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Obesity

(Obesity and the kidney)

Prof. Andrzej Więcek, FRCP (Edin.)
Dept. Nephrology, Endocrinology and Metabolic Diseases
Medical University of Silesia, Katowice, Poland

awiecek@spskm.katowice.pl
Obesity - the public health problem in Western Countries
Mortality due to leading global risk factors

- High blood pressure
- Tobacco
- High cholesterol
- Underweight
- Unsafe sex
- High BMI
- Physical inactivity
- Alcohol
- Indoor smoke from solid fuels
- Iron deficiency
- Urban air pollution
- Zinc deficiency
- Vitamin A deficiency
- Unsafe healthcare injections
- Occupational risk factors for injury
- Lead exposure
- Illicit drugs

High BMI
National Health and Nutrition Examination Survey (USA)

BMI > 30 kg/m²
- NHANES III 1988-1994 – 23%
- NHANES 1999-2000 – 31%
- Projected 2008 – 39%

Obesity Trends Among U.S. Adults
BRFSS, 1987

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults
BRFSS, 1988

BMI ≥30

Obesity Trends Among U.S. Adults
BRFSS, 1993

BMI ≥30

Obesity Trends Among U.S. Adults
BRFSS, 1994

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults
BRFSS, 1996

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults
BRFSS, 1999

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults
BRFSS, 2002

BMI ≥30

Obesity Trends Among U.S. Adults
BRFSS, 2004

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults
BRFSS, 2005

BMI ≥30

Obesity Trends Among U.S. Adults
BRFSS, 2006

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Obesity Trends Among U.S. Adults

BMI ≥30

U.S. Obesity Trends 1985-2006, CDC (www.cdc.gov)
Prevalance of obesity (BMI >30 kg/m²) among incident dialysis patients by year of dialysis initiation in USA

Kramer H. Contrib Nephrol, 2006:151
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

Kramer H., Contrib. Nephrol., 2006, 151, 1-18
Association between obesity and kidney disease: A systematic review and meta-analysis

Y Wang¹, X Chen¹, Y Song², B Caballero¹ and LJ Cheskin¹

¹Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA and ²Division 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. 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) in part because of the concurrent dramatic rise in the prevalence of end-stage renal disease (ESRD), which has more than doubled in the past decade. 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.

Interventions to prevent KD and its progression to ESRD have the potential to save many lives as well as decrease health-care costs. Identifying modifiable risk factors for KD is critical in order to develop effective, population-based strategies. 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. 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. 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. Two major obstacles to prospectively studying risk
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.

Test for heterogeneity: Q=40.96, P=0.001; Pooled RR (95% CI): 1.83 (1.57–2.13).

Wang Y. et al., Kidney Int., 2008; 73 18-23
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.

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
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.

Graft survival analysis.

Srinivals and Meier-Kriesche. Contrib Nephrol, 2006:151
Relative risk for graft loss by BMI

Srinivals and Meier-Kriesche. Contrib Nephrol, 2006:151
The relationship between obesity and stage 3 CKD may be mediated through cardiovascular disease risk factors.

Obese individuals had a 68% increased odds of developing stage 3 CKD (OR, 1.68; 95% CI, 1.10 to 2.57; \(p=0.02\)), which became nonsignificant in multivariable models (OR, 1.09; 95% CI, 0.69 to 1.73; \(p=0.7\)).

<table>
<thead>
<tr>
<th>Model</th>
<th>Sample Size/No. of Patients With CKD</th>
<th>BMI Category</th>
<th>OR (95% CI)</th>
<th>(P)</th>
<th>(P) for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2,676/212</td>
<td>overweight</td>
<td>1.29 (0.93-1.81)</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Age- and sex-adjusted*</td>
<td></td>
<td>obese</td>
<td>1.68 (1.10-2.57)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>overweight</td>
<td>1.06 (0.75-1.50)</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>obese</td>
<td>1.09 (0.69-1.73)</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension free</td>
<td>2,147/126</td>
<td>overweight</td>
<td>1.09 (0.72-1.67)</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Age- and sex-adjusted*</td>
<td></td>
<td>obese</td>
<td>1.70 (0.95-3.03)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>overweight</td>
<td>0.91 (0.59-1.41)</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>obese</td>
<td>1.10 (0.59-2.06)</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes free</td>
<td>2,632/196</td>
<td>overweight</td>
<td>1.31 (0.93-1.84)</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Age- and sex-adjusted*</td>
<td></td>
<td>obese</td>
<td>1.25 (0.78-2.01)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>overweight</td>
<td>1.10 (0.77-1.56)</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>obese</td>
<td>0.87 (0.53-1.44)</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of prevalent CVD</td>
<td>2,626/197</td>
<td>overweight</td>
<td>1.32 (0.93-1.86)</td>
<td>0.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Age- and sex-adjusted*</td>
<td></td>
<td>obese</td>
<td>1.77 (1.15-2.73)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>overweight</td>
<td>1.05 (0.73-1.75)</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>obese</td>
<td>1.10 (0.69-1.77)</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison between the impact of body mass index (BMI) on all-cause mortality in the general population versus the maintenance hemodialysis population – OBESITY PARADOX

Kalantar - Zadeh K., Kidney Int., 2003, 63, 793-808
WHR, but not BMI, is associated with cardiac events in patients with CKD.
Population attributable risk (PAR) of KD due to overweight and obesity in the United States and industrialized countries – elimination of overweight and obesity can decrease incidence of kidney disease about 30%

<table>
<thead>
<tr>
<th></th>
<th>USA$^b$</th>
<th></th>
<th>Industrialized countries$^c$</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Men</td>
<td>Women</td>
<td>All</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td><strong>Prevalence (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>34.1</td>
<td>39.7</td>
<td>28.6</td>
<td>33.6</td>
<td>38.1</td>
<td>29.3</td>
</tr>
<tr>
<td>Obesity</td>
<td>32.2</td>
<td>31.1</td>
<td>33.2</td>
<td>16.6</td>
<td>12.9</td>
<td>20.1</td>
</tr>
<tr>
<td><strong>PAR (%) of overall KD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>12.0</td>
<td>11.0</td>
<td>10.5</td>
<td>11.8</td>
<td>10.6</td>
<td>10.7</td>
</tr>
<tr>
<td>Obesity</td>
<td>21.1</td>
<td>13.2</td>
<td>23.4</td>
<td>12.1</td>
<td>5.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Total</td>
<td>33.1</td>
<td>24.2</td>
<td>33.9</td>
<td>24.0</td>
<td>16.5</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>PAR (%) of non-kidney cancer/RCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>12.5</td>
<td>19.0</td>
<td>12.1</td>
<td>12.4</td>
<td>18.4</td>
<td>12.3</td>
</tr>
<tr>
<td>Obesity</td>
<td>23.4</td>
<td>9.3</td>
<td>24.7</td>
<td>13.6</td>
<td>4.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Total</td>
<td>36.0</td>
<td>28.3</td>
<td>36.8</td>
<td>26.0</td>
<td>22.4</td>
<td>28.9</td>
</tr>
<tr>
<td><strong>PAR (%) of kidney cancer/RCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>9.6</td>
<td>7.7</td>
<td>9.8</td>
<td>9.4</td>
<td>7.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Obesity</td>
<td>18.6</td>
<td>14.2</td>
<td>22.4</td>
<td>10.5</td>
<td>6.4</td>
<td>14.9</td>
</tr>
<tr>
<td>Total</td>
<td>28.2</td>
<td>21.8</td>
<td>32.2</td>
<td>20.0</td>
<td>13.8</td>
<td>24.9</td>
</tr>
</tbody>
</table>

IOTF, International Obesity Task Force; KD, kidney disease; NHANES, National Health and Nutrition Examination Surveys; PAR, population attributable risk; RCC, renal cell carcinoma.

$^a$RRs were based on our meta-analysis (see Table 3).

$^b$Prevalence estimates were based on NHANES 2003-2004 data.$^{26}$

$^c$Prevalence estimates were based on IOTF’s estimates.

Wang Y, et al., Kidney Int., 2008; 73 18-23
Potential mechanisms of renal injury in patients with obesity and obesity initiated metabolic syndrome

Hemodynamic factors: Obesity and renal hemodynamic studies showing the impact of overweight and obesity on GFR, ERPF, FF.

Bosma et al. Contrib Nephrol, 2006:151
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>
<td>↑</td>
</tr>
<tr>
<td>(high fat diet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese dogs</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>(high fat diet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese humans</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate. *The GFR changes refer to the early phases of obesity before major loss of nephron function has occurred.
Hemodynamic consequences of obesity leading to hyperfiltration and hypertension

AA, afferent arteriole; EA, efferent arteriole

Mechanism for insulin resistance in metabolic syndrome

- High Calorie/High Fat
- Low Physical Activity
- Visceral Obesity
- K
- Adrenomedullin adiponectin
- TNFα Angiotensinogen NEFA
- Salt
- ROS
- Insulin Resistance

Stimulation
Inhibition

Adipose tissue as an endocrine organ

Axelsson J., Blood Purif., 2008; 26: 23-29

Adipose tissue
- Aberrant signaling in obesity
  - reinforced by renal dysfunction

Liver
- CRP

Cytokines
- IL-6, TNF-α
- Resistin
- Visfatin

Blood lipids and glucose
- Insulin resistance
- Triglycerides
- HDL cholesterol

Muscle tissue
- Insulin resistance
- Catabolic state

Cardiovascular system
- Blood pressure
- Pro-atherogenic phenotype
- Adhesion molecules
- Endothelial dysfunction?

Adipokines
- Free fatty acids
- Leptin, adiponectin
- AHSG?
Biologically active substances with local and/or systemic action produced by adipose tissue (1)
(The mature adipocytes: a highly specialized endocrine cells)

- Apelin
- Obestatin
- PA I-1
- TGF-β
- Tissue factor (TF)
- Complement factors (e.g. adipsin)
- TNF-α
- Acylation stimulation protein (ASP)
- Agouti Protein
- Angiotensinogen, Renin, ACE
- Chymase, cathepsin D,G
- Angiotensin II
- Prostaglandins (PGI2, PGF2α)
- Insulin growth factor-1 (IGF1)
Biologically active substances with local and/or systemic action produced by adipose tissue (2)
(The mature adipocytes: a highly specialized endocrine cells)

- Vascular endothelial growth factor (VEGF)
- Macrophage inhibitor factor (MIF)
- Sex hormones (in women: testosterone, estradiol and estrone)
- Glucocorticoids
- Leptin
- Adiponectin
- Resistin
- Visfatin
- IL-6
- NO
- PPAR-γ
- Atrial natriuretic peptide (ANP)
- 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

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
Mechanism of kidney injury caused by obesity

Potential mechanisms of renal dysfunction related to inflammatory cytokines and lipotoxicity in obesity and obesity initiated metabolic syndrome

Cardiovascular and renal effects of leptin

Adipose Tissue

Heart rate ↑

Blood pressure ↑

$U_{Na} V$ ↓ (chronic effect)

$U_{Na} V$ ↑ (acute effect)

IS ↑

NO ↑

Blood pressure ↓

Engeli S. et al. Horm Metab Res, 2000; 32; 490
Na\(^+\), K\(^+\)-ATPase activity increase in dose-dependent manner according to leptin concentration in non-obese rat kidney

Leptin effect on kidney function in obese and lean rats

Effect of obesity to shift renal pressure natriuresis curve to higher arterial pressure

Possible mechanism underlying the development of salt-sensitive hypertension and CKD in metabolic syndrome

Visceral adiposity

- PAI-1↑
- IL-6↑
- TNFα↑
- Adiponectin↓
- Leptin↑

Liver

- CRP↑
- fibrinogen↑
- CD4+ Th1

Microinflammation

- Dislipidaemia

Skeletal muscles and liver

- Activation of immune system

Insulin resistance

- Activation of sympathetic nervous system

Atherosclerosis

- Ischemic nephropathy

Diabetes

- Diabetic nephropathy
- Obesity Related Glomerulopathy
- Hypertensive nephropathy

Cardiovascular disease

- Chronic kidney disease

Sleep apnoea syndrome

Chudek J., Adamczak M., Nieszporek T., Więcek A. Contrib. Nephrol., 2006; 151, 70
Obesity and impaired renal function increase adipokines concentration

Axelsson J, Stenvinkel P. Curr Opin Nephrol Hyperten 2008; 17: 25-31
FIG. 1. Scatterplot of TGF-β₁ plasma levels in nonobese (n = 29), overweight (n = 29), and obese (n = 46) hypertensive patients. TGF-β₁ = transforming growth factor-β₁.
Staining for collagen type IV in rats infused for three weeks with solvent (C,E) or leptin (D,F).

Leptin-induced proliferation

(□) Glomerular Endothelial Cells; (■) mesangial cells;

*P < 0.05; **P < 0.01 vs. unstimulated controls

Leptine increase TGF-β1 expression in endothelial glomerular cells
Leptin and renal fibrosis

Wolf and Ziyadeh. Contribution to Nephrology 2006:151
Kidney section of rats infused with solvent for 72 hours revealed no glomerular PCNA staining, suggesting very low basal proliferation in normal glomeruli (A). In contrast, in leptin-infused animals PCNA-expressing cells are found in glomeruli (arrow; B)

Relationship of proteinuria and weight changes in diet-group patients

![Graph showing the relationship between proteinuria and weight change.](image)

$R = 0.62, p < 0.01$

Morales E. et al., Am. J. Kidney Dis., 2003, 41: 319-327
Leptin induced proteinuria – effect of 3 weeks leptin infusion

Wolf G. et. al., Kidney Int., 1999, 56, 860-872
• Adiponectin serum concentration and mRNA expression are decreased in:
  • Obese
  • Diabetes mellitus
  • Hypertension
  • Coronary artery disease
• PPRγ activators, ACEi, ARBs, rilmenididine, ribonabant – increase adiponectin serum concentration and mRNA expression

Maeda N. et al., Diabetes, 2001, 50, 2094-2099
Adiponectin↓↓↓↓ scavenger receptors↑↑↑↑ NO↑↑↑↑ TIMP↓↓↓↓ VCAM-1↓↓↓↓ ICAM-1↓↓↓↓ E-selectin↓↓↓↓ TNF-α↓↓↓↓ lipids accumulation in monocyte derived macrophages↓↓↓↓ transformation of macrophages into foam cells↓↓↓↓ scavenger receptors↓↓↓↓ superoxide↓↓↓↓ PDGF-BB↓↓ FGF↓↓ HB EGF↓↓ TNF-α↓↓ lipids accumulation in monocyte derived macrophages↓↓ transformation of macrophages into foam cells↓↓ scavenger receptors↓↓ superoxide↓↓ PDGF-BB↓↓ FGF↓↓ HB EGF↓↓ TNF-α↓↓ glucose utilization↑↑ fatty acid oxidation↑↑ insulin signalling↑↑ glucose uptake↑↑ gluconeogenesis↓↓ anti-atherogenic actions insulin-sensitizing actions A. Wiecek, M. Adamczak, J. Chudek: Nephrol Dial Transplant, 2007
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

AMPK activity is increased by adiponectin and regulates podocyte permeability

- NG – normal glucose
- HG – High glucose
- ACAR - AMPK activator
- ARA - AMPK inhibitor

ZO-1 (tight junction protein) localization is regulated by adiponectin and AMPK in podocytes

• NG — normal glucose
• HG — High glucose
• ACAR - AMPK activator
• ARA - AMPK inhibitor

Adiponectin restores normoalbuminuria and increases AMPK activity

The increased incidence of obesity-related glomerulopathy is plotted as a percentage of total native renal biopsies received over a 15-year period.

Obesity-Related Glomerulopathy


Focal and segmental glomerulosclerosis

- Hypertrophic podocytes that contain intracytoplasmic droplets of fat resorption (arrow) and prominent nucleoli (arrow)

Electron microscopy. Large-sized podocyte with intracytoplasmic lipids and focal foot process fusion (uranyl acetate and lead citrate stain, original magnification)

Global mesangial matrix increase in both glomeruli

- Glomerulus with glomerulomegaly from an extremely obese patient and glomerulus without glomerulomegaly from a control of the same age

Mild fusion of podocytes and condensations of cytoskeletal filaments with a parallel orientation to the glomerular basement membrane
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 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>
</tr>
</tbody>
</table>

*P<0.001*

Renal survival (endpoints defined as doubling of serum creatinine or ESRD) over time in ORG, O-FSGS, and control I-FSGS.

Renal survival in patients with obesity-associated FSGS (OB.-FSGS) and idiopathic FSGS (I-FSGS)

**Risk factors associated with glomerular lesions in extremely obese patients and normal-weight controls**

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P-value</td>
<td>OR 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.79 (0.90-3.57)</td>
<td>0.097</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00 (0.73-1.37)</td>
<td>0.977</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg m&lt;sup&gt;-2&lt;/sup&gt;)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.99 (1.59-2.50)</td>
<td>&lt;0.001</td>
<td>1.99 (1.59-2.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.51 (1.15-1.98)</td>
<td>0.003</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.43 (1.05-1.96)</td>
<td>0.026</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum fasting glucose (mmol L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.29 (0.96-1.74)</td>
<td>0.087</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.21 (0.84-1.74)</td>
<td>0.302</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.77 (0.35-1.68)</td>
<td>0.508</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Serra A et al. Kidney Int; (2008) 73, 947–955*
Glomerular areas in extremely obese (EO) patients with or without sleep apnea syndrome (SAS) and in controls

Evolution of serum creatinine in obese vs normal weight patients after unilateral nephrectomy

Probability of normal renal function in obese (dashed line) and nonobese (solid line) patients (log-rank test, $P < 0.001$) after unilateral nephrectomy.

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

Body weight and food intake in rats treated with telmisartan, valsartan, or in untreated controls

Sugimoto K., et al., Hypertension, 2006, 47, 1003-1009
Fat mass and serum leptin levels in rats treated with telmisartan, valsartan or in untreated controls

Sugimoto K. et al., Hypertension, 2006, 47, 1003-1009
Changes in BMI (□) and proteinuria (line) in the (top) diet group and (bottom) control group.

Morales E. et al., Am. J. Kidney Dis., 2003, 41: 319-327
Telmisartan decrease albuminuria in obese patients with hypertension

** P<0.01 vs baseline

Redón i wsp. Pharmacogenomics J. 2005;5:14–20
• Obesity is important factor associated with:
  – obesity-associated focal segmental glomerulosclerosis (FSGS)
  – progression of others already existing (np. IgA nephropathy, ADPKD)
  – progression of kidney graft nephropathy
  – Increase probability of preeclampsia
Thank you for your attention!

Katowice
Conclusion:

Obesity has been shown to increase the risk of both the development and the progression of renal failure, even after correction for other comorbid conditions.
• Szczury z nadciśnieniem samoistnym i otyłe szczury Zucker wykazują oporność na efekt natriuretyczny leptyny


• To osłabienie działania natriuretycznego i diuretycznego leptyny może być spowodowane przez wzrost podstawowej aktywności układu współczulnego u tych szczurów lub stymulacją układu współczulnego przez leptynę, co prowadzi do nasilenia reabsorpcji sodu

1. U osób otyłych oporność na uszkadzające kłębuszki działanie leptyny

2. Glomerulopatia towarzysząca otyłości wykazuje znamienną zależność od hiperfiltracji indukowanej zwiększonym poborem pokarmów oraz hipertriglicerydemi}

Stężenie adiponektyny u hemodializowanych chorych (HD)

P < 0,001

Adiponectin (µg/ml)

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>71</td>
<td>33</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 2</td>
<td>50 ± 2</td>
</tr>
</tbody>
</table>

• Hamowanie układu RAS może zwiększać liczbę młodych, świeżo zróżnicowanych adipocytów które są bardziej insulinowrażliwe niż starsze, większe adipocyty

• Fakt ten może wyjaśniać obserwacje, że hamowanie układu RAS może zmniejszać ryzyko rozwoju cukrzycy typu 2
Probability of negative proteinuria in obese (dashed line) and nonobese (solid line) patients

Rate of progression of renal insufficiency (slope of GFR expressed as the change in ml/min per year) in relation to high and low levels of LDL cholesterol, in mmol/l, and the amount of urinary total protein excretion, above and below a cut-off level of 3.0 g per 24 h.

Samuelsson O i wsp., Nephrol Dial Transplant, 1997; 12; 1908-1915
Endothelin-1 expression in HUVECs is induced by leptin. HUVECs were incubated with various concentrations of leptin for 24 hours (A) and with 500ng/mL leptin for several time periods (B) to demonstrate dose- and time-dependent ET-1 induction. ET-1 content in cell culture supernatants was measured with ELISA. The results represent the mean±SEM of at least 3 experiments. *P<0.05 compared with unstimulated HUVECs.

Wpływ czynników wytwarzanych przez tkankę tłuszczową na śródbłonek naczyń

**Tkanka tłuszczowa**

- ↑ Leptyna
- ↑ IL-6
- ↑ FFA
- ↓ Adiponektyna
- ↑ Angiotensyna II
- ↑ TNFα

- ↑ CRP

- ↑ Molekuły adhezyjne

**Endoteliu**m

- ↑ MCP-1
- ↑ M-CSF

Wpływ leczenia telmisartanem lub walsartanem vs grupa kontrolna na objętość i liczbę adipocytów u szczurów

Sugimoto K et al. Hypertension 2006, 47, 1003-1009
Regulacja czynności układu sercowo-naczyniowego przez AGT i Ang II uwalniane z tkanki tłuszczowej

Adipose tissue

Large adipose depots
- pAGT↑
- Ang II
- NE↑
- Blood pressure↑

Perivascular adipocytes
- Ang II↑
- NE↑
- Vascular resistance↑

Tkanka tłuszczowa uczestniczy w:

• Regulacji łaknienia
• Regulacji ciśnienia tętniczego
• Insulinooporności
• Angiogenezie
• Powiklaniach miażdżycowych
• Zaburzeniach hemostazy i hematologicznych
• Regulacji układu odpornościowego
• Regulacji funkcji neuroendokrynnych
• Glomerulopatii zależnej od otyłości

Dlatego też przemiany zachodzące w tkance tłuszczowej powinny interesować również nefrologa!
Rola leptyny w patogenezie przewlekłej choroby nerek (CKD)

- Leptyna stymuluje proliferację komórek śródbłonka kłębuszków nerekowych zarówno in vitro jak i in vivo oraz transkrypcję i sekrecję TGRβ1 – cytokiny uczestniczącej w procesie włóknienia

- Podawanie leptyny u szczurów powoduje białkomocz oraz rozplem komórek macierzy kłębuszków nerkowych

Wolf G. et al., Kidney Int., 1999, 56, 860-872
Liczba chorych u których występuje białkomocz w kolejnych latach po jednostronnej nefrektomii u osób otyłych

Podsumowanie

- W leczeniu uszkodzenia nerek w przebiegu otyłości korzystny wpływ wywiera:
  - Zmniejszenie (normalizacja) masy ciała
  - Inhibitory konwertazy (prylaty, ACEi)
  - Blokery receptora AT$_1$ dla AlI (sartany, ARBs); szczególnie korzystne działanie telmisartanu
  - Blokery receptora mineralokortykoidowego (badania doświadczalne z eplerenonem)
Obesity - the public health problem in Western Countries
Adjusted survival-curve obtained from a Cox proportional hazard analysis for two levels of baseline triglycerides (Tg) in patients with PCKD and GN

Massy ZA i wsp., Nephrol Dial Transplant, 1999; 14; 2392-2397
The most important adipokines, chemokines release by adipocytes and matrix of adipose tissue responsible for CV and renal disease (1)

- PA I-1
- TGF-β
- Tissue factor (TF)
- Complement factors (e.g. adipsin)
- Adipocyte complement- related protein (Adipo-a)
- TNF-α
- Acylation stymulation protein (ASP)
- Agouti Protein
- Angiotensinogen, Renin, ACE
- Chymase, cathepsin D,G
- Angiotensin II
- Prostaglandins (PGI₂, PGF₂α)
- Insulin growth factor-1 (IGF1)
Pooled RR and 95% CI of KD in 18 general population cohort studies according to BMI categories

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>Number of cohorts</th>
<th>Underweight (BMI &lt; 18.5)</th>
<th>Normal (18.5 ≤ BMI &lt; 25)</th>
<th>Overweight (25 ≤ BMI &lt; 30)</th>
<th>Obesity (BMI ≥ 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender difference</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All studies</td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>11</td>
<td>0.63 (0.48–0.85)</td>
<td>1 (ref)</td>
<td>1.31 (1.18–1.45)</td>
<td>1.49 (1.36–1.63)</td>
</tr>
<tr>
<td>Women</td>
<td>11</td>
<td>1.11 (0.98–1.25)</td>
<td>1 (ref)</td>
<td>1.41 (1.32–1.50)</td>
<td>1.02 (1.78–2.07)</td>
</tr>
<tr>
<td>KD excluding kidney cancer/RCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Men</td>
<td>3</td>
<td>0.73 (0.52–1.03)</td>
<td>1 (ref)</td>
<td>1.59 (1.12–2.26)</td>
<td>1.33 (1.08–1.63)</td>
</tr>
<tr>
<td>Women</td>
<td>4</td>
<td>1.14 (1.00–1.30)</td>
<td>1 (ref)</td>
<td>1.48 (1.32–1.66)</td>
<td>1.99 (1.77–2.24)</td>
</tr>
<tr>
<td>Kidney cancer/RCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8</td>
<td>0.45 (0.27–0.78)</td>
<td>1 (ref)</td>
<td>1.21 (1.15–1.27)</td>
<td>1.53 (1.38–1.69)</td>
</tr>
<tr>
<td>Women</td>
<td>7</td>
<td>0.86 (0.59–1.26)</td>
<td>1 (ref)</td>
<td>1.38 (1.28–1.49)</td>
<td>1.87 (1.69–2.07)</td>
</tr>
<tr>
<td>BMI assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly measured</td>
<td>9</td>
<td>0.76 (0.56–1.04)</td>
<td>1 (ref)</td>
<td>1.38 (1.22–1.56)</td>
<td>1.78 (1.33–2.40)</td>
</tr>
<tr>
<td>Self-reported</td>
<td>9</td>
<td>1.07 (0.94–1.20)</td>
<td>1 (ref)</td>
<td>1.39 (1.27–1.53)</td>
<td>1.84 (1.56–2.17)</td>
</tr>
<tr>
<td>Specific KD outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KD excluding kidney cancer/RCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>3</td>
<td>1.30 (0.52–3.24)</td>
<td>1 (ref)</td>
<td>1.26 (1.10–1.45)</td>
<td>1.34 (0.86–2.09)</td>
</tr>
<tr>
<td>ESRD</td>
<td>2</td>
<td>NR†</td>
<td>1 (ref)</td>
<td>1.68 (1.49–1.90)</td>
<td>4.07 (2.87–5.76)</td>
</tr>
<tr>
<td>Kidney stone</td>
<td>3</td>
<td>1.08 (0.95–1.22)</td>
<td>1 (ref)</td>
<td>1.41 (1.18–1.69)</td>
<td>1.75 (1.36–2.25)</td>
</tr>
<tr>
<td>Kidney cancer/RCC</td>
<td>10</td>
<td>0.70 (0.51–0.95)</td>
<td>1 (ref)</td>
<td>1.31 (1.23–1.40)</td>
<td>1.71 (1.53–1.93)</td>
</tr>
</tbody>
</table>

BMI: body mass index; CI: confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; KD, kidney disease; RR, relative risk; RCC, renal cell carcinoma.

*Data from one study shown in Table 1 are excluded in this table.

bGender difference. ***P < 0.001; **P < 0.01.

†NR, No results were reported for underweight.

Wang Y. et al., Kidney Int., 2008; 73 18-23
In this retrospective cohort study of 320,252 adults who were followed for 15 to 35 years, the rate of ESRD increased in a stepwise manner as body mass index (BMI) increased.

Age-, sex-, and race-adjusted rates of ESRD increased from 10 per 100,000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m²) to 108 per 100,000 among those with extreme obesity (BMI 40 kg/m²).

This relationship was not affected by blood pressure levels or diabetes.

**Implications**

High BMI is a potentially modifiable risk factor for ESRD.
The most important adipokines, chemokines release by adipocytes and matrix of adipose tissue responsible for CV and renal disease (2)

- Vascular endothelial growth factor (VEGF)
- Macrophage inhibitor factor (MIF)
- Sex hormones (in women: testosterone, estradiol and estrone)
- Glucocorticoids
- Leptin
- Adiponectin
- Resistin
- Visfatin
- IL-6
- NO
- PPAR-γ
- Atrial natriuretic peptide (ANP)