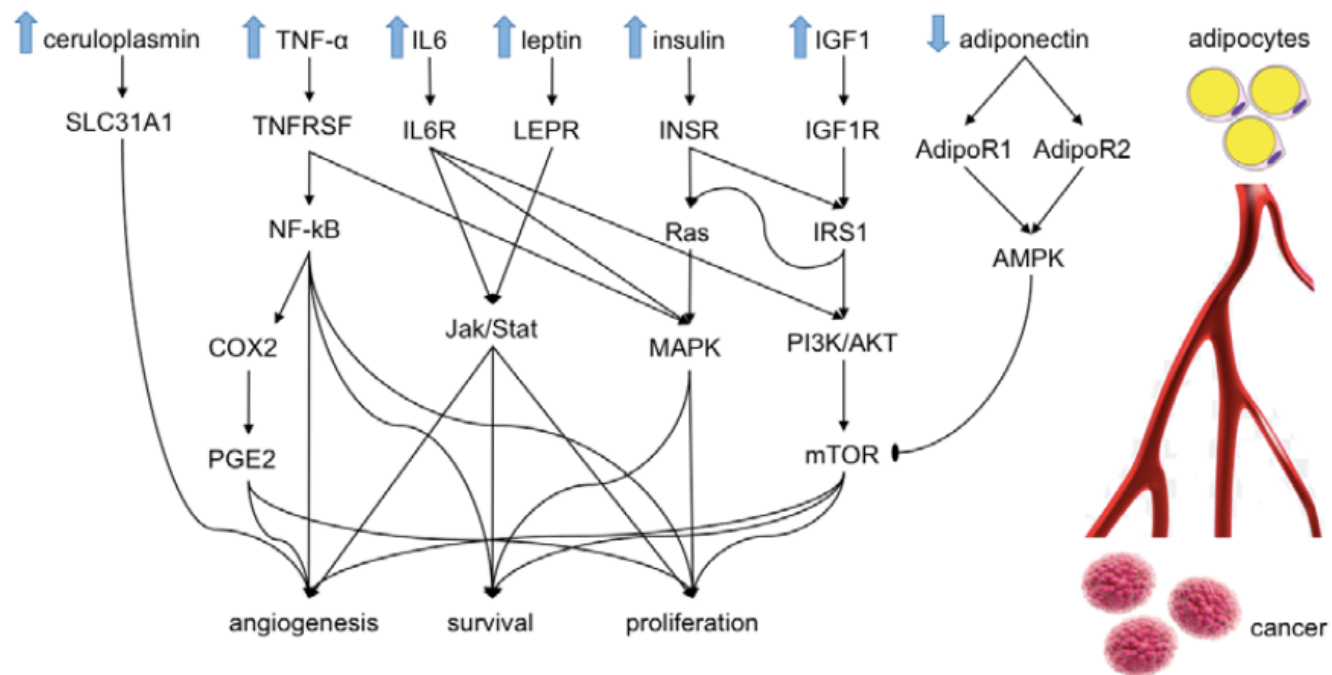
MAIN POINTS

- Large numbers of people are obese and thus more at risk for developing kidney stones.
- Because obesity is associated with numerous co-morbidities, it is somewhat difficult to attribute its total impact on stone risk. However, there have been studies indicating an independent association between visceral obesity and kidney stone formation.
- Calcium oxalate and uric acid stones are the most common stone found in obese patients, with calcium oxalate stones still being the most prevalent in obese and non-obese populations. The increased levels of uric acid stones, however, are enriched amongst obese stone formers.
- The inflammation and oxidative stress that are known to be associated with obesity may play a role in stone risk.
- One must also be aware that certain approaches to weight reduction may promote kidney stone formation.



Review

The Role of Obesity in Renal Cell Carcinoma Patients: Clinical-Pathological Implications





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Obesity and the Kidney - Talk Outline

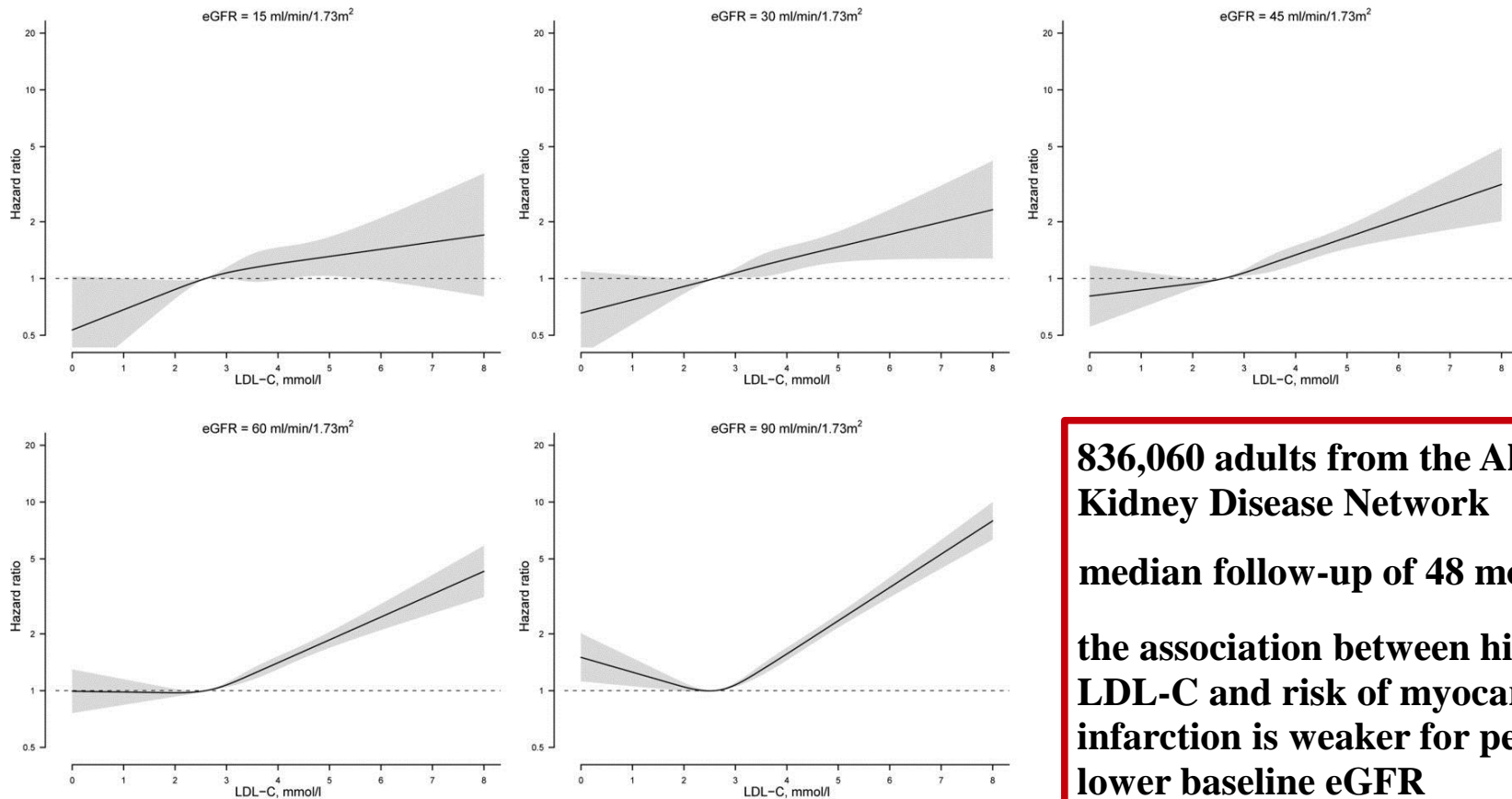
- Reverse Epidemiology of Obesity in Hemodialysis Patients (Obesity Paradox)

What is meant by Reverse Epidemiology?

- While obesity, hypertension and hypercholesterolemia (and other parameters) are well-established indicators of poor cardiovascular health and death in general population,
- Reverse epidemiology holds that these states actually increase the chance of survival in many people including dialysis patients.

Adjusted relation between LDL-C and HR of myocardial infarction by eGFR as a continuous variable

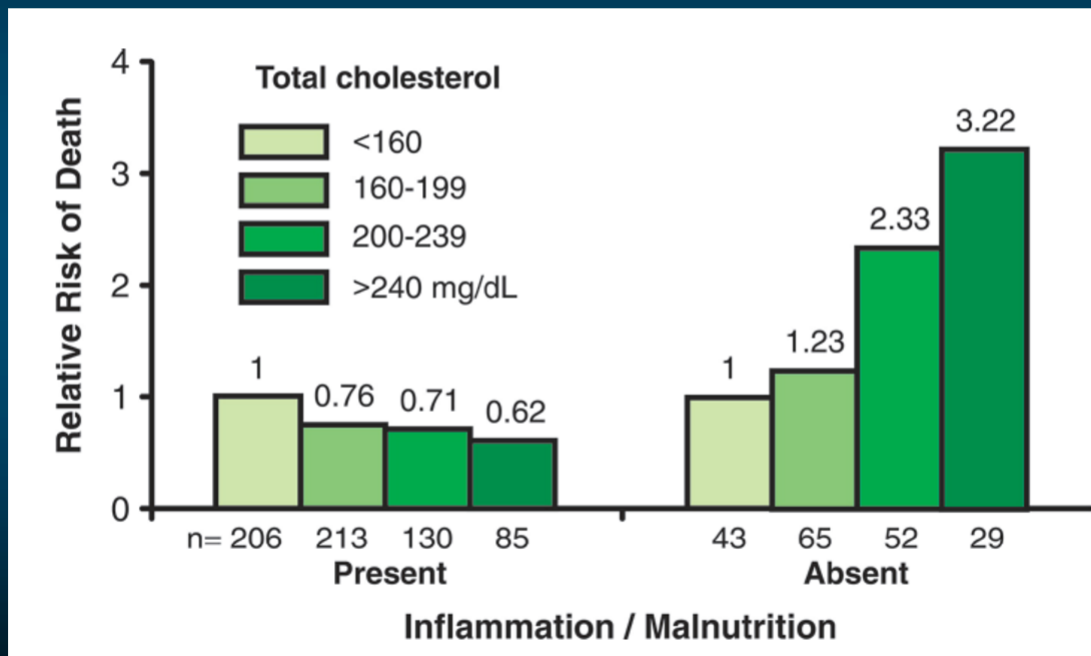
JASN



**836,060 adults from the Alberta
Kidney Disease Network**
median follow-up of 48 months
**the association between higher
LDL-C and risk of myocardial
infarction is weaker for people with
lower baseline eGFR**

Relative risk for all-cause mortality associated with cholesterol in ESRD

The Choices for Healty Outcomes in Caring for ESRD

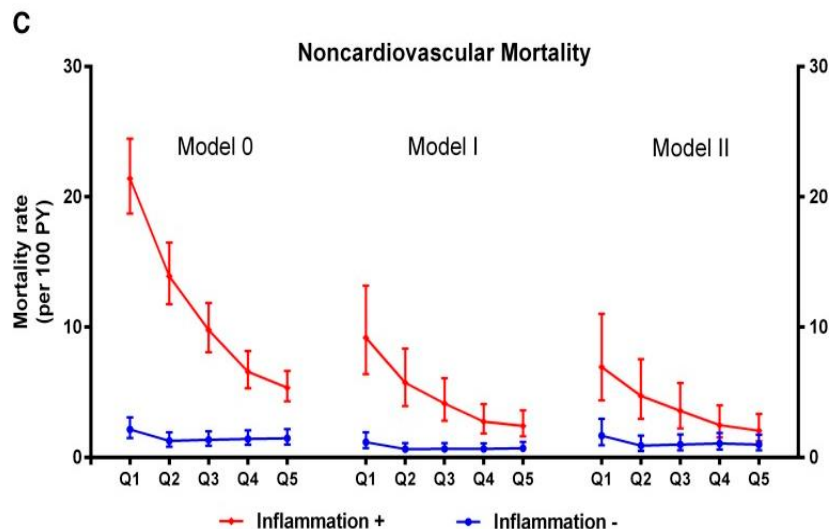
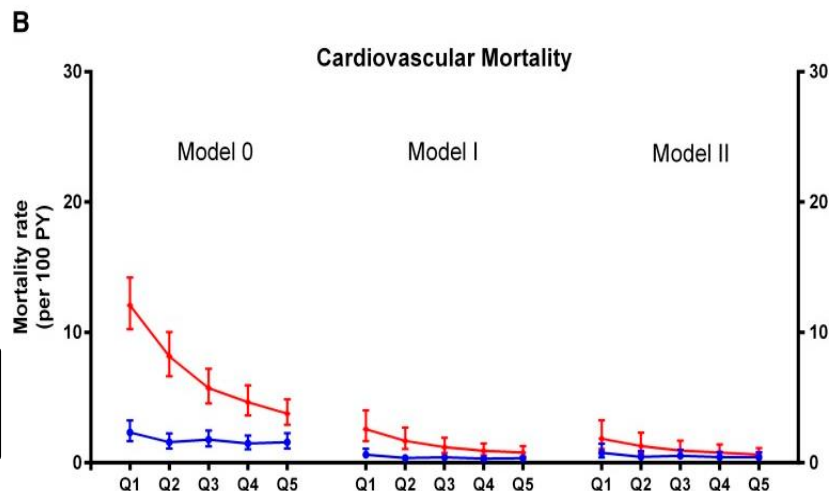
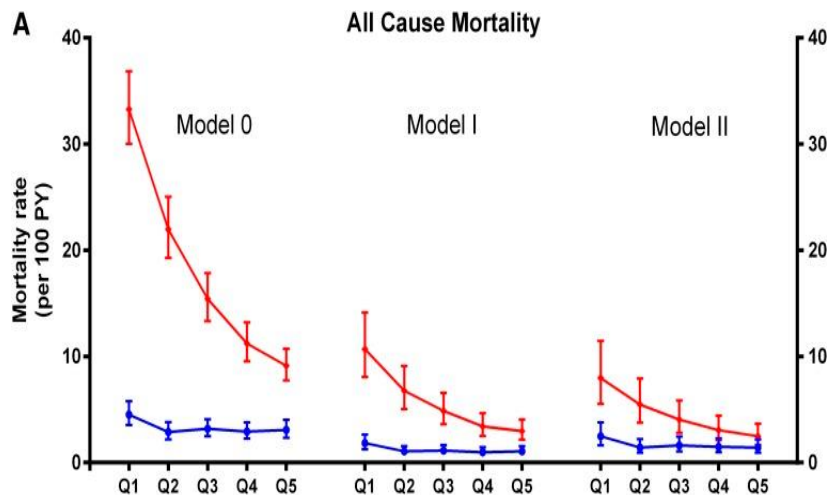


Liu Y, JAMA 291: 451-459, 2004

Inflammation Modifies the Paradoxical Association between Body Mass Index and Mortality in Hemodialysis Patients

Peter Stenvinkel,^{✉*} Iain A. Gillespie,[†] Jamie Tunks,[‡] Janet Addison,[†] Florian Kronenberg,[§] Tilman B. Drueke,^{||} Daniele Marcelli,[¶] Guntram Schemthaler,^{**} Kai-Uwe Eckardt,^{††} Jürgen Floege,^{‡‡} Marc Froissart,^{§§} and Stefan D Anker,^{||} on behalf of the ARO Steering Committee

+ INFLAMMATION - NO INFLAMMATION



No protective effect was associated with higher BMI quintiles in noninflamed patients. Conversely, higher BMI associated with lower all-cause mortality risk in inflamed patients. Thus, whereas a protective effect of high BMI was observed in inflamed patients, this effect was mitigated in noninflamed patients.

Reverse Epidemiology of CV Risk factors

It is not only OBESITY & BMI !!

Table 2. Reverse Epidemiology of Cardiovascular (CV) Risk Factors in Dialysis Patients: The Effect of CV Risk Factors in Maintenance Dialysis Patients Is the Opposite of the General Population

Risk Factors of Cardiovascular Disease	Direction of the Associations Between Risk Factors and Outcomes	
	General Population	Maintenance Dialysis Patients
Body mass index (BMI)	High BMI and obesity are generally deleterious.	High BMI, or weight for height, and moderate obesity are protective. Underweight is deleterious. ⁵⁷
Serum cholesterol	Hypercholesterolemia, high LDL, and low HDL are deleterious.	Hypercholesterolemia (and maybe high LDL) is protective. Low serum cholesterol is deleterious. ⁵⁰
Blood pressure (BP)	Hypertension and even borderline high BP are deleterious.	Pre-dialysis low BP may indicate a deleterious state. ⁵⁸
Serum creatinine	A mild to moderate increase in serum creatinine is an independent risk factor of CVD.	An increased predialysis serum creatinine level is associated with a better survival. ¹⁴
Total plasma homocysteine	A high level is a risk factor for increased CVD in the general population and likely in dialysis patients.	Several recent studies have found that a low level is associated with increased risk of cardiovascular disease and mortality. ⁵¹
Serum iron	A high serum iron level is associated with hemochromatosis and poor outcome.	A low iron and transferrin saturation level has been recently found to be associated with higher mortality and hospitalization in dialysis patients. ⁵⁹
Intact parathyroid hormone (PTH)	In general, a high intact PTH level is considered to be associated with adverse outcome.	Dialysis patients with lower intact PTH may have a worse long-term survival. ⁶⁰
Advanced glycation endproducts (AGEs)	Patients with higher AGE levels, such as diabetic patients, have a poor outcome.	A recent report indicates a paradoxically reverse association between lower AGE levels and higher mortality in dialysis patients. ⁶¹
Energy (calorie) and/or protein intake	A high energy and food intake may be associated with risk of obesity and increased mortality.	Increased protein intake is associated with better survival. ⁶²

Abbreviations: CVD, cardiovascular disease; MD, maintenance dialysis; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Possible Explanations for Reverse Epidemiology of BMI

1- Hemodynamic State
in Obese Individuals

2- Tumor Necrosis
Factor-Receptors

3- Neurohormonal
Alterations

4- Survival Bias & Time
Discrepancies Between
Competitive Risk
Factors: Overnutrition
Versus Undernutrition

5- Malnutrition–
Inflammation Complex
Syndrome

6- Endotoxin –
Lipoprotein Hypothesis

Original Contribution

Mortality Prediction by Surrogates of Body Composition: An Examination of the Obesity Paradox in Hemodialysis Patients Using Composite Ranking Score Analysis

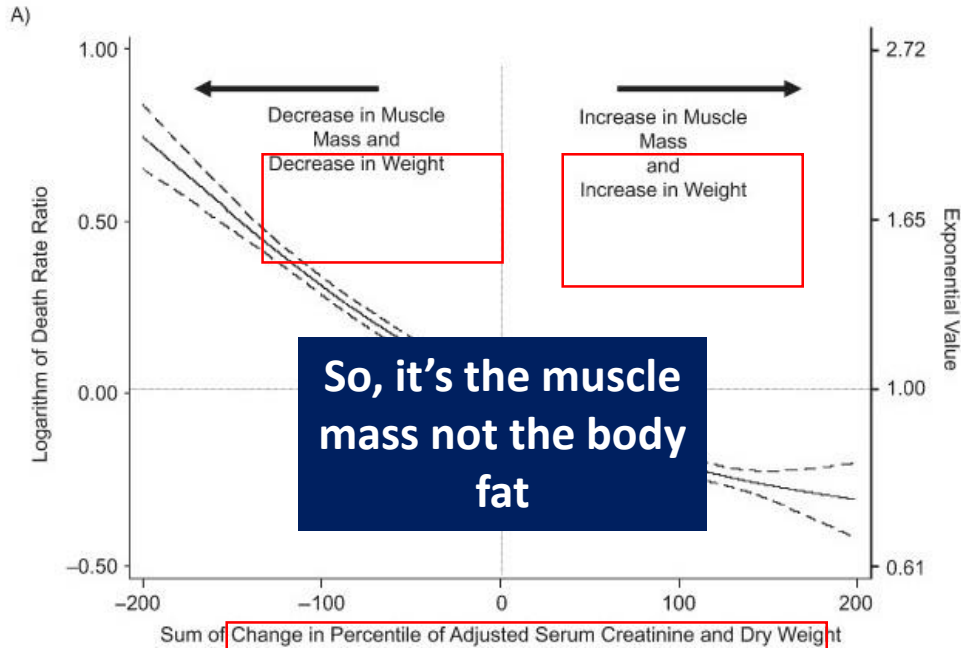


Figure 5. Association of mortality with changes in dry weight (measured using body mass index (weight (kg)/height (m)²)) and serum creatinine over the first 6 months of the cohort in 50,831 hemodialysis patients. Each patient first received a percentile score between -100 and 100 according to the percentile rank of the change in dry weight or serum creatinine. The sum of scores resulted in a number between -200 and 200 (A), as did the difference (B). The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status, dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Dashed lines are 95% pointwise confidence bands.

Kalantar-Zadeh et al. Am J Epidemiol. 2012;175(8):793–803

Mortality Prediction by Surrogates of Body Composition: An Examination of the Obesity Paradox in Hemodialysis Patients Using Composite Ranking Score Analysis

- The **protective** effect conferred by high BMI is limited to those patients with **normal or high muscle mass**.
- High BMI patients with inferred **high body fat** have **increased and not decreased mortality**.

Home Messages

- Obesity related to increased kidney stress and injury
- Kidney injury may occur to other pathologies in obese people
- Obesity affect the kidney by multiple clinical consequences
- High muscular mass associated with better survival in HD patients



...grazie per l'attenzione!