Metabolic Syndrome, Obesity, Hypertension and Chronic Kidney Disease

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Obesity - the public health problem not only in a Western Countries
In USA:
- the age-adjusted prevalence of obesity (BMI ≥ 30 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 (BMI ≥25) were 68.0%, 72.3% and 64.1%

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

In Europe:
- the prevalence of obesity (BMI ≥ 30 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

1990

1998

2006

BMI ≥30 kg/m²

No Data          <10%           10%–14%
20%–24%          25%–29%           ≥30%
15%–19%          20%–24%

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Regional variation in prevalence of obesity (BMI ≥ 30 kg/m²) in Europe

Prevalence of overweight and obesity in children

Changes in prevalence of overweight and obesity in adults

Body-Mass Index and mortality among 1.46 million white adults

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

A White Women

B White Men

de Gonzales et al. NEJM 2010; 363: 2211-9
The cluster of co-morbidities associated with and aggravated by obesity

- Metabolic syndrome
- Diabetes mellitus
- High blood pressure
- Cardiovascular disease
- Chronic kidney disease
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>BMI<30) vs normal weight.

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

Wang Y. et al., Kidney Int., 2008; 73 18-23
Association between **obesity** and **kidney disease** based on cohort studies in the general populations – obesity (BMI≥30) vs normal weight.

Wang Y. et al., Kidney Int., 2008; 73 18-23
Association between the development of CKD (estimated GFR 64 ml/min per 1.73 m²) and weight change per year

HR increase even among patients with normal BMI!

Baseline BMI between 18.5 and 23.0 kg/m²

Baseline BMI > 23.0 kg/m²

Adjustment for age, baseline GFR, BMI, HDL, cholesterol, FBG, uric acid, and regular exercise.

Ryu S., J Am Soc Nephrol. 2008 May 21
Relationship of proteinuria and weight changes in diet-group patients

\[ R=0.62, \ p<0.01 \]
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

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

Molnar M et al. Kidney Int. 2011, 80, 218–224
Allograft survival rates in kidney transplant recipients with and without metabolic syndrome (MS)

![Graph showing graft survival rates over years with and without metabolic syndrome.](image_url)

- No MS: n=178
- MS: n=52

Significance level: p=0.008

Hricik D E CJASN 2011;6:1781-1785

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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

Serra A et al. Kidney Int; 2008, 73, 947–955
Renal biopsy findings in OB-FSFS and I-FSGS

<table>
<thead>
<tr>
<th></th>
<th>Per cent of normal glomeruli</th>
<th>Per cent of glomeruli with FSG lesions</th>
<th>Per cent of glomeruli with GGS</th>
<th>Glomerular diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB-FSG (n=15)</td>
<td>61±24</td>
<td>19±23</td>
<td>18±18</td>
<td>256±24</td>
</tr>
<tr>
<td>I-FSG (n=15)</td>
<td>57±20</td>
<td>24±12</td>
<td>18±20</td>
<td>199±26</td>
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<td><strong>P&lt;0.001</strong></td>
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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

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

- \( \uparrow \) renin angiotensin system
- \( \uparrow \) aldosterone
- \( \uparrow \) sympathetic nervous system
- \( \uparrow \) insulin resistance
- \( \uparrow \) salt intake
- Altered adipokines: \( \uparrow \) leptin, \( \uparrow \) fetuin A, \( \uparrow \) resistin, \( \downarrow \) adiponectin, \( \uparrow \) tumor necrosis factor, \( \uparrow \) free fatty acids
- \( \uparrow \) endothelin 1
- \( \downarrow \) brain natriuretic protein
- \( \uparrow \) plasminogen activator inhibitor 1
- Infiltrating macrophage phenotypic switch
Obesity and renal hemodynamic, renal reabsorption and neurohormonal activity

<table>
<thead>
<tr>
<th>Model</th>
<th>Arterial pressure</th>
<th>Heart rate</th>
<th>Cardiac output</th>
<th>Renal sympathetic activity</th>
<th>Plasma renin activity</th>
<th>Na⁺ balance</th>
<th>Renal tubular reabsorption</th>
<th>GFR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese rabbits</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>(high fat diet)</td>
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<td></td>
</tr>
<tr>
<td>Obese dogs</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>(high fat diet)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Obese humans</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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</tbody>
</table>

GFR, glomerular filtration rate. *The 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.
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 vessels/endothelial cells in red, and the extracellular matrix as black.

Adipose tissue as endocrine organ

- **Visfatin** - Insulin secretion
- **Apelin** - Blood pressure
- **Resistin** - Insulin resistance
- **RBP-4** - Insulin resistance
- **Adiponectin** - Glucose homeostasis, Fatty acid catabolism
- **Leptin** - Energy balance
- **TNFα, MCP-1** - Inflammation

Infiltration and polarization of macrophages in fat tissue in obese patients

Galic S et al. Molecular and Cellular Endocrinology, 2010, 316, 129-139
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-1β, 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

Adipocyte RAS

**Systemic Effects**

- Contribute to Systemic RAS

- Obesity
  - Hypertension, Diabetes
  - Atherosclerosis, AAA

**Local Effects**

- Regulate:
  - Adipocyte Growth and Differentiation
  - AT1aR and AGT expression
  - Inflammation, Oxidative Stress
  - Local Blood Flow
  - Lipolysis
  - Local AngII concentrations

**Obesity**

Hypertension, Diabetes
Atherosclerosis, AAA

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

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

- ↓ lipids accumulation in monocyte derived macrophages
- ↓ scavenger receptors
- ↓ transformation of macrophages into foam cells
- ↓ superoxide
- ↓ VCAM-1
- ↓ ICAM-1
- ↓ E-selectin
- ↑ TIMP
- ↑ NO
- ↓ TNF-α
- ↓ PDGF-BB
- ↓ FGF
- ↓ HB EGF
- ↑ glucose utilization
- ↑ fatty acid oxidation
- ↑ insulin signaling
- ↑ glucose uptake
- ↓ gluconeogenesis

anti-atherogenic actions

insulin-sensitizing actions

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

## Conditions and mediators known to regulate adiponectin levels

<table>
<thead>
<tr>
<th>Down-regulation</th>
<th>Up-regulation</th>
</tr>
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<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>Hyperinsulinaemia</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Leptin</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Renin–angiotensin blockade</td>
</tr>
<tr>
<td>β-receptor agonists</td>
<td>Cannabinoid type 1 receptor antagonists</td>
</tr>
<tr>
<td>Conjugated linoleic acid</td>
<td></td>
</tr>
</tbody>
</table>

*Sharma A.M. et al. Diabetologia 2005, 48, 1035-1037*
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-κB 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-κB has anti-inflammatory effects. It could by 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

Ehrhart-Bornstein et al. PNAS 2003; 25: 14211
Pathomechanism of salt dependent hypertension and CKD in metabolic syndrome

TG Feedback, tubulo-glomerular feedback
Oxidative stress in adipose tissue in obese patients

Regulation of oxidant stress and by adiponectin

**A**

<table>
<thead>
<tr>
<th></th>
<th>Urine H$_2$O$_2$/creatinine (nmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>50±5</td>
</tr>
<tr>
<td>Ad/−−</td>
<td>150±10</td>
</tr>
<tr>
<td>Ad/−− gAd</td>
<td>50±5</td>
</tr>
<tr>
<td>Ad/−− fAd</td>
<td>50±5</td>
</tr>
<tr>
<td>Ad/−− AICAR</td>
<td>50±5</td>
</tr>
</tbody>
</table>

**B**

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.

Harcourt BE et al. Kidney Int. 2011, 80, 190–198
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)

Harcourt B.E. et al. Kidney Int. 2011, 80, 190–198

**Albumin/creatinine ratio**

- Low – low GE-containing diet
- High - high–AGE-containing diet

* p<0.05

**Plasma cystatin C**
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)

Harcourt B.E. et al. Kidney Int. 2011, 80, 190–198

**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

**Harcourt BE et al. Kidney Int. 2011, 80, 190–198**

**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, *** p<0.001 vs lean low AGE, † p<0.05 vs obese.
Advanced glycation endproducts (AGEs) – impact on inflammatory parameters- murine study

**Kidney MCP-1**
(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

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*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, ***p<0.001 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 ± 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 ± 2.1 % of the baseline values)

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

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

Mallamaci F et al. JASN 2011; 22: 1122-28
Ramipril prevents the rise in proteinuria in overweight and obese patients

Mallamaci F et al. JASN 2011; 22: 1122-28
Anti-proteinuric effect of ramipril

Differences in Urinary Protein Excretion
(Ramipril versus Placebo)

B.M.I. (Kg/m²) <25 25 - 30 >30

Mallamaci F et al. JASN 2011; 22: 1122-28
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