

# *Metabolic Syndrome: Why Should We Look For It?*

Dafna Rippel, MD, MHA and Andrew Ignaszewski, MD, FRCPC

## CardioCase presentation

### Andy's fatigue



Andy, 47, comes to you complaining of stress at work which is affecting his sleep.

Upon questioning, he admits to some fatigue, but is otherwise asymptomatic. He does not have diabetes, high blood pressure (BP), or a positive family history of heart disease. He is a non-smoker, a social drinker and he leads a sedentary lifestyle.

Andy's physical exam shows:

- Height: 1.70 m
- Weight: 95 kg
- Waist circumference: 1.02 m
- BP: 140/86 mmHg

The rest of his physical examination reveals no abnormalities.

Blood work shows:

- Fasting blood glucose (FBG): 6.8 mmol/L
- Total cholesterol: 4.8 mmol/L
- LDL-cholesterol: 3.4 mmol/L
- HDL-cholesterol: 0.8 mmol/L
- Fasting triglycerides: 2.8 mmol/L

According to the Framingham risk score, Andy has a five per cent (low) risk of a hard cardiovascular event (which includes myocardial infarction [MI] and coronary death) over the next 10 years.

**For Andy's diagnosis, go to page 22.**

*What's your CardioCase diagnosis?*

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*Andy's risk of a hard cardiovascular event is five per cent. Are there any arguments for doubling this number?*

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*Could Andy's risk be lowered to two per cent?*

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# CardioCase

## CardioCase discussion

### Metabolic Syndrome

Metabolic Syndrome is composed of five main metabolic derangements that include central (visceral) obesity, fasting hyperglycemia (including Type 2 diabetes, impaired glucose tolerance test [IGT] and impaired fasting glucose [IFG]), hypertension and dyslipidemia (*i.e.*, low HDL-cholesterol [HDL-C] and elevated triglycerides).

These cardiovascular risk factors have been well-known for many years, but only in 1988 did Reaven<sup>1</sup> cluster several of them, laying the foundation for what we today call Metabolic Syndrome. The purpose of Reaven's study was to try and define a population that is at particularly high risk for atherosclerotic cardiovascular disease.

Several mechanisms have been postulated in the pathogenesis of this syndrome. Insulin resistance is the most important of these mechanisms; however, visceral obesity, hypertriglyceridemia and hypertension are highly correlated with it.<sup>1</sup> It is also believed that central obesity is an early step in the etiological cascade leading to full-blown Metabolic Syndrome.

#### Diagnostic criteria

Three main, different definitions for Metabolic Syndrome are shown in Table 1. All of the definitions use IGT, IFG, or Type 2 diabetes as indirect clinical evidence for insulin resistance.

In 1998, the World Health Organization (WHO) emphasized insulin resistance as the major underlying risk factor for Metabolic Syndrome and required hyperinsulinemia or elevated fasting glycemia and two or more additional factors for its diagnosis (Table 1).

#### What's wrong with Andy?

Andy is diagnosed as having full-blown Metabolic Syndrome (waist, BP, triglycerides, HDL-cholesterol and increased FBG). Framingham risk score does not take into account Metabolic Syndrome, just as it does not include family history.

His actual risk may be two to three times higher than what was calculated.

**For Andy's treatment, go to page 24.**

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)<sup>3</sup> presented a different tool for diagnosis. Their classification of Metabolic Syndrome attempted to avoid focusing on one etiological mechanism to facilitate the clinical diagnosis. Instead, the panel required the presence of any three out of these five criteria:

- waist circumference > 102 cm in men and > 88 cm in women,
- triglyceride level > 1.69 mmol/L,
- HDL-C > 1.03 mmol/L for men and > 1.3 mmol/L for women,
- BP > 130/85 mmHg and
- fasting glucose level > 6.1 mmol/L.

No single parameter is regarded as the mainstay for the diagnosis of Metabolic Syndrome.

#### About the authors

**Dr. Dafna Rippel** is an Internist, Medical Trainee, Healthy Heart Program, St. Paul's Hospital, Vancouver, British Columbia and Adjunct Professor, School of Nursing, University of British Columbia, British Columbia.

**Dr. Andrew Ignaszewski** is a Staff Cardiologist, St. Paul's Hospital and Medical Director, Healthy Heart Program, Vancouver, British Columbia. He recently received a large grant to open the Metabolic Syndrome Clinic in Vancouver, with the emphasis on lifestyle changes.

**Table 1**  
**Criteria sets proposed for clinical diagnosis of Metabolic Syndrome**

Parameter	WHO - 1988	ATP III - 2001	IDF
<b>Essential for diagnosis</b>	IGT, IFG, DM-II, plus any two of the following features ↓	None, but any three of the following five features ↓	Increased WC
<b>Body weight</b>	Waist-to-hip ratio: men > 0.90 women > 0.85 and/or BMI > 30 kg/m <sup>2</sup>	Waist circumference men > 102 cm women > 88 cm	Increased WC (population specific) plus any two of the following ↓
<b>Lipid</b>	TG > 1.69 mmol/L and/or HDL-C: men > 0.9 mmol/L women > 1 mmol/L	TG > 1.69 mmol/L ----- HDL-C men > 1.03 mmol/L women > 1.3 mmol/L	TG > 1.69 mmol/L ----- HDL-C men > 1.03 mmol/L women > 1.3 mmol/L or on HDL-C Rx
<b>BP</b>	> 140/90 mmHg	> 130/85 mmHg	> 130 mmHg systolic or > 85 mmHg diastolic or on hypertension Rx
<b>Glucose</b>	IGT, IFG, DM-II	> 6.1 mmol/L (includes diabetes)	> 5.6 mmol/L (includes diabetes)
<b>Other</b>	Microalbuminuria		

WHO: World Health Organization  
IGT: impaired glucose tolerance test  
BMI: body mass index  
WC: waist circumference

IDF: International Diabetes Federation  
IFG: impaired fasting glucose  
HDL-C: high density lipoprotein cholesterol  
Rx: prescription

ATP III: Adult Treatment Panel  
DM-II: Type 2 diabetes mellitus  
TG: triglycerides

Modified from: Grundy SM, Cleeman JI, Daniels SR, et al: Diagnosis and management of the metabolic syndrome: An American Heart Association/ National Heart, Lung and Blood Institute Scientific Statement. *Circulation* 2005; 112(17):2735-52.

Unfortunately, both the above definitions missed a big portion of the non-Caucasian populations (*e.g.*, Asians, *etc.*), who are at higher risk for developing diabetes and cardiovascular disease (CVD) at lower levels of adiposity. This led to a world-wide definition of Metabolic Syndrome, proposed by the International Diabetes Federation (IDF) in 2005.<sup>4</sup> Central obesity was agreed upon as essential, with a list of ethnic-specific cut-off points for its diagnosis integrated into the definition. This classification has yet to be accepted in Canada.

### *Why should we diagnose Metabolic Syndrome? What are its cardiovascular impacts?*

According to Statistics Canada, 32% to 34% of all deaths in 2002 were due to CVD. The prevalence rate of Metabolic Syndrome in Ontario, Manitoba, Alberta, Quebec and Saskatchewan, in 2004, in adults aged 18 to 74 years, was 26%.<sup>6</sup> Prevalence of Metabolic Syndrome

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changes by ethnic group. For example,

- the First Nations' people are at the higher rate of 42%,
- South Asians are at 26% and
- the Chinese are at 11%.<sup>7</sup>

Metabolic Syndrome is also highly age-dependent. According to the Center for Disease Control in the US, the risk for Metabolic Syndrome increases from seven per cent for young adults aged between 20 and 29 years and gradually increases up to a 44% risk for those individuals aged between 60 and 69 years.<sup>7</sup>

Unfortunately, these numbers could also reflect future increases in diabetes and CVD.

Many studies illustrate an association between Metabolic Syndrome and an increased risk of CVD mortality, as well as total mortality, myocardial infarction (MI), stroke and diabetes.<sup>9-10</sup>

The results of the Multiple Risk Factor Intervention Trial (MRFIT)<sup>9</sup> were recently published. This 18-year follow-up mortality study included 10,950 men of which 4,588 of them had Metabolic Syndrome (41.9%). In those with full-blown Metabolic Syndrome, an increased risk for CVD and coronary heart disease (CHD) mortality of more than three times was discovered. A linear ratio was found between the number of Metabolic Syndrome

### Andy's treatment...

Andy should start exercising and lose weight. If he does not do this, he will become diabetic (FBG > 7 mmol/L) and he will need to be started on:

- 81 mg of acetylsalicylic acid, daily
- Metformin, 1000 mg to 1500 mg, daily
- Thiazolidinedione (if his glucose is still elevated)
- Statin therapy will keep his LDL-C below 2.5 mmol/L
- Niacin or a fibrate should be used if the total cholesterol/ HDL-cholesterol ratio is > 4 mmol/L
- ACE inhibitors as per the HOPE<sup>8</sup> study

By changing his lifestyle, losing weight and exercising, Andy could postpone/prevent the development of diabetes, control his BP, decrease his triglycerides and LDL-cholesterol and increase his HDL-cholesterol. Furthermore, his average Framingham score could decrease from five to two per cent and medical therapy would not be necessary.

**Go to page 26 for Andy's followup.**

parameters and mortality (either CVD or CHD and total mortality). The addition of two factors (seven all together) increased the CVD mortality by 5.68, compared to men with no risk factors. In several other studies, the relative hazard ratios for CVD outcomes ranged from two to five.

Thus, by diagnosing Metabolic Syndrome, we are able to offer treatment to this high-risk population, with the goal of decreasing CVD mortality and diabetes rates.



## Treatment

Patients should undergo a full cardiovascular risk assessment, according to the Framingham study.

Except for the aggressive control of the risk factors, there is currently no specific therapy for Metabolic Syndrome. The Steno-2 study,<sup>11</sup> conducted on Type 2 diabetics and microalbuminuria showed that “a target driven, long-term, intensified intervention aimed at multiple risk factors” was highly beneficial and “reduces the risk of cardiovascular and microvascular events by about 50%.”<sup>11</sup>

First-line treatment for controlling the risk factors involved in Metabolic Syndrome is by aggressive life-style changes, which should include:

- smoking cessation,
- alteration to existing diet and
- an increase in physical activity.

## Diet

Changes to diet include:

- less atherogenic compositions,
- calorie restriction
- increased intake of vegetables, fruits and fibres and
- aiming to lose five to 10% of body weight in the first six to 12 months of lifestyle modification.

Diet should include decreased amounts of:

- saturated fats,
- trans fatty acids,
- cholesterol and
- simple carbohydrates.

## Physical activity

Moderate intensity, daily aerobic exercise for at least 30 minutes, should replace a sedentary

lifestyle. High-risk patients should exercise in medically supervised places.

According to specific guidelines,<sup>12-14</sup> when lifestyle changes are not sufficient, drug therapy should be added.

*Except for the aggressive control of the risk factors, there is currently no specific therapy for Metabolic Syndrome.*

## Dyslipidemia

According to the Canadian Guidelines,<sup>12</sup> LDL-C will be the primary target, as long as triglycerides are < 5.6mmol/L. Statins are the drug of choice, followed by ezetimibe and bile acid sequestrates.<sup>12</sup> Statins were found to reduce the risk of major cardiovascular events in high-risk patients with Metabolic Syndrome by reducing all apolipoprotein B containing lipoproteins.<sup>15</sup> Drug therapy—to increase HDL-C—might be considered only after achieving the LDL-C target and can be achieved with the use of niacin.

## Blood pressure

The Canadian guidelines<sup>13</sup> suggest a restriction in salt intake to reach a BP target of 140/90 mmHg. In patients with established diabetes or chronic kidney disease, one should aim for a lower BP goal of 130/80 mmHg.<sup>13</sup>

The decision of which drug to use will be according to the Canadian Guidelines. In patients with diabetes, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are suggested as a first-line treatment,<sup>13,16</sup> followed by hydrochlorothiazide (HCTZ) and the long acting dihydropyridine

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### Andy's followup

Andy decided to change his lifestyle. He began walking 40 minutes a day and following a low-fat, low-calorie diet, with decreased amount of simple carbohydrates.

Within six months:

- He lost five kilograms
- His waist circumference abated to 99 cm
- His BP decreased to 125/80 mmHg
- His FBG decreased to 6.1 mmol/L
- His lipid profile ameliorated to a total cholesterol of 4.1 mmol/L
- LDL-cholesterol decreased to 2.9 mmol/L
- HDL-cholesterol increased to 0.9 mmol/L
- His fasting triglycerides lowered to 2.0 mmol/L

According to the 2001 ATP III guidelines, Andy no longer has Metabolic Syndrome. His Framingham risk score has dropped to two per cent. He is considered a low-risk patient and as such, his LDL-cholesterol target should be < 3.5 mmol/L, which he has already achieved.

He still needs to be followed regularly to make sure he is persistent in adhering to his lifestyle changes.

Andy has chosen the way of a healthy lifestyle and he has won.

CCB as second-line therapy. Beta-blockers might be added in case of intolerance to ACE inhibitors or ARBs. For all other individuals, either HCTZ, beta-blockers (in patients who are younger than 55 years of age), ACE inhibitors or ARBs should be the first-line treatment. One should remember that there are clinical trials which show the protective effects of ACE inhibitors and ARBs in preventing diabetes in specific populations.<sup>5,13</sup>


### Fasting hyperglycemia

According to the current guidelines,<sup>14</sup> there is no indication of drug therapy for IFG, although some recent studies have shown that patients benefit from taking metformin and sometimes thiazolidinedione (TZD) in preventing Type 2 diabetes. However, while it is known that TZD may increase body weight, it is not clear whether or not they will decrease one's chances of CVD. The Canadian Diabetes Association

Guidelines<sup>14</sup> also suggest a hemoglobin A1C of less than seven per cent when there is a history of Type 2 diabetes.

Low dose acetylsalicylic acid is recommended for Metabolic medium- and high-risk patients.

### Final thoughts...

By diagnosing Metabolic Syndrome (whether it is a syndrome or "just" an accumulation of risk factors), we are able to identify a high-risk group of patients with preventable morbidity and mortality. Avoiding Metabolic Syndrome requires continuous team effort for diagnosis, aggressive lifestyle intervention, medical treatment and follow up. 

## References

1. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988; 37(12):1595-607.
2. World Health Organisation (1999) Report of a WHO consultation: Definition of metabolic syndrome in definition, diagnosis, and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus. World Health Organisation, Department of Noncommunicable Disease Surveillance.
3. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285(19): 2486-97.  
or: <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf>
4. The IDF consensus worldwide definition of the metabolic syndrome. 2005: [http://www.idf.org/webdata/docs/Metac\\_syndrome\\_def.pdf](http://www.idf.org/webdata/docs/Metac_syndrome_def.pdf)
5. Grundy SM, Cleeman JI, Daniels SR, et al: Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation* 2005;112(17): 2735-52.
6. To avoid metabolic syndrome is relatively simple? 30 minutes of physical activity once a week. Medical Research News Published: Monday, 25-Oct-2004. <http://ww2.heartandstroke.com> and:<http://ww2.heartandstroke.ca/Page.asp?PageID=33&ArticleID=581&Src=heart&From=SubCategory>
7. Anand SS, Yusuf S, Vuksan V, et al: Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: The Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000; 356(9226):279-84.
8. Ford ES, Giles WH, Dietz WH et al: Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; 287(3):356-9.
9. Eberly LE, Prineas R, Cohen JD, et al: Metabolic syndrome: Risk factor distribution and 18-year mortality in the multiple risk factor intervention trial. *Diabetes Care* 2006; 29(1):123-30.
10. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 2005; 365(9468):1415-28.
11. Gaed P, Vedel P, Larsen N, et al.: Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *NEJM* 2003; 348(5):383-93.
12. Genest J, Frohlich J, Fodor G, et al: Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *Canadian Medical Association Journal* 2003; 169(9):921-24.  
[http://www.hypertension.ca/CHEP2006/CHEP\\_2006\\_complete.pdf](http://www.hypertension.ca/CHEP2006/CHEP_2006_complete.pdf)
13. Canadian Diabetes Association Clinical Practice Guideline Expert Committee. Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003; 27(Suppl2): S1-S141.
14. Pyorala K, Ballantyne CM, Gumbiner B, et al.: Reduction of cardiovascular events by simvastatin in nondiabetic coronary heart disease patients with and without the metabolic syndrome: Subgroup analyses of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 2004; 27(7):1735-40.
15. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE Study and MicroHOPE substudy. *Lancet* 2000; 355(9200):253-9.

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