Obesity and Chronic Kidney Disease

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Epidemic Obesity and type 2 Diabetes in Asia

단계1 지방 세포가 커진다

단계2 염증 인자가 대량 분비

단계3 Insulin 수용체를 변질

단계4 식후 고혈당이 나타난다

단계5 고혈압이 발생한다

단계6 당 자질 호르몬 Adiponectin 분비 감소

From BRIC
Obesity

--- indirectly

... initiates a cluster of disorders including insulin resistance, glucose intolerance, dyslipidemia, atherosclerosis, and high blood pressure.

--- directly

... 2 indices of renal damage: (1) albuminuria/proteinuria

(2) Pathological changes ...podocyte hypertrophy, mesangial expansion, glomerular enlargement

--- > 2\textsuperscript{nd} FSGS
## Renal Disturbances in Obesity

<table>
<thead>
<tr>
<th>Microalbuminuria/proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular hyperfiltration/hypertension</td>
</tr>
<tr>
<td>Glomerulomegaly with/wo focal or segmental glomerulosclerosis</td>
</tr>
</tbody>
</table>

- Enhanced progression of other renal diseases
  - (reduced renal mass, IgAN, and post-KT chronic graft dysfunction)
- Diabetic nephropathy
- Reduced renal survival after kidney transplantation
- Carcinoma of the kidney
- Increased formation of kidney stones
Obesity induced renal problems

1. Hypertension

2. Obesity-related glomerulopathy (ORG)
1. Obesity-induced hypertension

Obesity

Normal subjects

Insulin resistance

- $\alpha_1$-subunit of Na-K ATPase
- Thiazide-sensitive NaCl co-transporters
- $\beta$-ENaC
-- set-point of natriuretic action by AT II

GFR elevation

- transient hyperinsulinemia
  - sodium reabsorption↑
  - vasodilatation NO↑
  - no change in BP
- chronic hyperinsulinemia
  - sodium reabsorption↑
  - vasodilatation NO↓
  - salt sensitivity
  - BP elevation

Hypertension

Relationship between obesity and pressure-natriuresis

Obesity-induced cardio-renal changes

<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>GFR¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese rabbits</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
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<td>(high fat diet)</td>
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<tr>
<td>Obese dogs</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Obese humans</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
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</tbody>
</table>

GFR, glomerular filtration rate. ¹The GFR changes refer to the early phases of obesity before major loss of nephron function has occurred.

2. ORG-pathology

BMI > 40 kg/m²

Obesity-induced glomerular hyperfiltration

Metabolic demand $\uparrow$

Very large natural variability in the glomerular number (4.3-8-fold)

Obesity-induced susceptibility of barotrauma; podocyte against GC pressure
Obesity-induced susceptibility of oxidative stress; podocyte against insulin and free radicals

- **Obesity**
  - Hyperinsulinemia
    - ↑ Generation of free radicals
    - ↓ Antioxidant enzymes
  - ↑ Oxidative stress
    - ↓ NO bioavailability
    - ↑ Glycooxidation products
    - ↑ Lipid peroxidation products
  - ↑ Renal injury; including podocytes
Obesity aggravates chronic renal disease
RR for the association between obesity and kidney diseases


Cumulative incidence of end-stage renal disease according to quartile of BMI; ‘1983 Okinawa survey → ‘2000 result

N=100,753(M;F, 47,504:53,249), ≥ 20 yrs

Cumulative incidence of end-stage renal disease and CKD-related death by BMI; the HUNT I study

N=75,000 for 21 yrs F-U HUNT 1 Study in Norway, prehypertension only factor except BMI

Pathomechanisms linking obesity (metabolic syndrome) with CKD

SNS activation

Inappropriate activation of the RAS and aldosterone systems

Adipokine alteration

Renal lipotoxicity

Fetuin A-Adiponectin-MAPK relationships

1. Obesity-induced SNS activation*

<table>
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<tr>
<th>Mechanisms of SNS activation in obesity</th>
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</thead>
<tbody>
<tr>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Increased free fatty acids</td>
</tr>
<tr>
<td>AT II</td>
</tr>
<tr>
<td>Increased central chemoreceptor sensitivity</td>
</tr>
<tr>
<td>Impaired baroreflex sensitivity</td>
</tr>
<tr>
<td>Hyperleptinemia</td>
</tr>
</tbody>
</table>

*Baroreceptor sensitive medullary neurons and nucleus tractus solitarius

2. Obesity-induced RAS activation

3. Obesity-induced adipokine alterations

- Increased:
  - TNFα, IL6, leptin
  - local RAS, resistin ...

- Decreased:
  - adiponectin ...

- Insulin resistance
- Inflammation
- Salt sensitive hypertension
- Dyslipidemia

- Glomerular hyperfiltration
- Albuminuria
- Glomerulosclerosis
- Interstitial fibrosis
- CKD

4. Working hypothesis; Renal lipotoxicity (in HF-induced renal damage in SHRs)

5. Another working hypothesis linking obesity-CKD-fatty liver disease: the role of fetuin-A, adiponectin, and AMPK
Mechanisms of obesity (metabolic-syndrome)-induced renal injury and potential targeted treatments

Effects and targets of some metabolic syndrome (obesity) treatment

... Weight loss, regular exercise, and a low-calorie, low-fat diet (1ST line Rx)

<table>
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<tr>
<th>Intervention</th>
<th>Effects</th>
<th>Target</th>
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<tbody>
<tr>
<td>BP control</td>
<td>Reduction of CVD risk&lt;sup&gt;22&lt;/sup&gt;, Reduction of risk of CKD progression&lt;sup&gt;83&lt;/sup&gt;</td>
<td>BP &lt;140/90 mmHg&lt;sup&gt;84&lt;/sup&gt;, BP &lt;130/90 mmHg could further reduce CVD and CKD risk&lt;sup&gt;85&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibrate therapy&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Decrease of triglycerides&lt;sup&gt;86&lt;/sup&gt;, Increase of HDL&lt;sup&gt;86&lt;/sup&gt;, Increase of insulin sensitivity, Anti-inflammatory and antihypertensive action&lt;sup&gt;86&lt;/sup&gt;, Reduction of mesangium-induced glomerular matrix deposition&lt;sup&gt;86&lt;/sup&gt;</td>
<td>AHA guidelines do not specify a target for triglyceride level but suggest reduction in non HDL-cholesterol as a secondary target if triglycerides &gt;2.26 mmol/l&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Thiazolidinedione therapy</td>
<td>Reduction of insulin resistance and improvement of glycemic control in patients with diabetes&lt;sup&gt;87&lt;/sup&gt;, Decrease of BP&lt;sup&gt;87&lt;/sup&gt;, Improvement of endothelial function&lt;sup&gt;87&lt;/sup&gt;, Antiproliferative and anti-inflammatory action&lt;sup&gt;87&lt;/sup&gt;, Decrease of angiotensin in and endothelin levels&lt;sup&gt;87&lt;/sup&gt;</td>
<td>AHA guidelines do not specify a target for fasting glucose level</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>Reduction of LDL-cholesterol, triglyceride and systemic inflammation&lt;sup&gt;88&lt;/sup&gt;, Possible improvement of endothelial function&lt;sup&gt;86,89&lt;/sup&gt; and inhibition of renal endothelin 1-mediated proteinuria&lt;sup&gt;88&lt;/sup&gt;</td>
<td>LDL-cholesterol &lt;1.80 mmol/l in very high-risk patients&lt;sup&gt;1,3&lt;/sup&gt;, LDL-cholesterol &lt;2.60 mmol/l in high-risk patients&lt;sup&gt;1,1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metformin therapy&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Improvement of glycemic control and insulin resistance&lt;sup&gt;90&lt;/sup&gt;, Improvement of endothelial function&lt;sup&gt;90&lt;/sup&gt;</td>
<td>AHA guidelines do not specify a target for fasting glucose level</td>
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Changes in median albumin:creatinine ratio 1 year after Bariatric surgery

Key points

1) Obesity (metabolic syndrome; MS) is a constellation of metabolic risk factors that predict increased risks of CVD and diabetes.

2) In cross-sectional and longitudinal studies, obesity is associated with CKD and microalbuminuria.

3) Abdominal obesity and insulin resistance are widely considered to be key mechanisms of obesity-mediated renal damage.

4) Limited studies suggest that treatment of obesity by way of lifestyle changes, pharmacotherapies, or both, can improve markers of renal function.

5) Increased recognition of obesity and early intervention for this condition could improve cardiovascular and renal outcomes.
“Knowing is not enough, we must apply. Willing is not enough, we must do.”

(“Es ist nicht genug zu wissen: man muss es auch anwenden; es ist nicht genug, zu wollen, man muss es auch tun.”

Johann Wolfgang Goethe, 1749–1832