Metabolic syndrome
an emerging threat to renal function

Eberhard Ritz
Heidelberg (Germany)
Metabolic syndrome: an emerging threat to renal function

- History
- The concept of metabolic syndrome
- The role of visceral obesity
- Renal function and renal disease in the metabolic syndrome
- Renal morphology in the metabolic syndrome
- Pathomechanisms linking visceral obesity to renal damage
Venus of Laussel
(Gravettien period,
25,000 years,
found 1911)
Obesity –
a longstanding German tradition

Venus of “Hohler Fels“
female mammoth ivory figurine; 35,000 years old (Aurignacien)

Conard, Nature (2009)460:737
Evolution of body mass index – historical perspective

changing relation of body mass between adorer and adoree
Evolution prepared humans well for surviving fasting, but poorly for combating fast food.

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• Hitzenberger K.  
  Ein Beitrag zum Stoffwechsel bei vaskulärer Hypertonie  
  

• Kylin E.  
  Hypertonie-Hyperglykämie-Hyperurikämie Syndrom  
  
  Kylin, Zentralblatt für Inn. Medizin (1923) 44:105

• Reaven 1988 (Banting lecture)  
  Syndrome X = insulin resistance  
  
  Reaven, Diabetes (1988) 37:1595
Definition of the metabolic syndrome
NCEP criteria

( *National Cholesterol Education Program; Adult Treatment Panel /// (ATPIII)*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>&gt;102 cm, &gt;88 cm</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL, &lt;50 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

*The NCEP criteria require at least three of the five risk factors.*

*JAMA (2001) 285: 2486*
Reviews/Commentaries/ADA Statements
ADA Statement

The Metabolic Syndrome: Time for a Critical Appraisal

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

Richard Kahn, PHD\textsuperscript{1}, John Buse, MD, PHD\textsuperscript{2}, Ele Ferrannini, MD\textsuperscript{3} and Michael Stern, MD\textsuperscript{4}

\textsuperscript{1} American Diabetes Association, Alexandria, Virginia
\textsuperscript{2} Division of Endocrinology and of General Medicine & Clinical Epidemiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina
\textsuperscript{3} Department of Internal Medicine, University of Pisa School of Medicine, Pisa, Italy
\textsuperscript{4} Division of Clinical Epidemiology, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas

Diabetes Care (2005) 28:2289
Voices of dissent

- Insulin resistance as the unifying aetiology uncertain
- Criteria arbitrary; no clear basis for including/excluding CVD risk factors and rationale for thresholds ill defined
- the CVD risk associated with ‘syndrome’ is no greater than sum of parts

The "father" of syndrome X:

The Metabolic Syndrome: Requiescat in Pace

Gerald M. Reaven

Values for insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy individuals, with at least a sixfold variation between the most insulin sensitive and most insulin resistant of these individuals. The more insulin resistant a person, the more insulin must be secreted to prevent this phenomenon, I cite 14 articles (3-16) that represent a small sample of those published on this topic in 2004; they were based primarily on retrospective analyses of population-based studies, conducted in several countries, with experimental data gathered for a variety of different reasons, in groups differing in terms of age, sex, and
Justification for the concept of the metabolic syndrome

- counselling tool for promoting public awareness
  (gaining momentum in public discussion)
- the prize one has to pay: not a good predictor of CV disease or diabetes
  (poor to resolve scientific issues)

Is the link between obesity and ESRD fully explained by the high prevalence of diabetes and hypertension in obesity?

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waist circumference
♂ 102 cm, ♀ 88 cm
Not all obesity is created equal

**Android (apple) vs. gynoid (pear) obesity**

A tribute to a pioneer: Jean Vague (1947)

(visceral obesity)

---

narrow waist:

I am female,
I am young,
I am not pregnant

Low B.S.
Why sex matters: a Darwinian look at human behaviour

---

J. Vague,
La différentiation sexuelle. Facteur determinant de l'obésité
Obesity and kidney

Ritz, Semin.Nephrol.(2009) 29:504

# kidney problems other than parenchymal renal disease,
(kidney cancer, nephrolithiasis)

# a specific form of primary kidney disease related to obesity
(focal segmental glomerulosclerosis FSGS)
Kambham, Kidn.Internat,(2001)59:489

# impact of obesity on primary kidney disease
(lgA-GN, kidney allograft, (pre)diabetic nephropathy , uninephrectomy …)
Bonnet,Am.J.Kidn.Dis.(2001)37:720
Obesity and non-neoplastic kidney disease
894 576 participants, 61% male, recruitment age 46±11 years

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25 kg/m²</td>
<td>1.14</td>
<td>(0.74-1.77)</td>
</tr>
<tr>
<td>25-50 kg/m²</td>
<td>1.59</td>
<td>(1.27-1.99)</td>
</tr>
<tr>
<td>diabetes</td>
<td>0.96</td>
<td>(0.59-1.55)</td>
</tr>
<tr>
<td>25-50 kg/m²</td>
<td>2.16</td>
<td>(1.89-2.46)</td>
</tr>
</tbody>
</table>

Prospective Studies Collaboration, Lancet (2009) 373:1083
Body mass index (BMI) at age 20 years – an important determinant of CKD in adult life

Risk of advanced CKD (S-creatinine > 3.4 mg/dl)

Swedish nationwide case control study

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>odds ratio</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>men</td>
<td>women</td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 25</td>
<td>3.1 (2.1-4.8)</td>
<td>3.0 (1.4-6.1)</td>
<td></td>
</tr>
</tbody>
</table>

BMI – an independent predictor of endstage renal disease in USA

Risk of ESRD attributable to obesity higher in young than in older subjects  
*(underestimate - at higher age competing CV risk?)*

Because of high CV mortality the old individuals have not had sufficient time to develop ESRD

Hazard ratio

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>&lt;18.5</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>35.0-39.9</th>
<th>&gt;40.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td>0.2</td>
<td>1.0</td>
<td>1.8</td>
<td>4.4</td>
<td>7.3</td>
<td>11.6</td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>0.8</td>
<td>1.0</td>
<td>1.9</td>
<td>3.1</td>
<td>5.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*cardiovascular death – competing risk factor?*

IgA glomerulonephritis
risk of renal function deterioration as a function of BMI

Bonnet, Am.J.Kidn.Dis.(2001) 37:720
Correlation between **BMI** and filtration fraction (FF) 
*index of glomerular hypertension*
even **within the normal range** of BMI

\[ r^2 = 0.205 \]

Indirect evidence for causality

Body weight reduction in morbid obesity by bariatric surgery

⇒ reduction of GFR, RPF and albuminuria

BMI 48±2.4 → 33±1.5 kg/m²

GFR

Glomerular Filtration Rate (ml/min)

P=0.01

RPF

Renal Plasma Flow (ml/min)

P<0.02

Albuminuria 16 → 5 µg/min

CKD in obese patients

**weight loss with diet** ⇒ **reduction of proteinuria**

“prospective controlled study”

• Stabilisation of CKD after bariatric surgery
  

• Focal-segmental glomerulosclerosis of 16-year old patient with extreme obesity – normalisation of proteinuria after “bariatric surgery“
  

• Oxalosis (± uremia) after bariatric surgery
  
  *Montagnac, Nephrol.Ther. (2011)7:38*
**Waist-hip ratio** superior to **BMI**
as predictor of chronic kidney disease (CKD)

ARIC and CHS studies;
21,258 participants with normal creatinine at baseline;
observation 9.3 years

- 1 SD increase in **waist-hip ratio**
- 22% higher risk of CKD
- 1 SD increase in **BMI**
- no significant increase

*Elsayed, Am.J.Kidn.Dis.(2008)52:29*

**waist-hip ratio** assesses **visceral fat**
**BMI** comprises both subcutaneous and visceral fat,
and also muscle, bone, ECC fluid

*Ritz, Am.J.Kidn.Dis.(2008)52:1*
Renal pathology in visceral obesity

Visceral obesity  →  microalbuminuria

Pinto-Sietsma, American Journal Kidney Disease (2003) 41:733

Glomerulomegaly, reduced podocyte number, segmental glomerulosclerosis


Glomerulomegaly, increased mesangial matrix, mesangial cell proliferation, podocyte hypertrophy


Tubular atrophy, interstitial fibrosis, arterial sclerosis

Hyperfiltration of young men with metabolic syndrome

1572 young men (mean age 18 years)

risk of hyperfiltration (Cockcroft-Gault Ccr > 2SD above median) →

6.9 times elevated

Visceral obesity and the kidney
(“normal weight obesity”)

even when corrected for body mass index (BMI) central fat distribution (waist-hip ratio) :

- greater risk of microalbuminuria
  \[ RR \ 1.7 \ (1.19-3.12) \]

- greater risk of diminished eGFR
  \[ RR \ 1.9 \ (1.19-3.12) \] lean
  \[ 2.0 \ (1.19-31.9) \] overweight
  \[ 2.7 \ (1.46-4.85) \] obese

Pinto-Sietsma, Am.J.Kidn.Dis.(2003) 41: 733
Visceral obesity predictor of microalbuminuria in type 1 diabetes

Waist circumference – a stronger predictor than BMI of new onset CKD in type 2 diabetics

Luk, Diabetes Care (2008) 31:2357
Causal role of metabolic syndrome in the genesis of albuminuria:

*Horses with metabolic syndrome develop albuminuria*

(apart from hyperinsulinemia, insulin resistance and dyslipidemia)

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*Venus of Willendorf 4000 BC*
Early renal malfunction / pathology linking metabolic syndrome with chronic kidney disease

- glomerular hypertension
- endothelial dysfunction
- vasoconstriction (vas efferens)
- matrix proliferation and expansion,
  - glomerular and interstitial

Metabolic syndrome and de novo CKD
9 year observation in nondiabetic individuals

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>unadjusted</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>eGFR &lt;60ml/min/1.73m²</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>increased s-creatinine</th>
<th>1%</th>
<th>3%</th>
<th>1.92</th>
<th>1.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>(♂&gt;1.5mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(♀&gt;1.2mg/dl)</td>
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</tbody>
</table>

even after adjustment for newly diagnosed hypertension and diabetes

metabolic syndrome independent additive risk

Metabolic syndrome risk factors and prevalence of chronic kidney disease or microalbuminuria

prevalence CKD (%)

prevalence microalbuminuria (%)

waist circumference: >102cm (men)
fasting glucose: >110mg/dl
HDL-C: <40mg/dl
triglycerides: >140mg/dl
blood pressure: >130/80mmHg

Metabolic syndrome and stage of diabetic nephropathy in type 1 diabetics

Thorn, Diabetes Care (2005) 28: 2019
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Glomerulomegaly, reduced podocyte number, segmental glomerulosclerosis


Glomerulomegaly ... increased mesangial matrix, mesangial cell proliferation, podocyte hypertrophy


Tubular atrophy, interstitial fibrosis, arterial sclerosis

Morbid obesity with “focal segmental glomerulosclerosis”


Progressive increase of “obesity related glomerulopathy”

(Columbia University, New York)

Glomerular hypertrophy and podocyte pathology in obesity related glomerulopathy

Beyond the glomeruli
Alexander M. et al
*Kidney pathological changes in metabolic syndrome*

**metabolic syndrome**

interstitial fibrosis; tubular atrophy

**control**

arterial sclerosis *(arrow)*
Extremely obese individuals despite normal renal function: marked glomerular lesions

Focal adhesions to Bowman’s capsule

Mesangial matrix increase

Hypertrophic podocytes with prominent nucleoli and intracytoplasmic fat droplets

Glomerulomegaly of extremely obese individual

Glomerulus of normal individual

Obesity related glomerulopathy
glomerular gene expression by microarray and real time PCR

Wu, Endocrinology (2006) 147:44
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Venus of Willendorf 4000 BC
Pathomechanisms linking metabolic syndrome with chronic kidney disease

*insulin resistance with compensatory hyperinsulinemia* →

- sodium retention and hypertension
- inappropriate activation of the RAS and aldosterone
- sympathetic overactivity
- oxydative stress
- leptin
- adiponectin

The insulin resistance paradox

- *insulin sensitivity* diminished in:
  - *muscle*
  - *adipose tissue*
  - *liver*
  - ...

- *but insulin sensitivity* not diminished in:
  - *kidney* → *increased sodium reabsorption*
  - Rocchini, Hypertension (1989) 14:367

  - *nervous system* → *increased sympathetic tone*
Normal subjects

Insulin resistance

- Transient hyperinsulinemia
  - Sodium reabsorption
  - Vasodilatation (NO)
  - No change in BP

- Chronic hyperinsulinemia
  - Sodium reabsorption
  - Vasodilatation (NO)
  - Salt sensitivity
  - BP elevation

Hypertension

Insulin resistance

- Antinatriuretic effect of insulin preserved
- Vasodilatory NO mediated effect abrogated
- (RAS upregulated)
activated RAS (renal, visceral adipocytes)


aldosterone secretion independent of classical stimuli (adipocyte derived secretagogue EKODE)

Epidydimal fat-cell-conditioned-medium for incubation with adrenocortical cells \((H295R)\)

fat cell supernatant of SHR/Ncp (but not of SHR) stimulates aldosterone secretion

Aldosterone secretion

\[ \text{control} \quad \text{SHR} \quad \text{SHR/Ncp} \]

\[ \text{no metabolic syndrome} \quad \text{metabolic syndrome} \]

\[ \text{cross-talk – visceral adipocytes “talking” to adrenals?} \]

The emerging role of aldosterone as a perpetrator of podocyte damage

• potential role of fat derived factors in podocyte injury in a model of metabolic syndrome


• in hypertensive rats with metabolic syndrome ROS production by podocytes as consequence of aldosterone overproduction


• **Eplerenone** → inhibition of podocyte injury and proteinuria

  Nagase, Hypertension (2006) 47:1084
Low plasma **adiponectin**

⇒ high urine albumin/creatinine ratio

![Graph showing correlation between plasma adiponectin and urine ACR](image)

$r = 0.6392$

$p = 0.0024$

Globular and full-length adiponectin decrease albumin permeability across podocyte monolayers
Adiponectin -/- mice

- higher albuminuria
- higher oxidant stress (amplified by diabetes)

Low water intake – higher risk of new onset hyperglycemia

Daily water intake

<table>
<thead>
<tr>
<th></th>
<th>&lt; 0.5 L/day</th>
<th>0.5 – 1.0 L/day</th>
<th>&gt;1.0 L/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset of</td>
<td>1.0</td>
<td>0.64</td>
<td>0.73</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>odds ratio</td>
<td></td>
<td>(0.49-0.83)</td>
<td>(0.50-0.97)</td>
</tr>
</tbody>
</table>

Roussel, Diabetes Care (2011) 34: 2551
Quartiles of plasma **Copeptin** correlated to metabolic syndrome

*(stable C-terminal arginine vasopressin prohormone)*

V1a-R ⇔ liver glycogenolysis; V1b-R ⇔ insulin and glucagon secretion

A polymorphism of the arginine vasopressin receptor gene (AVP-R1a) is correlated with features of the metabolic syndrome

6065 middle aged individuals in South Sweden follow-up 1994-2009

- carriers of the rs 1042615 variant
- triglyceride concentration $1.36 \pm 0.77$ vs $1.42 \pm 0.89$ mmol/l ($p=0.001$)
- fasting blood glucose $5.20 \pm 1.44$ vs $5.12 \pm 1.22$ mmol/l ($p=0.067$)

I thank you for your invitation to discuss the obesity epidemic and its renal impact.

Prof. e. ritz@t-online.de