Obesity and the kidney

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Obese female mammoth ivory figurine produced at least 35000 calender years ago (Aurignacien period) and found in the „Hohler Fels” cave in southwestern Germany.

Obesity in the Paleolithic era
The Venus of Willendorf is a superbly crafted sculpture of a naked obese woman from the stone age

Colman M.D. E.
Plan of the lecture

- Epidemiology of obesity
- Obesity and survival
- Obesity, metabolic syndrome and CKD
- Pathogenesis of OR FSGS
- Clinical picture of OR FSGS
- Differences between OR and I FSGS
- Treatment of OR FSGS
- Conclusions
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Prevalence of obesity

**In USA:**
- the age-adjusted prevalence of obesity (BMI ≥ 30 kg/m²) 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/m²) 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
Prevalence of obesity in Poland

Obesity (BMI > 30 kg/m²)

22%
= 6.5 mln

Zdrojewski T. et al., NATPOL III Study, 2011
Trends in the obesity in Poland during the years 2011 – 2035

Zdrojewski T. et al., NATPOL III Study, 2011
Prevalence of obesity in Turkey

- Obesity and overweight are increasing in Turkey according to the field surveys that were carried out a decade apart (TEKHARF 1990 and 2000). The overall prevalence of obesity in adults was 18.6% in the year 1990. Ten years later in 2000, the prevalence was 21.9%, which shows a relative increase rate of 17.7%. As it is true for most of the countries, overweight is more common in men and obesity is more prevalent among women in Turkey.

Yumuk V.D., Obes Rev. 2005, 1: 9-10
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The cluster of co-morbidities associated with and aggravated by obesity

- Metabolic syndrome
- Diabetes mellitus
- High blood pressure
- Cardiovascular disease
- Chronic kidney disease

OBESITY
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

de Gonzales et al.  
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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, haematuria and serum creatinine level.

Hazard ratios for diabetic and nondiabetic ESRD by body mass index percentile subgrups

Figure 2. Hazard ratios for diabetic and nondiabetic end-stage renal disease (ESRD) by body mass index (BMI) percentile subgroup. Model 2 is adjusted for sex, country of origin, period of enrollment in the study, and systolic blood pressure (above or below the 95th age-specific and sex-specific percentiles). Black boxes indicate significant results ($P < .001$).

Metabolic syndrome and risk for development of estimated GFR <60 ml/min per 1.73 m²

Figure 2. Metabolic syndrome and risk for development of estimated GFR <60 ml/min per 1.73 m².

### Prospective studies of metabolic syndrome and incidence of albuminuria

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample size</th>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucove et al. [66]</td>
<td>2008</td>
<td>2,380</td>
<td>ACR &gt; 30 mg/g</td>
<td>1.26 (0.99–1.60)</td>
</tr>
<tr>
<td>Tozawa et al. [67]</td>
<td>2007</td>
<td>6,371</td>
<td>Dipstick positive proteinuria</td>
<td>2.09 (1.55–2.81)</td>
</tr>
<tr>
<td>Watanabe et al. [68]</td>
<td>2010</td>
<td>34,986</td>
<td>Dipstick positive proteinuria</td>
<td>1.76 (1.57–1.98)</td>
</tr>
<tr>
<td>Bonnet et al. [69]</td>
<td>2006</td>
<td>2,738</td>
<td>Albuminuria ≥ 20 mg/L or dipstick positive</td>
<td>1.87 (1.25–2.81)</td>
</tr>
</tbody>
</table>

ACR albumin-to-creatinine ratio

Tanner RM et al.: Curr Hypertens Rep 2012; 14: 152-159
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).
Overweight significantly increases the risk of IgA nephropathy progression.

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

Distribution of body mass index (BMI) in dialysis patients (based on USRDS)

- Underweight: 17%
- Ideal: 16%
- Overweight: 28%
- Obese: 25%
- Severely obese: 7%

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Factors implicated in the pathogenesis of CKD in obesity

- ↑ renin angiotensin system
- ↑ aldosterone
- ↑ sympathetic nervous system
- ↑ insulin resistance
- ↑ salt intake, AGE 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
Effects of overweight or obesity on the kidney

- **Hemodynamic**
  - ↓Effective plasma flow
  - ↑/N glomerular filtration rate
  - ↑glomerular filtration fraction
  - ↑albuminurias

- **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 dialysis patients
  - ↑graft loss in kidney transplant recipients

- **Other**
  - ↑renal cell carcinoma
  - ↑nephrolithiasis
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

White adipose tissue in lean (A) and obese (B) subjects

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.

• 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

![Diagram showing the relationship between obesity, adipocytes, and various biomarkers](attachment:image)

<table>
<thead>
<tr>
<th>Table 1. List of hormones, cytokines, chemokines, growth factors and complement proteins produced by the adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Leptin</td>
</tr>
<tr>
<td>● Adiponectin</td>
</tr>
<tr>
<td>● Visfatin</td>
</tr>
<tr>
<td>● Apelin</td>
</tr>
<tr>
<td>● Resistin</td>
</tr>
<tr>
<td>● Agouti signalling protein</td>
</tr>
<tr>
<td>● Acylation stimulating protein</td>
</tr>
<tr>
<td>● Nitric oxide (NO)</td>
</tr>
<tr>
<td>● Renin</td>
</tr>
<tr>
<td>● Angiotensin II</td>
</tr>
<tr>
<td>● PAI-1</td>
</tr>
<tr>
<td>● Tumour necrosis factor-α (TNF-α)</td>
</tr>
<tr>
<td>● Interleukins-1β, 6, 8, 10</td>
</tr>
<tr>
<td>● Monocyte chemoattractant protein-1 (MCP-1)</td>
</tr>
<tr>
<td>● Migration inhibitory factor (MIF)</td>
</tr>
<tr>
<td>● Prostaglandin E2 (PGE2)</td>
</tr>
<tr>
<td>● Hepatocyte growth factor (HGF)</td>
</tr>
<tr>
<td>● Vascular endothelial growth factor (VEGF)</td>
</tr>
<tr>
<td>● Nerve growth factor (NGF)</td>
</tr>
<tr>
<td>● Heparin-binding epidermal growth factor-like growth factor (HB EGF)</td>
</tr>
<tr>
<td>● Insulin-like growth factor-1 (IGF-1)</td>
</tr>
<tr>
<td>● Complement factor D (adipsin)</td>
</tr>
</tbody>
</table>

The major physiological functions of adipose tissue secretory products in 2012

Physiologic/pathophysiologic significance of an adipocyte RAS

Perivascular white adipose tissue (pWAT) as a paracrine regulator of inflammation and atherosclerosis

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

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., Kidney Int. 1999, 56, 860-872
Paracrine TGF-b 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
Circulating adiponectin concentrations

Scherer Ph. E., Diabetes, 2006, 55, 1537-1545
The pleiotropic role of adiponectin in the cardiovascular system

Adiponectin:

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

**Anti-atherogenic actions**

**Insulin-sensitizing actions**

Effects of adiponectin on podocytes

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

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

Potential mechanisms of renal dysfunction related to inflammatory cytokines and lipotoxicity in obesity and obesity initiated metabolic syndrome
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Obesity associated FSGS (focal segmental glomerulosclerosis)

- Large series: Kambham N. et al., Kidney Int. 2001; 59:1498 - 1509

- 2% of renal biopsies compared to idiopathic FSGS:
  - Less proteinuria
  - Higher S-albumin
  - Lower S-cholesterol
  - Less glomerular alteration
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

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## Renal biopsy findings in OB-FSGS 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><strong>OB-FSG (n=15)</strong></td>
<td>61±24</td>
<td>19±23</td>
<td>18±18</td>
<td>256±24</td>
</tr>
<tr>
<td><strong>I-FSG (n=15)</strong></td>
<td>57±20</td>
<td>24±12</td>
<td>18±20</td>
<td>199±26</td>
</tr>
</tbody>
</table>

*P<0.001*
Glomerular area:

58567,15 µm²  

25056,56 µm²

BMI = 41.8 kg/m²  
BMI = 22.3 kg/m²

HE ×200

Karkoszka H. , Katowice, Pl
Glomerular areas in extremely obese (EO) patients with or without sleep apnea syndrome (SAS) and in controls

Comparison of glomerular density (GD) and glomerular volume (GV) in renal biopsy specimens of health kidney donors, patients with IgA nephropathy or in patients with obesity – related glomerulopathy (ORG)

A) Kidney transplant donor
(36-year-old normotensive woman with estimated GFR of 109 ml/min per 1.73 m2 and body mass index of 24.8 kg/m2).

(B) Patient with obesity-related glomerulopathy
(23-year-old normotensive man with estimated GFR of 79 ml/min per 1.73 m2 and body mass index of 32.5 kg/m2).

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Obesity - induced renal injury and potential targeted treatments

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).

Relationship of proteinuria and weight changes in diet-group patients

![Graph showing the relationship between proteinuria change and weight change. The Pearson correlation coefficient (R) is 0.62, and the p-value is less than 0.01.](image)

Morales E. et al., Am. J. Kidney Dis., 2003, 41: 319-327
GFR and renal plasma flow in obese subjects before and after weight loss (48 kg after gastroplasty)

Bariatric surgery has shown benefit in treating type 2 diabetes, hyperlipidaemia and obesity

Potential benefit of bariatric surgery

- Improved lipid profile
- Decreased need for antihypertensive medication
- Improved insulin sensitivity and glucose tolerance
- Improved parameters of renal function

Decrease mortality and morbidity

Improves quality of life

Potential adverse impact of bariatric surgery on renal function, exacerbated by postoperative renal failure and renal calcium oxalate precipitation

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

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

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

Mallamaci F et al. JASN 2011; 22: 1122-1128
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Obesity and kidney

Pathogenic factors

- Hypertension
- RAA and SNS activation
- Insulin resistance / diabetes mellitus
- Hyperlipidemia (mesangium proliferation)
- Hyperleptinemia
- Hypoadiponectinemia
- Increased abdominal pressure
Obesity and kidney

*Pathogenic factors*

- Glomerular hyperfiltration
- Endothelial proliferation in glomeruli
- Increase TGF-β1 production by endothelial cells in glomeruli
- Overexpression TGF β receptors on mesangial cells
- Increase collagen type IV deposition in glomerular matrix
- Increase angiogenesis
- Increased AGE and RAGE
Obesity and kidney

*Clinical and therapeutical aspects*

- Proteinuria (up to nephrotic range)
- No symptoms of nephrotic syndrome
- Kidney biopsy not recommended
- Treatment:
  - reduction of body weight
  - bariatric therapy?
  - blockeres of the RAS
  - cessation of cigarette smoking
Thank you for your attention!

Andrzej Wiecek

Katowice