Visceral Fat Obesity and Metabolic Syndrome
Classification of obesity with respect to morbidity

Android Obesity ↔ Gynoid Obesity
(Prof. Vague)

Central Obesity ↔ Peripheral Obesity
(Prof. Bjorntorp)

Upper Body Obesity ↔ Lower Body Obesity
(Prof. Kissebah)

Visceral Obesity ↔ Subcutaneous Obesity
(Our Group)
A novel technique for the determination of body fat by computed tomography

Tokunaga, K., Matsuzawa, Y. et al. Int. J. Obes. 7:437, 1983
Visceral Fat and Cardiovascular Risk

Visceral/ Subcutaneous Fat Ratio

Glucose

Triglyceride

Mean BP

Stroke Index

Visceral/ Subcutaneous Fat Ratio

Metabolism 1987  Am J Cardiol 1989  Hypertension 1990
Visceral fat type Obesity (VFO)  
SubQ fat type Obesity (SFO)  

Int J Obesity 1983, Metabolism 1987
VFA is more important than BMI for Obesity-related metabolic risk factors

VFA (cm$^2$)

BMI (kg/m$^2$)

<100 > 100 <100 > 100

p<0.0001  p<0.0001  n.s.  p<0.0001

Number of risk factors

1.0

Diabetes Care 2007
The VACATION-J Study

Visceral Fat Accumulation and Coronary Artery Disease Investigation in Japanese

12,443 (M10080, F2363) general subjects, who received annual health check-up

at 9 centers across Japan

Annals of Medicine, 2012
VFA (Visceral Fat Area) and cardiac risks

**Male (total) N=10080**
- age 51.7 ± 10.0 years
- Median VFA (cm²) 115.9

**Female (total) N=2363**
- age 53.8 ± 9.6 years
- Median VFA (cm²) 74.2
Body Mass Index ≥25 kg/m²

Viscera Fat (cm²)

Male (n=3927)

Female (n=661)

SubQ Fat (cm²)

Male (n=3927)

Female (n=661)

Number of cardiovascular risks

Body Mass Index ≥25 kg/m²

Numberr of cardiovascular risks

Body Mass Index ≥25 kg/m²

Number of cardiovascular risks

Viscera Fat (cm²)

SubQ Fat (cm²)
What differs, Visceral Fat and Subcutaneous Fat?
Body Mapping Project

Human and Mouse gene expression database

BodyMap is a data bank of expression information of human and mouse genes, novel or known, in various tissues or cell types and various timings. The first generation map was created by random sequencing of clones in 3’-directed cDNA libraries.

Analysis of expressed genes in human tissues

Nature Genetics 3: 173
Expressed genes in human fats

Visceral fat

- Mitochondrial proteins
- Nuclear proteins
- Membrane proteins
- Cytoskeleton proteins
- Secreted proteins
- Cytoplasmic Proteins
- Ribosomal proteins

SubQ fat

- Signal transduction
- Energy production

Gene 1997
Adipocytokine

- Insulin resistance
- TNF-a
- Vascular stenosis
- HB-EGF
- Inflammation
- MCP-1
- IL-6
- Unknown factors

- PAI-1
- Thrombosis
- Leptin
- Lipodystrophy

Adiponectin

- Collagen-like Domain
- Globular Domain

GenBank Jan 27th 1995, BBRC 1996
Adipose tissue functions as an endocrine organ

**Visceral Adiposity**

- "Adipocytokines"

  - TNFα
  - Leptin
  - Resistin
  - IL-6

**Cardiovascular disease**

- Protective
- Harmful

**Hypo-adiponectinemia**

- Coronary heart disease
- Type 2 diabetes
- Hypertension
- Stroke
- etc.

*Plasma Adiponectin (µg/ml)*

*BMI (kg/m²)*

*Plasma Adiponectin (µg/ml)*

*Circulation 1999*

*p<0.01*
The Metabolic Syndrome

Visceral fat accumulation↑

Dysregulated Adipocytokines
- Adiponectin↓
- MCP1, IL6, PAI-1, etc

Risk factor accumulation↑
- BS↑
- BP↑
- TG↑, HDL-C↓

Atherosclerotic Diseases↑

Over-Eating → Physical Inactivity
“Waist Circumference is a tool to estimate visceral fat area”
VFA and Waist Circumference

Male (total) N=3865

p<0.01
r=0.623

Female (total) N=1282

p<0.01
r=0.676

The VACATION-J study
Japanese Concept of Metabolic Syndrome


Visceral Fat Accumulation

mild
1. Raised BP
2. HyperTG and/or LowHDL-C
3. Elevated FPG

at least 2
International Criteria of the Metabolic Syndrome (IDF, AHA/ NHLBI)

1. Abdominal Obesity (Increased Waist Circ.)
2. Hyper TG
3. Low HDL-C
4. Raised BP
5. Elevated FPG

at least 3
Aim for diagnosis of MetS

Japanese criteria

1) To select individuals, whose risk factors can be improved by reducing visceral fat
   “OK, I should reduce visceral fat.”

AHA criteria and others

2) To select individuals, who have high-risk for cardiovascular diseases
   “Oh, I am in a bad shape, and should do something or see doctors”
Local Practice in Osaka
MetS-oriented Health promotion to ~5,000 City Employees (2003-2006 yr)

AMAGASAKI CITY

Osaka Univ Hospital

Official Cooperation
MetS-oriented health promotion

Public health nurses, Dieticians, & Physicians interview and consult risked subjects
One-year Visceral Fat Reduction associated with the decrease of the number of Risk Factors

2,336 Men (age 48.0±10.5 years)

One-year changes in number of risks

One-year changes in VFA (cm$^2$)

VF Reduced Subjects

Total 2/3

N=182 N=455 N=923

N=571 N=159 N=46

p<0.0001

Diabetes Care 2007
One-year Visceral Fat Reduction associated with the increase of serum adiponectin

Males (N=1619)
age 45.7 ± 10.4 years

One-year changes in serum adiponectin

Females (N=405)
age 45.9 ± 9.3 years

One-year changes in serum adiponectin

One-year changes in VFA (cm²)

p < 0.0001
r = -0.189

p = 0.0147
r = -0.121
4 years-follow up of Visceral Fat changes and Cardiovascular Events

Subjects with visceral fat accumulation (VFA $\geq 100$ cm$^2$ at year 2004)

Follow-up period (month)

Cumulative incidence of cardiovascular events (%)

VFA unchanged or increased group (N=381)

VFA decreased group (N=879)

p=0.0049

Atherosclerosis 2010
Is Japanese Met.S Concept effective for the reduction of risks and prevention of CVD?
Next Target
Primary Prevention in Community
Health checkup and promotion system, by Japanese government (2008~)

55 million Employees and Citizens (40~74 years old)

“Annual health checkup”

“Duty for Employers & Communities”

Health Promotion Program by Public Health Nurse
Government Health Promotion (2008~)

- Mets
  - pre Mets with smoking
  - Standard support; consultation and follow-up
    - Consultation and Suggestion to Physician
- pre Mets
  - No risk with smoking
  - Medical information
- No risk
  - risk++
  - Consultation and Suggestion to Physician
Intensive support vs Control (after one year, Age and BMI adjusted)

BMI

Intensive support vs Control

SBP

(minHg)

TG

(mg/dl)

FPG

(mg/dl)

Ministry of Health, Labour and Welfare, Tsusita group, 2010
Mechanism of Lipid disorders in Metabolic Syndrome
Etiology of Dyslipidemia in the Metabolic Syndrome

Liver

- Glycerol-3P
- Acyl CoA
- Hepatic Insulin resistance
- ACS↑
- FABP (?)
-Portal FFA↑
-ACS↑

Visceral fat

- Visceral fat
- ACS↑
- FABP (?)

Hepatic Insulin resistance

- TG↑
- Apo B
- MTP↑
- VLDL↑
- Degradation↓

Portal FFA↑

Small intestine

- CM↑
- MTP↑
- Peripheral Insulin resistance

HDL↓

LPL↓

Remnant sdLDL↑

VLDL↑

LPL↓
Dyslipidemia in the Metabolic Syndrome

- Increased plasma TG and apo B100
- Increased IDL-cholesterol
- Small dense LDL
- Low HDL-cholesterol
- Postprandial hyperlipidemia
VFA is a determinant of lipid disorders

<table>
<thead>
<tr>
<th>Remnant</th>
<th>BMI</th>
<th>VFA</th>
<th>SFA</th>
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<tbody>
<tr>
<td><em>ApoB</em></td>
<td>0.120</td>
<td>0.493**</td>
<td>-0.088</td>
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<tr>
<td><strong>VLDL-C</strong></td>
<td>0.148</td>
<td>0.347*</td>
<td>-0.036</td>
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<td><strong>IDL-C</strong></td>
<td>0.069</td>
<td>0.319*</td>
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<td><strong>LDL-C</strong></td>
<td>-0.052</td>
<td>0.299*</td>
<td>-0.132</td>
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<tr>
<td><strong>HDL2-C</strong></td>
<td>-0.410*</td>
<td>-0.308*</td>
<td>-0.156</td>
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<tr>
<td><strong>HDL3-C</strong></td>
<td>-0.030</td>
<td>-0.090</td>
<td>-0.011</td>
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</tbody>
</table>

*p<0.05, **p<0.001

Kobayashi, Circ J, 2001
Scattered Plots of Visceral Fat Area Against Large LDL, Small LDL, and Very Small LDL

- High LDL-C group (○)
- Low LDL-C group (●)

Postprandial high TG level is a strong risk factor for CV events and death

Subjects: Japanese population with normal cholesterol levels, n=11,068

Non-fasting TG Levels
- <84mg/dL
- 84-115mg/dL
- 116-165mg/dL
- ≥166mg/dL

Relative Risk
- <84mg/dL
- 84-115mg/dL
- 116-165mg/dL
- ≥166mg/dL

*: p<0.05, **: p<0.01, ***: p<0.001, 15.5 years follow up

Postprandial high TG level is a strong risk factor for CV events and death.

High remnant lipoproteinemia

high risk status of cardiovascular disease

Cumulative event-free probability

Remnants $\leq 3.3$ mg/dl

Remnants $> 3.3$ mg/dl, $\leq 5.1$ mg/dl

Remnants $> 5.1$ mg/dl

$P = 0.003$ by log-rank test

Months after enrollment

Changes of metabolic markers after visceral fat reduction

<table>
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<tr>
<th></th>
<th>n=14</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>FBS (mg/dl)</td>
<td>126±44</td>
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<tr>
<td></td>
<td></td>
<td>Insulin (μU/ml)</td>
<td>15±5</td>
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<tr>
<td></td>
<td></td>
<td>Triglyceride (mg/dl)</td>
<td>253±232</td>
</tr>
</tbody>
</table>

* p<0.05

Drug treatment of dyslipidemia in metabolic syndrome

- Fibrates
- n-3 Fatty Acids
- Statins
- Ezetimib
Fibrates

- PPAR $\alpha$ agonist
- Enhancement of $\beta$ -oxidation of FFA
- Suppression of VLDL production & secretion
- Enhancement of LAL activity
- Suppression of apo CIII
- Clearance of remnant lipoprotein
- Apo A1/ A2 production
Effect of Fibrates (PPARα agonist) lipid management and beyond lipids
Bezafibrate and Adiponectin (BIP study)

Plasma adiponectin (µg/ml)

Baseline
2-years

Placebo
Bezafibrate

***
Effect of Bezafibrate on plasma adiponectin

Plasma adiponectin (%change)

Time (weeks)

- Cont
- Beza
Effect of PPAR-α agonist on Adiponectin (in vivo and in vitro study)

Hiuge et al, ATVB
Effect of Bezafibrate on AMI Incidence in MetS

Log-rank P = 0.02

BIP STUDY

Event incidence (%)

AMI risk 29%

0 1 2 3 4 5 6
years

1,470 Cases with Metabolic Syndrome

ハザード比 0.71 (0.54～0.95)

placebo (n=730)
Bezafibrate (n=740)

Arch Intern Med 2005
Thank you for your kind attention