The 19th Budapest Nephrology School
(Nephrology, Hypertension, Dialysis, Transplantation)

26-31 August 2012

Metabolic Syndrome, Obesity, Hypertension and Chronic Kidney Disease

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Obesity - the public health problem not only in a Western Countries
Obese female mammoth ivory figurine produced at least 35000 calendar 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
Obesity Trends Among U.S. Adults

BMI ≥30 kg/m²

1990

1998

2006

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

Regional variation in prevalence of obesity (BMI ≥ 30 kg/m²) in Europe

Prevalence of overweight or obesity in children

Attributions of responsibility for addressing the problem of childhood obesity, according to the political ideology of the respondents

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The cluster of co-morbidities associated with and aggravated by obesity

- Metabolic syndrome
- Diabetes mellitus
- High blood pressure
- Chronic kidney disease
- Cardiovascular disease
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.
Estimated hazard ratio for death from any cause according to Body-Mass Index (BMI) among black women who never smoked

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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.

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)

Hunley TE et al. Curr Opin Nephrol Hypertens., 2010; 19: 227-
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
Metabolic syndrome and risk for development of estimated GFR <60 ml/min per 1.73 m²

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitiyakara 2007</td>
<td>1.36</td>
<td>0.89</td>
<td>2.09</td>
<td>1.40</td>
<td>0.16</td>
</tr>
<tr>
<td>Kurella 2005</td>
<td>1.43</td>
<td>1.18</td>
<td>1.73</td>
<td>3.66</td>
<td>0.00</td>
</tr>
<tr>
<td>Lucove 2008</td>
<td>1.29</td>
<td>1.05</td>
<td>1.59</td>
<td>2.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Luk 2008</td>
<td>1.31</td>
<td>1.12</td>
<td>1.54</td>
<td>3.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Ninomiya 2006</td>
<td>2.08</td>
<td>1.23</td>
<td>3.52</td>
<td>2.73</td>
<td>0.01</td>
</tr>
<tr>
<td>Rashidi 2007</td>
<td>1.88</td>
<td>1.26</td>
<td>2.80</td>
<td>3.10</td>
<td>0.00</td>
</tr>
<tr>
<td>Ryu 2009</td>
<td>2.12</td>
<td>1.56</td>
<td>2.89</td>
<td>4.75</td>
<td>0.00</td>
</tr>
<tr>
<td>Sun 2010</td>
<td>1.30</td>
<td>1.24</td>
<td>1.36</td>
<td>11.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Tozawa 2007</td>
<td>1.36</td>
<td>0.84</td>
<td>2.19</td>
<td>1.26</td>
<td>0.21</td>
</tr>
<tr>
<td>Watanabe 2010</td>
<td>2.12</td>
<td>1.80</td>
<td>2.49</td>
<td>9.12</td>
<td>0.00</td>
</tr>
</tbody>
</table>

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

Individual components of metabolic syndrome and their risk for development of eGFR <60 ml/min per 1.73 m²

Table 3. Individual components of metabolic syndrome and their risk for development of eGFR <60 ml/min per 1.73 m²

<table>
<thead>
<tr>
<th>Components of Metabolic Syndrome</th>
<th>Number of Studies/Patients</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated blood pressure</td>
<td>8/26,405</td>
<td>1.61 (1.29, 2.01)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>8/26,405</td>
<td>1.14 (1.03, 1.26)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>8/28,721</td>
<td>1.27 (1.11, 1.46)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>8/26,632</td>
<td>1.23 (1.12, 1.36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Obesity</td>
<td>9/28,897</td>
<td>1.19 (1.05, 1.34)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

eGFR, estimated GFR; CI, confidence interval.

Number of components of metabolic syndrome and its associations with development of eGFR <60 ml/min per 1.73 m²

<table>
<thead>
<tr>
<th>Number of Components of Metabolic Syndrome</th>
<th>Number of Studies/Patients</th>
<th>Odds Ratio (95% CI)(^a)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/7460</td>
<td>1.42 (0.91, 2.22)</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>6/24,158</td>
<td>1.39 (1.09, 1.78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>5/23,371</td>
<td>1.42 (1.22, 1.67)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4</td>
<td>5/23,497</td>
<td>1.66 (1.53, 1.79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5</td>
<td>3/22,134</td>
<td>1.96 (1.71, 2.24)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(eGFR\), estimated GFR; CI, confidence interval.
\(^a\)\(P\) for trend 0.02.
Odds ratio for chronic kidney disease associated with individual components of the metabolic syndrome

Tanner RM et al.: Curr Hypertens Rep 2012; 14: 152-159
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).

**Abbreviation**
- CKD: chronic kidney disease
- ESRD: end-stage renal disease
- KS: kidney stone
- KC: kidney cancer
- RCC: renal cell carcinoma

*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
Association between the development of CKD (eGFR 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.

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.

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 MS](image)
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Factors implicated in the pathogenesis of CKD in obesity

- ↑ renin angiotensin system
- ↑ aldosterone
- ↑ sympathetic nervous system
- ↑ insulin resistance
- ↑ salt 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
  - \( \uparrow \) glomerular filtration rate
  - \( \uparrow \) glomerular filtration fraction
  - \( \uparrow \) albuminuria

- **Structural**
  - \( \uparrow \) kidney weight
  - \( \uparrow \) glomerular planar surface
  - Mesangial expansion
  - Podocyte injury

- **Pathologic**
  - Glomerulomegaly
  - Glomerulosclerosis
  - Obesity related glomerulopathy

- **Chronic kidney disease**
  - \( \uparrow \) onset of kidney disease
  - \( \uparrow \) progression to kidney failure
  - \( \uparrow \) proteinuria

- **End-stage renal disease**
  - \( \uparrow \) incidence and prevalence
  - Survival advantage in hemodialysis
  - \( \uparrow \) graft loss in kidney transplant recipients

- **Other**
  - \( \uparrow \) renal cell carcinoma
  - \( \uparrow \) 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.

**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)
Physiologic/pathophysiologic significance of an adipocyte RAS

Adipocyte RAS

**Systemic Effects**
- Contribute to Systemic RAS

**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

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
Adiponectin

**anti-atherogenic actions**
- lipids accumulation in monocyte derived macrophages
- scavenger receptors
- superoxide
- VCAM-1
- ICAM-1
- E-selectin

**insulin-sensitizing actions**
- TNF-α
- NO
- TIMP
- PDGF-BB
- FGF
- HB EGF
- glucose utilization
- fatty acid oxidation
- insulin signalling
- glucose uptake
- gluconeogenesis

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.

Glomerular hyperfiltration
Increased renal sodium absorption
Increased vasoactive hormones
Elevated systemic blood pressure

Obesity

Insulin resistance

Dietary protein

Inflammatory cells

AGE inhibitor

Lipid peroxidation

AGEs

RAGE

RAGE-independent pathway

Cytosolic superoxide
Mitochondrial superoxide
NF-κB

Growth factors
Inflammatory cytokines (MCP-1, MIF)

Altered vessel permeability, glomerular sclerosis

Obesity-related renal dysfunction

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

Low – low AGE-containing diet
High – high AGE-containing diet
* p<0.05
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)

**Plasma MCP-1**

*(monocyte chemotactic protein-1)*

**Urine 8-isoprostane**

**Plasma MIF**

*(macrophage migration inhibitory factor)*

Low – low AGE-containing diet
High – high AGE-containing diet
* p<0.05

Confirmation of microarray data of gene expression in the glomeruli of ORG patients by real time PCR

The distribution of VEG, TGF α, and GLUT1 in the glomeruli of ORG patients and controls by immunohistochemistry staining.

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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-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><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

Obesity-Related Glomerulopathy

Focal and segmental glomerulosclerosis

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

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

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
Glomerular area:

58567,15 $\mu$m$^2$

25056,56 $\mu$m$^2$

BMI = 41.8 kg/m$^2$

BMI = 22.3 kg/m$^2$

HE $\times$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

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).

Relationship of proteinuria and weight changes in diet-group patients

R=0.62, p<0.01

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)

Study results for obese patients before and after bariatric surgery

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>110.54 ± 18</td>
<td>86.33 ± 17*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>43.83 ± 8.1</td>
<td>34.04 ± 6.7*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>132.55 ± 13</td>
<td>120.8 ± 11*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78.71 ± 9.2</td>
<td>72.15 ± 8*</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>80.32 ± 14</td>
<td>69.6 ± 13*</td>
</tr>
<tr>
<td>eGFR CG-LBW (ml/min)</td>
<td>76.26 ± 9</td>
<td>86.63 ± 18*</td>
</tr>
<tr>
<td>eGFR CKD-Epi (ml/min)</td>
<td>80.99 ± 18</td>
<td>103.6 ± 19*</td>
</tr>
<tr>
<td>eGFR-adjusted CKD-Epi (ml/min/BSA in m²)</td>
<td>102.25 ± 50</td>
<td>98.02 ± 45</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.87 ± 0.8</td>
<td>1.65 ± 0.7*</td>
</tr>
</tbody>
</table>

* P value < 0.05

Abouchacra S et al.: Int Urol Nephrol, Published on line 03 March, 2012
Exercise augments weight loss induced improvement in renal function in obese metabolic syndrome individuals

Nora E. Straznicky\textsuperscript{a}, Mariee T. Grima\textsuperscript{a}, Elisabeth A. Lambert\textsuperscript{a}, Nina Eikelis\textsuperscript{b}, Tye Dawood\textsuperscript{a}, Gavin W. Lambert\textsuperscript{a}, Paul J. Nestel\textsuperscript{c}, Kazuko Masuo\textsuperscript{a}, Carolina I. Sari\textsuperscript{a}, Reena Chopra\textsuperscript{a}, Justin A. Mariani\textsuperscript{d} and Markus P. Schlaich\textsuperscript{b}

Objective Metabolic syndrome (MetS) obesity is an independent risk factor for chronic kidney disease. This study was conducted to examine the effects of lifestyle interventions on renal parameters and putative metabolic, neuroadrenergic and hemodynamic mediators of renal injury.

Methods Untreated men and women (mean age 55 ± 1 years; BMI 32.7 ± 0.6 kg/m\textsuperscript{2}) without pre-existing renal dysfunction, who fulfilled MetS criteria were randomized to dietary weight loss (WL, \(n=13\)), weight loss combined with aerobic exercise (WL + EX, \(n=13\)), or no treatment (control, \(n=12\)). Estimated glomerular filtration rate (eGFR), 24 h urinary albumin excretion, plasma renin activity (PRA), muscle sympathetic nerve activity (MSNA), baroreflex sensitivity (BRS), anthropometric, metabolic and fitness variables were measured at baseline and week 12.

Conclusion Moderate weight loss in obese MetS patients is associated with a reduction in albuminuria and an improvement in eGFR which is augmented by exercise co-intervention. \textit{J Hypertens} 29:553–564 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2011, 29:553–564

Keywords: aerobic exercise, albuminuria, metabolic syndrome, obesity, renal function, sympathetic nervous system, weight loss

Abbreviations: BRS, baroreflex sensitivity; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; MDRD, Modification of Diet in Renal Disease; MetS, metabolic syndrome; MSNA, muscle sympathetic nervous activity; NEFA, non-esterified fatty acids; OGTT, oral glucose tolerance test; PRA, plasma renin activity; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; \(\dot{V}O_{2\max}\), maximal oxygen consumption during incremental cycle ergometry protocol; WL, weight loss by hypocaloric diet; WL + EX, weight loss by hypocaloric diet and aerobic exercise.
a) Resting muscle sympathetic nerve activity expressed as burst incidence before and after 12 weeks lifestyle intervention with weight loss by caloric restriction (WL), weight loss by caloric restriction and aerobic exercise (WL+EX), or no treatment (Control).

b) Individual and average changes in MSNA burst incidence

Straznicky N.E. et al., J. Hypertens., 2011, 29, 553-564
Individual and average changes in serum creatinine (a) and eGFR (b) after 12 weeks lifestyle intervention with weight loss by caloric restriction (WL), weight loss by caloric restriction and aerobic exercise (WL+EX) or no treatment (Control).

Straznicky N.E. et al., J. Hypertens., 2011, 29, 553-564
Bariatric surgery has shown benefit in treating type 2 diabetes, hyperlipidaemia and obesity.
The incidence of type 2 diabetes mellitus per 1000 person-years in the bariatric surgery and control groups, according to deciles of baseline glucose levels (A), serum insulin levels (B) and BMI (C)

Changes of the glycated hemoglobin (A), fasting plasma glucose (B), average number of diabetes medications (C) and BMI (D) in obese patients with diabetes mellitus who received bariatric surgery or intensive medical therapy only.

Effect of surgical interventions on glomerular hyperfiltration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>After surgery</th>
<th>Before surgery</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Brochner-Mortensen 1980</td>
<td>123</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Chagnac 2003</td>
<td>110</td>
<td>39.59</td>
<td>8</td>
</tr>
<tr>
<td>Navarro-Diaz 2006</td>
<td>117.9</td>
<td>33.99</td>
<td>61</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 0.78, \text{df}=2 (P=0.68); I^2 = 0\% \\
Test for overall effect: \( Z = 4.70 (P = 0.00001) \)
Potential adverse impact of bariatric surgery on renal function, exacerbated by postoperative renal failure and renal calcium oxalate precipitation

Adverse impact of bariatric surgery on renal function

Postoperative renal failure

Late complications

Oxalate stone

Oxalate nephropathy

ESRD

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: 1122-28
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
The increased incidence of obesity-related glomerulopathy (ORG) is plotted as a percentage of total native renal biopsies received over a 15-year period.
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
Hyperfiltration and hypertension - hemodynamic consequences of obesity

HTN, hypertension; Na, sodium; AA, afferent arteriole; EA, efferent arteriole

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?
  - blockers of the RAS
  - cessation of cigarette smoking
Hypertension – Obesity – Metabolic Syndrome – Kidney Disease
The Morbid Pathway

- Hypertension
- Obesity
- Glomerulosclerosis
Hypertension – Obesity – Metabolic Syndrome – Kidney Disease
The Morbid Pathway

- Obesity
- Metabolic Syndrome
- Glomerulosclerosis
Hypertension – Obesity – Metabolic Syndrome – Kidney Disease
The Morbid Pathway
Hypertension – Obesity – Metabolic Syndrome – Kidney Disease
The Morbid Pathway
Thank you for your attention!

Andrzej Wiecek
Katowice