Metabolic Syndrome and the Urology Patient

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Metabolic Syndrome is a cluster of adverse features including abdominal obesity, hypertension, dyslipidemia and insulin resistance that are linked to an increased chance of cardiovascular diseases and diabetes.
Metabolic Syndrome and the Urology Patient

The presence of three of these five markers are required for diagnosis of metabolic syndrome:

- Low levels of high-density lipoprotein (HDL) (men < 40 mg/dL, women < 50 mg/dL)
- Elevated triglyceride levels (>150 mg/dL)
- Elevated fasting blood glucose levels
- Elevated blood pressure
- Waist circumference greater than 40 inches for men and 35 inches for women
## Metabolic Syndrome: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnostic requirements</th>
<th>NCEP</th>
<th>WHO:</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 of the following</td>
<td></td>
<td>Type 2 db or IGT, 2 of the following; if GT normal, 3</td>
<td>Waist circumference (WC); ethnicity specific</td>
</tr>
<tr>
<td>Central Obesity</td>
<td>WC</td>
<td>BMI &gt;30 and/or waist hip ratio</td>
<td>European WC</td>
</tr>
<tr>
<td></td>
<td>&gt;40 in. (♂)</td>
<td>&gt;0.9 (♂)</td>
<td>≥37 in. (♂)</td>
</tr>
<tr>
<td></td>
<td>&gt;35 in. (♀)</td>
<td>&gt;0.85 (♀)</td>
<td>≥31 in. (♀)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian WC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥35 in. (♂)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥31 in. (♀)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>NCEP</strong></th>
<th><strong>WHO</strong></th>
<th><strong>IDF</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>BP $\geq 130/85$ mm Hg or treatment</td>
<td>BP $\geq 140/90$ mm Hg or treatment</td>
<td>BP $\geq 130/85$ mm Hg or treatment</td>
</tr>
<tr>
<td>Lipids</td>
<td>TG $\geq 150$ mg/dL and/or HDL $&lt;40$ mg/dL ($\boldsymbol{\text{♂}}$), $&lt;50$ mg/dL ($\boldsymbol{\text{♀}}$)</td>
<td>TG $\geq 150$ mg/dL and/or HDL $&lt;35$ mg/dL ($\boldsymbol{\text{♂}}$), $&lt;39$ mg/dL ($\boldsymbol{\text{♀}}$)</td>
<td>TG $\geq 150$ mg/dL and/or HDL $&lt;40$ mg/dL ($\boldsymbol{\text{♂}}$), $&lt;50$ mg/dL ($\boldsymbol{\text{♀}}$) or treatment</td>
</tr>
<tr>
<td>Glucose</td>
<td>FPG $\geq 100$ mg/dL</td>
<td>IGT or type 2 diabetes</td>
<td>FPG $\geq 100$ mg/dL or type 2 diabetes</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Micro-albuminuria</td>
<td></td>
</tr>
</tbody>
</table>
Unresolved Issues

- Criteria for diagnosis ambiguous or incomplete
- Unifying etiology uncertain
  - Insulin resistance or intra-abdominal obesity?
- Treatment of syndrome similar to treatment for each of its components

**Bottom Line:**
- *Metabolic Syndrome is a marker of CVD and diabetes risk*
- *Effective lifestyle interventions reduce all metabolic risk factors*

Kahn et al., 2005
BMI or Waist Circumference?

189 cm, 93 kg = BMI 26

Waist circumference > Testosterone

190 cm, 94 kg = BMI 26

Waist circumference < Testosterone
Measuring Waist Circumference

High Risk
Men: >40” (>102 cm)
Women: >35” (>88 cm)
Asian Men: >35” (>90 cm)
Asian Women: >31” (>80 cm)

To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest.
Factors Contributing to Insulin Resistance

Genetics & Aging

Acquired:
- Central obesity
- Sedentary lifestyle
- High fat diet
- Medications
Abdominal Obesity

• Excess intra-abdominal adiposity characterized by accumulation of visceral fat around and inside abdominal organs
  – Increase flux of FFA to liver
  – Increase in insulin resistance
• Waist circumference correlates with intra-abdominal obesity
Risk factors for obesity

- High fat, energy dense diet
- Family history
- Age
- Sedentary lifestyle/physical inactivity
- Ethnicity
- Stopping smoking
Visceral Fat: the Vicious Circle

Tissue factors, PAI-1
Fibrinolysis-related

TNFα, IL-1, IL-6, IL-8, IL-10
Inflammation-related

PAI-1, CRP, Serum amyloid A
Acute phase proteins

LPL, ApoE, FFA, Glycerol
Lipid-related

Cortisone, Cortisol
Androgens, Estrogens

Inflammation-related and Energy homeostasis

Adiponectin, leptin, resistin, visfatin

Inflammation-related and Vascular homeostasis

VEGF, angiotensinogen

T ↓ T ↓ T ↓ T ↓
The close association of type 2 diabetes with cardiovascular disease has led to the hypothesis that they both share a common antecedent - *Metabolic Syndrome*.

- The *Metabolic Syndrome* reflects the clustering of central obesity with several other major cardiovascular disease risk factors.

- **Insulin resistance**
- **Hypertension**
- **Dyslipidaemia**
- **Impaired glucose regulation or diabetes**
- **Central obesity**
Diabetic polytrauma

- visceral obesity
- hyperinsulinemia
- insulin resistance
- glucose intolerance
- hyperglycemia
- arterial hypertension
- atherogenic dyslipidemia
- hyperuricemia
- prothrombotic state
- dysfibrinolysis
- inflammation
Metabolic Syndrome

Genetic

Lifestyle

Insulin Resistance

Abdominal Obesity

Dyslipidemia

Hypertension

Glucose Intolerance

Metabolic Syndrome

Type 2 Diabetes & CVD
Type 2 Diabetes: A Progressive Disease

Pre-diabetes: insulin resistance

Onset Diabetes: beginning of insulin deficiency

Diabetes: insulin deficiency

Lifestyle Management

Lifestyle Management Alone or with Glucose Lowering Meds

Lifestyle Management Glucose Lowering Meds Insulin

Meds
MNT to Prevent and Treat Type 2 Diabetes

Prevent Obesity/Insulin Resistance

Prevent Type 2 Diabetes

Diagnosis Type 2 Diabetes

Reduce Insulin Resistance

Beta Cell Loss/Match Food and Medication

Pre-Diabetes

MNT & Physical Activity

MNT, Physical Activity & Weight Loss

MNT, Physical Activity, Energy Restriction

MNT, Physical Activity, Carb Counting, Medications

Metabolic Control

Beebe, 2003
Metabolic Syndrome and the Urology Patient

• **Metabolic Syndrome**: The link between type 2 diabetes and cardiovascular disease?

• A disturbing feature of diabetes has been the clustering of diabetes with other well-known cardiovascular risk factors, in particular *central (abdominal) obesity*.

• The occurrence of central obesity, hypertension and disturbed blood lipids is dramatically increased in people with diabetes.

• People with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) also have a substantial increase in cardiovascular risk factors and, like people with diabetes, higher cardiovascular risk.
Metabolic Syndrome and the Urology Patient

**Metabolic Syndrome**: Key underlying defects

- Impaired glucose regulation
- Hypertension
- Obesity
- Insulin resistance
- Dyslipidaemia

S Bandi Mackay Urology
How common is **Metabolic Syndrome**?

- The condition is widespread among the adult population in developed nations, and increases in frequency with age. However, it isn't just adults who are affected - the condition is also afflicting an increasing number of children and adolescents as the worldwide epidemic of obesity spreads across the age groups.
Prevalence of Metabolic Syndrome

Affects nearly \( \frac{1}{4} \) of adults

- 24\%-50\% with coronary heart disease
  - 50\% with hypertension
  - 85\% with low HDL and high TG
  - 87\% with type 2 diabetes

Ford et al. 2002; Alexander et al., 2003; Duncan et al., 2004
Table: Metabolic Syndrome: IDF consensus definition (2005)

<table>
<thead>
<tr>
<th>Central Obesity</th>
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</thead>
<tbody>
<tr>
<td>Waist circumference</td>
</tr>
<tr>
<td>- ethnicity specific*</td>
</tr>
</tbody>
</table>
| - for Europids: Male ≥ 94 cm  
Female ≥ 80 cm                        |
| plus any two of the following:                                                 |
| Raised Triglycerides ≥150mg/dL (1.7mmol/L) or specific treatment for this lipid abnormality |
| Low HDL Cholesterol <40mg/dL (1.03 mmol/L) in males  
<50mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality |
| Raised blood pressure  Systolic: ≥130 mmHg or  
Diastolic: ≥85 mmHg or  
Treatment of previously diagnosed hypertension |
| Impaired fasting glycaemia  Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes  
If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome. |
Metabolic Syndrome and the Urology Patient

• **Metabolic Syndrome**: Overall risk factors

There is now broad agreement on the overall risk factors which must be taken into account when defining the metabolic syndrome. These have been called ‘the deadly quartet’.

- Impaired glucose regulation
- Hypertension
- Dyslipidaemia
- Obesity
Metabolic Syndrome and the Urology Patient

Figure 1. This diagram depicts the important links between androgen deficiency and key components of metabolic syndrome, especially obesity, hypertension, and dyslipidemia, together with glucose abnormalities (hyperglycemia) and insulin resistance (Mulligan et al, 2006).
What are the health implications of having **Metabolic Syndrome**?

- Each component of metabolic syndrome acts to significantly increase the risk of developing one or more diseases. For example, excess abdominal fat is associated with increased risk of **type 2 diabetes** and **heart disease**; **hypertension** is the most important risk factor for **stroke**; high blood LDL and low HDL increase the risk of **heart disease**, and insulin resistance can be the first step on the road to **type 2 diabetes**.

- In brief, having **type 2 diabetes** significantly increases the risk of developing **heart disease**, **kidney disease** and **blindness**, and also of having to undergo limb amputations (due to gangrene). The rapid increase in incidence of **Metabolic Syndrome**, not only among adults but also in children and adolescents, represents a potential 'time bomb' for the future adult populations of developed nations.
After a two year Visit to the United States, Michelangelo's David is Returning to Italy . . .
The health consequences of obesity

- Cancer
- Gall-bladder disease
- Respiratory disease
- Kidney Failure
- Hypertension
- Stroke
- Type 2 Diabetes
- Atherosclerosis
- Heart failure
- Type 2 Diabetes
**Is There a Relationship Between Reduced T Levels and T2D?**

- Men with low T are at a greater risk of developing T2D, and that low T may even predict the onset of diabetes.

Figure 2. Postulated relationship among androgen deficiency, diabetes, insulin resistance (IR), metabolic syndrome (MetS), and erectile dysfunction (ED). The framework presented in this diagram postulates a bidirectional relationship between obesity and IR, as well as between obesity and MetS and between IR and type 2 diabetes (T2D).
What can be done to reduce my risk of developing *Metabolic Syndrome*, or to help overcome the syndrome if I already have it?

- First and foremost, if you are undergoing treatment for any of the components of *Metabolic Syndrome* (or for the actual diseases associated with it, such as diabetes or heart disease) it is essential that you take the advice of your professional health carer(s). Your doctor and/or dietitian will be aware of your particular circumstances and can prescribe treatment that is tailored to best meet your requirements. The following advice is of a general nature only, but is useful for reducing the risk (or severity) of metabolic syndrome.
  - Increase activity levels
  - Improve health through better eating habits
  - Lose some weight (if overweight or obese)
  - Quit smoking (if you are a smoker)
  - Reduce stress levels
  - Take any medications prescribed by your doctor (or severity) of metabolic syndrome.
Overview

• Metabolic Syndrome

• Lifestyle Therapy
  – Weight Loss
  – Physical Activity
  – Whole Grains/Fiber
  – Fat
  – Alcohol

• Behavioral Change Strategies
Clinical Management of Metabolic Syndrome

Goals

↓ risk CVD
↓ risk type 2 diabetes
↓ LDL-C, BP, glucose levels

Therapies

Lifestyle
Medications
Aspirin
Smoking cessation

Grundy et al., 2005
Lifestyle Therapy

**Weight Loss**

- Body weight by 7-10%

**Physical Activity**

- 30-60 minutes/day physical activity

**Nutrition**

- Whole grains & fiber
- Sat fats, *trans* fats, cholesterol
- 25-35% kcals/total fat

Grundy et al., 2005
Modest Weight Loss Benefits (~5% BW)

- Prevent or delay type 2 diabetes
- ↓ Systolic and diastolic blood pressure
- ↓ Circulating inflammatory markers (C-reactive protein and cytokines)
- Potential improvement in TG, total and LDL cholesterol levels

Klein et al., 2004
Current Knowledge of Weight Management

- At ~6 months, individuals can lose 5-10% of starting weight
- Regardless of intervention, plateaus and regain expected; compensatory mechanisms protect against weight loss
- With support, modest weight loss can be maintained

Douketis et al., 2005; Curioni et al., 2005
Modest Weight Loss and Risk of Diabetes

Lifestyle interventions = ↓ risk 58%

- Modest weight loss: ≥7% of starting weight
- Low calorie, low saturated fat diet
- Physical activity: 150 min per week
- Education and monthly contact

Lindström et al. 2003¹; Lindström et al. 2003², DPP, 2002
# Lifestyle: More Effective Than Meds for Reducing Diabetes Risk

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medication</th>
<th>% Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP</td>
<td>Metformin</td>
<td>31%</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Acarbose</td>
<td>25%</td>
</tr>
<tr>
<td>TRIPOD</td>
<td>Troglitazone</td>
<td>55%</td>
</tr>
<tr>
<td>XENOS</td>
<td>Orlistat</td>
<td>37%</td>
</tr>
<tr>
<td>DPP &amp; Finnish Diabetes Prevention Study</td>
<td>Lifestyle only</td>
<td>↓ 58%</td>
</tr>
</tbody>
</table>

DPP Research Group, 2002; Chiasson et al., 2002; Buchanan et al., 2002; Torgerson et al., 2004; Tuomilehto et al., 2001; ADA and NIDDKD, 2004
Key Habits of Successful Losers

- Lower calorie diet
- Low-fat, high-carbohydrate diet
- Minimum 60 minutes/day of exercise
- Eat breakfast every day
What about exercise?
Benefits of Physical Activity

- Increases insulin sensitivity, independent of weight loss
  - Activates Glut 4 glucose transporters
  - Suppresses hepatic glucose release
- Modest amounts improve glucose tolerance and lipids
- Effect on insulin sensitivity is 24-72 hrs; must be done regularly
- Reduced risk of type 2 diabetes

Duncan et al., 2003; Sigal et al., 2004
Being Fit Reduces Risk of Obesity in Men

- Physical fitness, regardless of BMI, decreases risk of mortality from all-cause and cardiovascular disease.

Lee et al., 1999
Fitness Associated with Lower Risk for Adverse CV Events in Women

- Weight not associated with outcomes.

Wessell et al., 2004
# Recommendations for Physical Activity

<table>
<thead>
<tr>
<th>Duration</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 minutes/day</strong></td>
<td>For <em>fitness and reduced risk</em> of chronic disease</td>
</tr>
<tr>
<td><strong>60 minutes/day</strong></td>
<td>For <em>prevention</em> of weight gain</td>
</tr>
<tr>
<td><strong>60-90 minutes/day</strong></td>
<td>To <em>avoid regain of weight loss</em></td>
</tr>
</tbody>
</table>
Whole Grain Benefits

• Lower risk of diabetes and heart disease
  – ↓ insulin, C-peptide, leptin and homocysteine
• Improved insulin sensitivity and ↓ risk of developing metabolic syndrome
• ↓ Mortality from CVD
• Less weight gain, ↓ BMI

Jensen et al., 2006; McKeown et al., 2004; Sahyoun et al., 2006; Liu et al., 2003; Koh-Benerjee et al, 2004; Steffen et al, 2003; Liese et al., 2003
Whole Grains & Diabetes Risk

Data from the Iowa Women’s Health Study

Approximately 3 servings of whole grains daily

21% risk reduction

Data from the Nurses’ Health Study

27% risk reduction

Meyer et al., 2000; Liu et al., 2000
Decreased Risk of Metabolic Syndrome: Whole Grains or Fiber?

**Whole Grain**
- Magnesium
- Phytochemicals
- Decreased insulin resistance
- Body weight

**Fiber**
- Insulin sensitivity
- Body weight
Benefits Beyond Fiber

Traditional Nutrients, Vitamins, and Minerals

Fiber

Resistant Starch

Lignan

Antioxidants

Plant Stanols and Sterols

Phytate

Inulin and Fructooligosaccharides
Dietary Fats and Insulin Resistance

- Controlled clinical trials show a direct association between saturated fat and insulin resistance
- Omega-3 fatty acids improve insulin sensitivity; data on MUFA, PUFA, and *trans* fats less clear
- Mediterranean-type diet associated with lower mortality
- Polyunsaturated fats as beneficial as monounsaturated fats

Louheranta et al., 2000; Riccardi et al., 2000; Denkins et al., 2002; Lovejoy, 2002; Trichopoulou et al., 2005
Benefits from Moderate Intake of Alcoholic Beverages

• Observational and small clinical trials suggest U- or J-shaped association, benefit from moderate consumption of alcohol (~15-30 g/day)

• Moderate amounts with food has no acute effect on blood glucose and insulin levels

• Light to moderate amounts of alcohol increases insulin sensitivity and raises HDL cholesterol

• Type of alcoholic beverage does not make a difference

Howard et al., 2004; Reynolds et al., 2003; Koppes et al., 2005; Freiberg et al., 2004; Rimm et al., 1996
Definition of Moderate

1 drink = ~15 g alcohol (ethanol)
= 12 oz beer (150 kcal)
= 1.5 oz 80 proof distilled spirits (100 kcal)
= 5 oz wine ( 100 kcal)
Alcohol: Blood Pressure And Triglycerides

• Blood pressure
  – Light-to-moderate amounts do not raise BP; chronic, excessive amounts of alcohol (>30-60 g/day) elevate BP

• Triglycerides (TG)
  – 30 g/day in men with fasting hypertriglyceridemia (200-750 mg/dL): no increase in TG
  – 30 g/day for 8 wks in non diabetic females: improved TG levels and insulin sensitivity
  – Excessive amounts of alcohol: increase VLDL synthesis - enhanced by genetics, high-fat diet and diabetes

Nanchahal et al., 2000; Pownall et al., 1999; Davies et al. 2002; Israelsson, 1986
Dietary Guidelines - Alcohol

- If choose to drink alcohol, limit daily intake to 1 drink or less for women, 2 drinks or less for men.

- Moderate amounts have no acute effect on glycemic control, blood pressure and triglycerides.

Data does not support recommending alcohol use for health benefits to people who do not currently drink.
• **Glycemic Index**

A difficulty of use is its variability.

- Australian potatoes: 87-101
- Canadian potatoes: 59-70
- US potatoes: 56-77
- Boiled rice: 45-112
- Bananas: 30-70
- Spaghetti: 45-65

<table>
<thead>
<tr>
<th>Food</th>
<th>GI (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>Potato, instant</td>
<td>85 ± 33</td>
</tr>
<tr>
<td>Cornflakes</td>
<td>81 ± 16</td>
</tr>
<tr>
<td>Bread, white</td>
<td>73 ± 36</td>
</tr>
<tr>
<td>Watermelon</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>Rice, long grain</td>
<td>71 ± 38</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Coke</td>
<td>58 ± 5</td>
</tr>
<tr>
<td>Snickers Bar</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>Banana</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Spaghetti</td>
<td>47 ± 27</td>
</tr>
<tr>
<td>Apple</td>
<td>38 ± 2</td>
</tr>
<tr>
<td>Kidney beans</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>M &amp; Ms</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Peanuts</td>
<td>14 ± 8</td>
</tr>
</tbody>
</table>
Lifestyle Change Counselling Strategies

- Self-monitoring
- Realistic Goals
- Stimulus Control
- Managing Stress
- Cognitive Restructuring
- Contingency Management

Diary
- 8-10% Weight loss
- Build good habits
- Exercise, yoga, meditation
- Thoughtful self-awareness
- Rewards
Counselling Strategies for Maintaining Lifestyle Changes

• Physical Activity

• Social Support

• Relapse Prevention
Counselling Tips

• Review food and physical activity records

• Review goals, problems and solutions
  – Ask individuals what they want to do
  – Promote realistic expectations
  – Write down and set realistic lifestyle goals - not weight loss goals - based on readiness to change

• Give positive encouragement; never criticize

• Look for & recommend support systems
Take Home Messages ...

- Metabolic syndrome is common
- Associated with increased risk of T2DM, TDT, ED, CAD, stroke and reduced survival
- Simple lifestyle changes and TRT reduce this risk
- Urologist may see patients with ED before a cardiac event
- An opportunity exists to screen for cardiac risk and refer for specialised advice whilst at the same time treating ED and providing lifestyle advice
- Patients do not need to collect risk factors – one is enough to justify action
- ED alone is a marker for cardiac risk