EXTRACORPOREAL NEPHROLOGY GROUP

OBESITY -CKD

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INTRODUCTION

- International criteria: >25 kg/m2 = Overweight.
  >30 kg/m2 = Obesity.

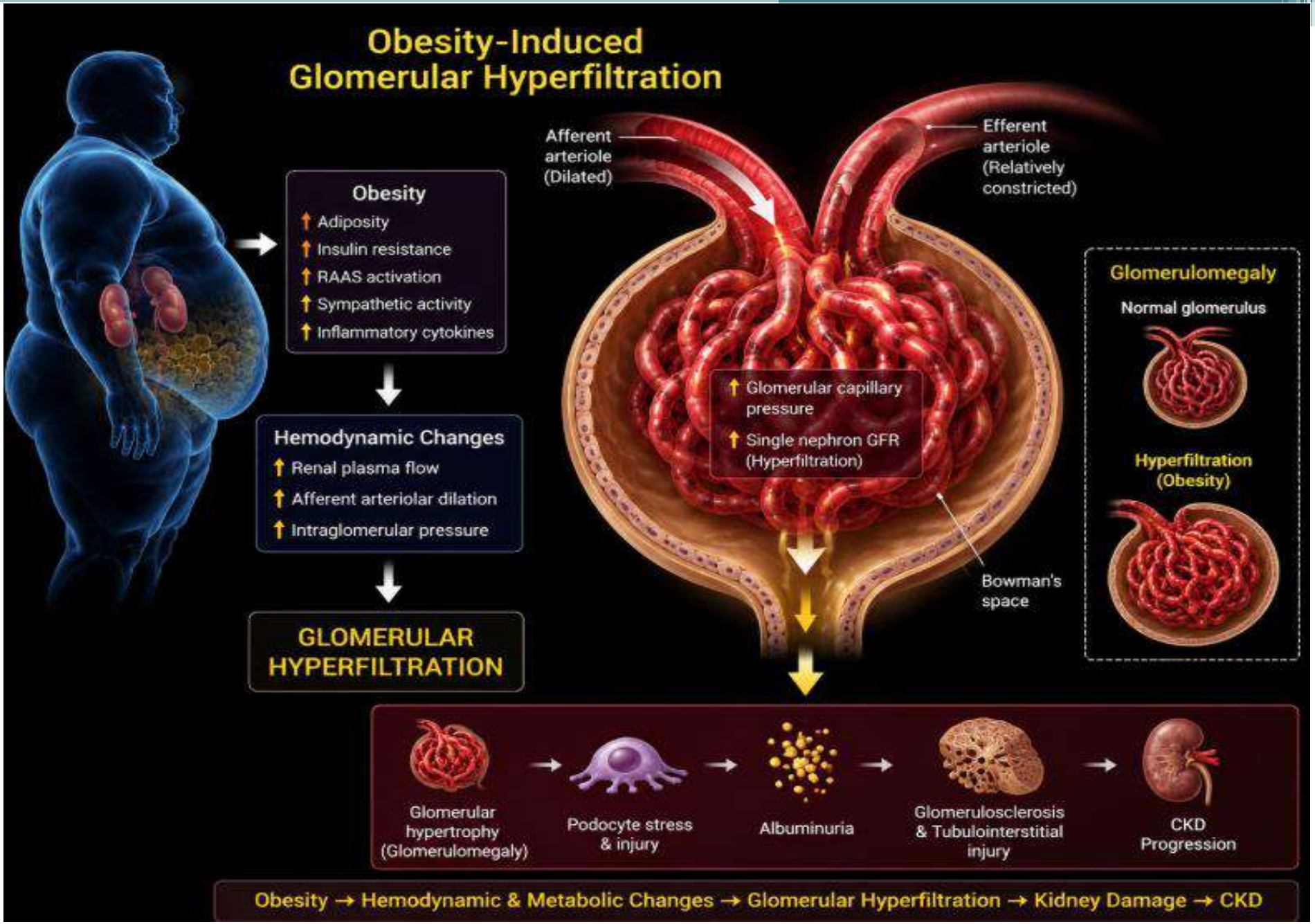
- Obesity is a major, modifiable risk factor that can directly cause and accelerate chronic kidney disease (CKD).

- Obesity → Kidneys respond with: Increased renal plasma flow + Increased GFR → resulting in hyperfiltration.

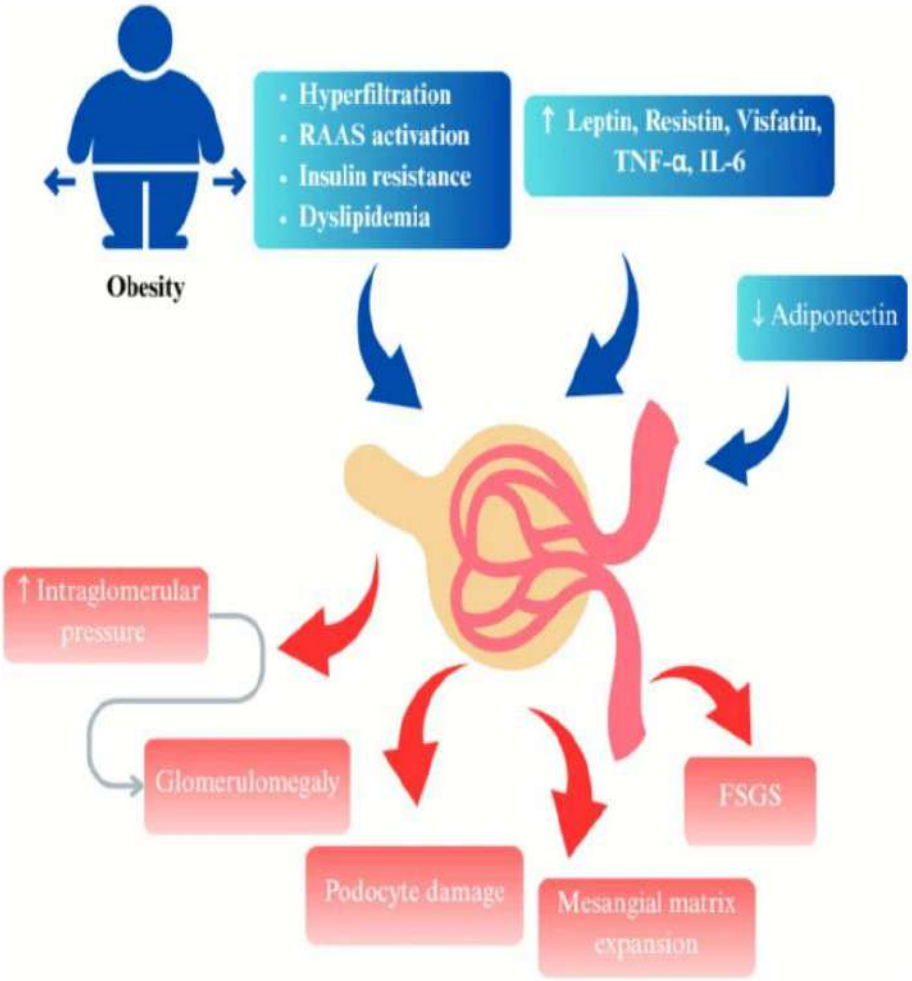
- Fatty kidney : Excessive triglyceride accumulation within tubular epithelial cell - lead to lipotoxicity, oxidative stress, and mitochondrial dysfunction.

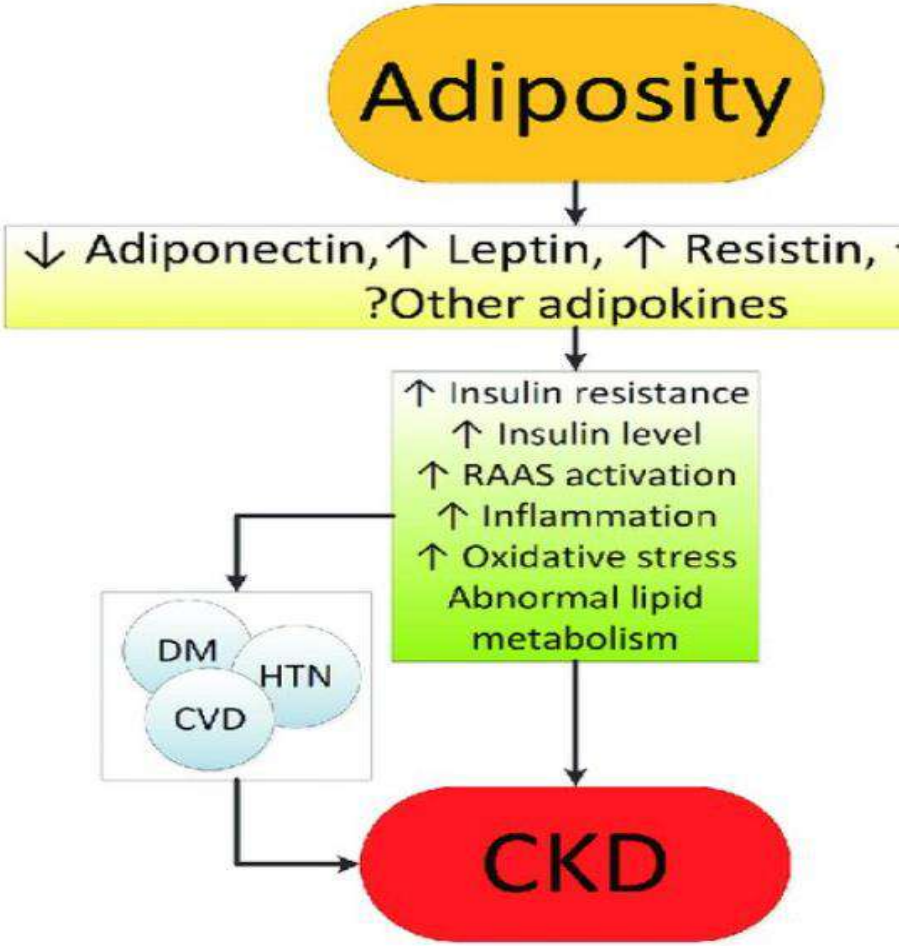
INTRODUCTION

- Visceral obesity → Insulin resistance → Hyperinsulinemia → Sodium retention → Hypertension → CKD progression.
- Adipose tissue secretes TNF-alpha • IL-6 • MCP-1 → Chronic low-grade inflammation.
- The **"Y-Y" Paradox, or Yajnik-Yudkin paradox** : 2003 Lancet commentary, highlights that South Asians possess higher visceral fat and lower muscle mass compared to Caucasians at similar BMIs → **"thin-fat"** phenotype → increases risk for type 2 diabetes and cardiovascular disease.
- The **obesity paradox** : Dialysis population: Moderate obesity often associated with improved survival → Better nutrition , protein reserves , less protein-energy wasting.
- Unlike classic nephrotic syndrome there is no edema --> Serum albumin often preserved because hyperfiltration predominant mechanism.


Obesity-Induced Glomerular Hyperfiltration
Obesity
Adiposity
Insulin resistance
RAAS activation
Sympathetic activity
Inflammatory cytokines
Hemodynamic Changes
Renal plasma flow
Afferent arteriolar dilation
Intraglomerular pressure
GLOMERULAR HYPERFILTRATION
Afferent arteriole (Dilated)
Efferent arteriole (Relatively constricted)
Glomerular capillary pressure
Single nephron GFR (Hyperfiltration)
Bowman's space
Glomerulomegaly
Normal glomerulus
Hyperfiltration (Obesity)
Glomerular hypertrophy (Glomerulomegaly)
Podocyte stress & injury
Albuminuria
Glomerulosclerosis & Tubulointerstitial injury
CKD Progression
Obesity → Hemodynamic & Metabolic Changes → Glomerular Hyperfiltration → Kidney Damage → CKD

PATHOGENESIS OF OBESITY - CKD

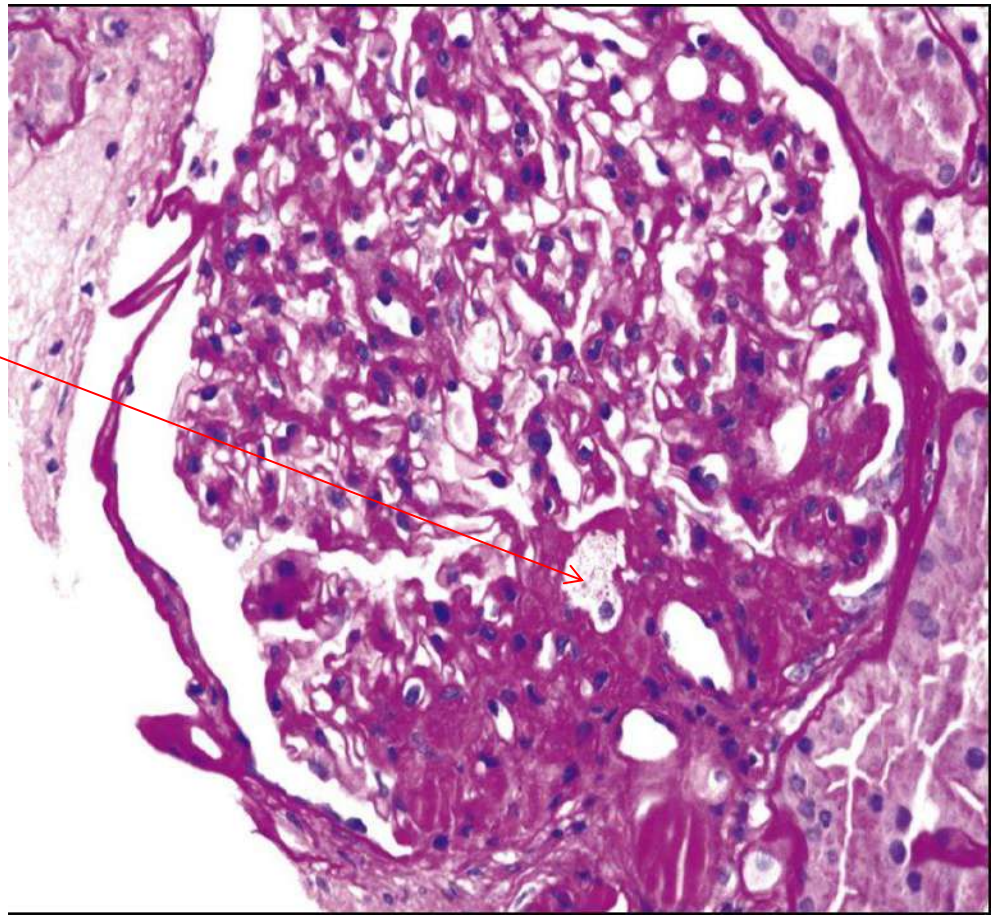




RENAL BIOPSY

Glomerulomegaly
- Podocyte stretch
- Podocyte loss
- Segmental sclerosis

[Predominantly Peri Hilar –
Hemodynamic stress is maximal near vascular entry]



TREATMENT

- Measure obesity correctly, and ask for weight history Assess visceral adiposity (Waist Hip ratio) .Identify OSA.
- Lifestyle intervention.
- Anti proteinuric medications – ARB /ACEI.
- SGLT2 inhibitor / MRA –finrenone when appropriate.
- GLP-1 receptor agonist when indicated.
- Consider bariatric surgery (Last resort).

The SELECT Trial

Semaglutide and Cardiovascular outcomes in obesity without diabetes

Lincoff et al, New England Journal of medicine, 2023

Question

Can Semaglutide reduce Cardiovascular risk associated with overweight and obesity without diabetes?

Methods

multi-center, double blind, randomized, placebo controlled, event driven superiority trial, 804 clinical sites in 41 countries

Primary End Point

Death from cardiovascular causes, non-fatal MI, non-fatal stroke

6.5% vs 8% (HR~0.8 P-value<0.001)

Inclusion Criteria

- Age≥ 45
- BMI≥ 27
- Established Cardiovascular disease

Semaglutide 8803 1:1 Placebo 8801

Duration 34.2±13.7 months

Follow up 39.8±9.4 months

Secondary End Point

Death from cardiovascular causes

2.5% vs 3% (HR~0.85 P-value<0.07)

Death from heart failure

HR~0.82

Death from any cause

HR~0.81

Mean Change in Body Weight

-9.39% vs -0.88%

Adverese events leading to permanent discontinuation of trial product

16.6% vs 8.2% (P-Value<0.001)

Exclusion Criteria

- History of Diabetes
- HbA1c≥ 6.5%
- On Glucose lowering medication or GLP-1 Agonist within the previous 90 days
- NYHA class IV heart failure
- ESRD or on Dialysis

Conclusion

Weekly subcutaneous Semaglutide 2.4 mg was superior to placebo in reducing the incidence of death in cardiovascular causes, nonfatal MI, or nonfatal stroke at a mean follow up 39.8 months in patients with preexisting cardiovascular disease and overweight or obesity but without diabetes. The incidence of adverse events was lower among patients who received semaglutide.

FLOW Trial: Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes

KidneyNews

Methods and cohort

Multinational, randomized, and placebo-controlled trial

Type 2 diabetes with chronic kidney disease

- eGFR, 25–50 mL/min/1.73 m² UACR, 100–5000 mg/g
- eGFR, 50–75 mL/min/1.73 m² UACR, 300–5000 mg/g

Study period: June 2019–May 2021

Median follow-up period: 3.4 years

Semaglutide (N = 1767)

Placebo (N = 1766)

Results

	Major kidney disease events	Annual rate of change in eGFR (mL/min/1.73 m²)	Major cardiovascular events
Semaglutide (N = 1767)	331	−2.2	212
HR, ETD (95% CI)	HR, 0.76 (0.66–0.88)	ETD, 1.16 (0.86–1.47)	HR, 0.82 (0.68–0.98)
p value	0.0003	<0.001	0.029
Placebo (N = 1766)	410	−3.4	254

ETD, estimated treatment difference.

Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes, major cardiovascular events, and death from any cause in participants with type 2 diabetes and chronic kidney disease.

Perkovic V, et al. **Effects of Semaglutide on Chronic Kidney Disease in Patients With Type 2 Diabetes.** *N Engl J Med* 2024; 391:109–121. doi: 10.1056/NEJMoa2403347

Visual abstract by Priyadarshini John, MD, DM, MSc