CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

The Metabolic Syndrome: A Growing Concern

By MARC ALLARD, MD, and GORDON MOE, MD

The metabolic syndrome has become a commonly discussed medical problem and a growing topic of interest for both researchers and the pharmaceutical industry. This issue of *Cardiology Rounds* discusses the concept of the metabolic syndrome, reviews the various definitions used to diagnose it, and describes risk factors associated with its development and the proposed mechanisms underlying these metabolic risk factors. Finally, current guidelines for the management of patients with the metabolic syndrome are presented, along with potential new drug treatments that may be available in the near future.

What is the metabolic syndrome?

The metabolic syndrome is a common term used to describe a clustering of metabolic risk factors that occur in an individual more than by chance alone. This clustering of cardiovascular (CV) risk factors has become much more prevalent in the general population and appears to be associated with an increasingly sedentary society and a global epidemic of obesity and diabetes.[1] The following are the hallmark features of this syndrome:

- insulin resistance
- central obesity
- atherogenic dyslipidemia
- hypertension.

It is now recognized that there are many other conditions and findings associated with this syndrome, such as renal disease, an elevation in inflammatory markers, and polycystic ovarian syndrome (Table 1). Given that many of the components of the syndrome are well-recognized CV risk factors, it is not surprising that individuals with the metabolic syndrome have up to a 5-fold increased risk of developing early atherosclerotic heart disease.[2]

Although the concept of the "metabolic syndrome" became popular only during the past decade, components of the syndrome have been described for close to a century. Previous names used to describe this condition include syndrome X,[3] the insulin resistance syndrome,[4] hypertriglyceridemic waist,[5] and "the deadly quartet."[6] Dr. E. Kylin was one of the first physicians to describe features of the syndrome. In 1923, he described the coexistence of hypertension, diabetes, and hyperuricemia, and proposed that a common mechanism was responsible for the development of these conditions.[7] A number of years later, Vague first described an association between upper body adiposity (android phenotype) and the development of diabetes, hypertension, gout, and atherosclerosis.[8] In 1988, Gerald M. Reaven hypothesized that insulin resistance was the common etiological factor in this clustering of metabolic disorders and referred to it as "syndrome X."[4] He also pointed out that these patients were at increased risk for the development of atherosclerosis.

Diagnosing metabolic syndrome

In recent years, many different criteria have been proposed for diagnosing an individual with the metabolic syndrome, as illustrated in Table 2**.** While these definitions all have similar components that include parameters for obesity, hypertension, dyslipidemia, and impaired glucose tolerance, there are significant differences between them. The World Health Organization (WHO) was the first group to formally define the syndrome in 1998.[9] Similar to the European Group for Insulin Resistance (EGIR) definition[10] and the American Academy of Clinical Endocrinologists (AACE) definition,[11] the WHO definition mandates that patients must demonstrate evidence of insulin insensitivity to meet the criteria for the metabolic syndrome. Unlike the WHO definition that includes patients with overt diabetes, the latter two definitions do not apply to patients once they develop type 2 diabetes.

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Table 1: Additional features associated with the metabolic syndrome[24]

Lifestyle
- Cigarette smoking
- Sedentary behaviour

Lipoproteins
- Increased apo B
- Decreased apo A-1
- Small dense LDL and HDL
- Increased apo C-111

Prothrombotic
- Increased fibrinogen
- Increased plasminogen activator inhibitor 1
- Increased viscosity

Inflammatory markers
- Increased white blood cell count
- Increased interleukin 6
- Increased tumour necrosis factor α
- Increased resistin
- Increased C-reactive protein
- Decreased adiponectin

Vascular
- Microalbuminuria
- Increased asymmetric dimethylarginine

Other
- Increased uric acid
- Increased homocysteine
- Non-alcoholic steatohepatitis
- Polycystic ovaries syndrome
- Obstructive sleep apnea

Other criteria have been proposed that do not mandate the presence of insulin insensitivity for diagnosis of the metabolic syndrome, including definitions from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[12] and the International Diabetes Federation (IDF).[13] While the NCEP ATP III allows any 3 of 5 diagnostic criteria to be present, the IDF requires the demonstration of central obesity, in addition to 2 other criteria. Furthermore, the IDF has recommended different waist measurements to define abdominal obesity based on ethnic background. For example, for individuals of European origin, waist circumferences ≥94 cm in men and ≥80 cm in women should be used to define abdominal obesity. Asian populations (excluding Japanese) should use waist circumference thresholds of ≥90 cm and ≥80 cm for men and women, respectively. For Japanese patients, they recommend using a waist circumference of ≥85 cm in men and ≥90 cm in women.

Table 3: New criteria for the clinical diagnosis of metabolic syndrome[14]

Measure (any 3 of 5 constitutes diagnosis of metabolic syndrome	Categorical cutpoints
Elevated waist circumference*†	≥102 cm (≥ 40 inches) in men ≥ 88 cm (≥ 35 inches) in women
Elevated triglycerides	≥150 mg/dL (≥ 1.7 mmol/L) or On drug treatment for elevated TG
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL (5.6 mmol/L) or on drug treatment for elevated glucose

* To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

† Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94-101 cm [37-39 inches] in men and 80-87 cm [31-34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡ Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG

Table 2: Previous criteria proposed for clinical diagnosis of metabolic syndrome[14]

Clinical measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	None
Insulin resistance	IGT, IFG,T2DM, or lowered insulin sensitivity* **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	None **but any 3 of the following 5 features**	IGT or IFG **plus any of following based on clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m²	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women†	BMI ≥25 kg/m²	Increased WC (population specific) **plus any 2 of the following**
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL and/ or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)‡	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance§	

T2DM indicates type 2 diabetes mellitus; WC = waist circumference; BMI = body mass index; TG = triglycerides.

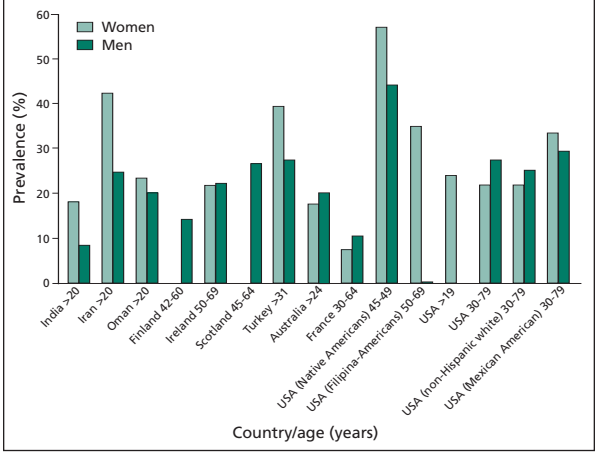
* Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (eg, 94 to 102 cm [37 to 39 in.]) Such patients may have a strong genetic contribution to insuliin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference.

‡ The 2001 definition identified fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L) in accordance with the American Diabetes Association's updated definition of IFG.

§ Includes family history of T2DM, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to T2DM.

Figure 1: Prevalence of the metabolic syndrome using the NCEP ATP III definition



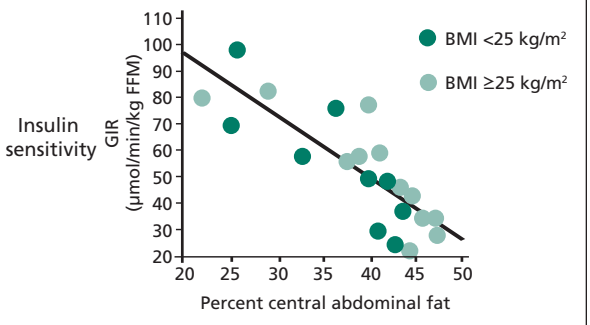
The American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) have published new criteria for the diagnosis of the metabolic syndrome that primarily uses the NCEP ATP III definition, with some minor modifications (Table 3).[14] The major difference is a lower threshold for impaired fasting glucose, which corresponds to the American Diabetes Association (ADA) criteria for impaired fasting glucose. Therefore, using this definition, patients meet the criteria for the metabolic syndrome if any 3 of the 5 criteria are met. A caveat to this is for individuals of Asian descent or patients with other conditions associated with the metabolic syndrome not included in the standard definition (eg, polycystic ovary disease, elevated C-reactive protein >3 mg/L, fatty liver, elevated total apoB). If these individuals have a moderately increased waist circumference (94-101 cm for men, 80-87 cm women) and 2 additional ATP III risk criteria, consideration should be made to manage them similarly to people with 3 ATP III risk factors.

Prevalence of the metabolic syndrome and obesity

Given the absence of a universally accepted definition of the metabolic syndrome, estimates of its prevalence vary. A detailed review reported the prevalence for men to be as low as 8% in India to as high as 24% in the United States.[15] For women, marked variation in prevalence was also seen, ranging from as low as 7% in France to as high as 43% in Iran. Figure 1 illustrates the different prevalence worldwide of the metabolic syndrome using the NCEP ATP III definition.

Data from the Third National Health and Nutrition Examination Survey (NHANES III) found the prevalence of the metabolic syndrome as defined by ATP III to be 22% in the United States.[16] Mexican Americans were at highest risk, with an age-adjusted prevalence of 31.9%. In addition, this survey illustrated that this is a disease of aging, with >40% of individuals aged >60 years meeting criteria for the metabolic syndrome. Although somewhat dated, an analysis of data from the Canadian Heart Health Surveys between 1986 and 1992 estimated the prevalence of the metabolic syndrome to be 14.4% using the ATP III definition.[17] Of particular concern is the significantly high prevalence of metabolic syndrome seen in the aboriginal population, where as many as 43.4% in aboriginal adults have been found to meet the criteria for this condition.[18]

Figure 2: Insulin sensitivity versus percentage abdominal fat in 22 healthy women[25]



Perhaps the biggest reason for the increasing prevalence of this syndrome is the rapidly increasing rate of obesity seen in the general population. It is estimated that >1 billion adults are overweight and that 300 million people worldwide are obese.[19] An alarming trend of increasing obesity has been seen in the United States, where obesity rates have increased from 12.8% between 1962 and 1964 to 32% between 1988 and 1992.[20] This trend has also been observed in Canada, with obesity rates more than doubling between 1985 and 1998, increasing from 5.6% to 14.8%, respectively.[21] In 2004, 5.5 million Canadians, representing nearly one-quarter of the population were obese, with an additional 8.6 million Canadians being overweight.[22] Of particular concern are children and adolescents, where the number of obese children has tripled in the past 25 years, to a current obesity rate of 8%.[23] Diet and inactivity are 2 of the largest contributors to this growing trend in obesity seen both in Canada and worldwide.

Pathogenesis of disease

To date, no single pathogenesis has been elucidated for this syndrome. Therefore, it is possible that this syndrome is a cluster of unrelated risk factors. Alternatively, some will argue that there is a common underlying mechanism that has not yet been fully determined.

The most universally accepted hypothesis for the pathogenesis of the metabolic syndrome is the development of insulin resistance.[24] As a result of overabundant visceral adipose tissue, there is excess circulating free fatty acids that create insulin resistance in sensitive tissues such as the liver and muscle. This relationship between visceral adiposity and insulin sensitivity has been demonstrated in humans,[25] as illustrated in Figure 2. In this study of 22 healthy women, insulin sensitivity was found to decrease in a linear fashion with increasing central abdominal fat. This helps to illustrate how some individuals with normal body weight – but increased central visceral fat – can still be "metabolically obese."

In the past, it was felt that adipose tissue was an inert organ; however, it is now recognized that visceral adipose tissue is metabolically active, secreting numerous cytokines. For example, it has been shown that proinflammatory cytokines such as interleukin 6, tumour necrosis factor alpha (TNF-α), and C-reactive protein are produced by visceral adipose tissue and that this may contribute to the insulin-resistant state.[26,27] In addition, there is downregulation of adiponectin, an anti-inflammatory cytokine, from visceral adipose tissue in patients

with the metabolic syndrome.[28] This explains the well-documented association between this syndrome and inflammation.[29] The combined impact of increased circulating free fatty acids, increased inflammation, and hyperinsulinemia likely contribute to the development of the atherogenic dyslipidemia and hypertension seen with this condition.[24]

Metabolic syndrome and CV risk

Numerous studies[2,30-32] have shown that people with the metabolic syndrome are at increased risk to develop atherosclerotic CV disease. The degree of risk varies, depending on the population studied and the definition used. Using the NCEP ATP III criteria, the increased risk for CV morbidity and mortality ranges from 1.5 to 4.65.[33] For example, analysis from NHANES III found that the metabolic syndrome is associated with a 2-fold increased risk of myocardial infarction (MI) and stroke.[32] This should not come as a big surprise, since many of the components of the syndrome are well-recognized independent CV risk factors.

There have been attempts to compare the ability of the metabolic syndrome to predict CV disease compared to the Framingham Risk score. While the metabolic syndrome may be a better predictor of future diabetes,[34] most of the published studies have found it to be inferior at predicting future coronary events.[34-36] When added to the Framingham risk score by Wannamethee et al,[34] it did not provide additional predictive value. In addition, analysis from the San Antonio Heart Study found that it had a false positive rate of 34% for predicting CV disease.[35]

Does the metabolic syndrome exist?

There are some investigators who are not entirely convinced that the metabolic syndrome – as defined – meets the criteria to be deemed a syndrome at all. In a joint statement,[37] both the American Diabetes Association and the European Association for the Study of Diabetes have discounted the value of diagnosing individuals with this condition. They argue that the metabolic syndrome is not very well-defined with ambiguous criteria and ill-defined thresholds. In addition, these groups express concern over labeling millions of individuals with a "presumed disease" when little is known about the underlying pathophysiology. Finally, they state that, at the present time, there is little evidence that the metabolic syndrome is a useful marker of CV risk beyond the risk associated with its individual components.

While some of this criticism is understandable, the purpose of the metabolic syndrome is to draw attention to risk factors that cluster in certain people and to remind clinicians to recognize these individuals prior to the development of diabetes or CV disease. Although the metabolic syndrome may not predict coronary heart disease as well as the Framingham Risk score, it does serve as a simple tool to identify high-risk individuals. The identification of one of the risk factors in a patient should prompt the search for others. Finally, the management of this syndrome focuses on prevention prior to the onset of disease, encouraging healthy lifestyle changes such as weight loss and exercise, rather than pharmacotherapy.

Table 4: Targets, goals and recommendations for clinical management of metabolic syndrome

Abdominal obesity	Goal: 10% weight loss first year
Physical inactivity	Goal: regular moderate-intensity physical activity
Atherogenic diet	Goal: reduced intakes of saturated fats, trans fats and cholesterol
Cigarette smoking	Goal and recommendation: complete smoking cessation
LDL-C	Goals: High-risk patients* LDL-C <1 g/L (2.6 mmol/L) Moderately high-risk patients† LDL-C <1.3 g/L (3.4 mmol/L) Moderate-risk patients‡ LDL-C <1.3 g/L (3.4 mmol/L) Recommendations – Lifestyle therapies§
High triglyceride or low HDL-C	Insufficient data to establish goal High-risk patients – consider adding fibrate or nicotinic acid
Elevated BP	Goals: BP <135/85 mm Hg. For diabetes or chronic kidney disease: BP <130/80 mm Hg.
Elevated glucose	Goals: maintenance or reduction in fasting glucose if >1 g/L (5.5 mmol/L) Hemoglobin A_{1C} <7.0% for diabetes
Prothrombotic state	Goals: reduction of prothrombotic state. High-risk patients – initiate low-dose aspirin or clopidogrel if aspirin contraindicated
Proinflammatory state	Recommendations: no specific therapies

* High-risk patients: those with established atherosclerotic cardiovascular disease, diabetes, or 10-year risk for coronary heart disease > 20%.
† Moderately high-risk patients: those with 10-year risk factor for coronary heart disease 10%-20%.
‡ Moderate-risk patients: those with metabolic syndrome but 10-year risk for coronary heart disease <10%.
§ Lifestyle therapies include weight reduction, regular exercise and antiatherogenic diet.

Even the critics of the metabolic syndrome appear to agree that this concept is a good paradigm for physicians and patients. For example, the American Diabetes Association has started the "Cardiometabolic Risk Initiative,"[38] which is a national effort focused on encouraging healthcare providers and the general public to focus on the prevention, recognition, and treatment of all cardiometabolic risk factors, helping patients achieve better health outcomes.

Management of the metabolic syndrome (Table 4)

The primary objective in the clinical management of a patient with the metabolic syndrome is to reduce their future risk for atherosclerotic disease and diabetes. This is accomplished by targeting modifiable underlying risk factors for the metabolic syndrome (obesity, physical inactivity, and an atherogenic diet) through lifestyle changes. The following guidelines are taken from the American Heart Association and National Heart, Lung and Blood Institute (AHA/NHLBI) scientific statement on the diagnosis and management of the metabolic syndrome.[14]

Given that central obesity is felt to be an important factor in the development of the metabolic syndrome, weight reduction is a top priority in those with large waist circumferences or increased body mass index

(BMI). The initial goal should be a 7%-10% reduction in weight over a 6- to 12-month period. This has been shown to improve obesity-related morbidity and mortality.[39] Weight loss should occur through an appropriate balance of diet (reducing caloric intake by 500-1000 calories a day) and physical activity. The ultimate goal is to achieve a BMI of <25 kg/m^2 and waist circumference of <102 cm in men and <88 cm in women. Once initial weight loss is achieved, efforts should then be focused on maintenance of weight loss for the long-term.

Addressing the problem of physical inactivity is extremely important, as exercise contributes to weight loss and has beneficial effects on metabolic risk factors. More importantly, physical activity has been shown to reduce overall atherosclerotic CV disease risk.[40] The current recommendations are for individuals to perform moderate intensity exercise for at least 30 minutes a day, 7 days a week. Individuals at high risk for cardiac events should initially exercise in a supervised setting, such as a cardiac rehabilitation program.

In addition to a reduction in total caloric intake, an anti-atherogenic diet is also recommended that is low in trans-fats, saturated fat, sodium, and simple sugars. Approximately 25%-35% of total calories should come from fat, with <7% of these from saturated fats. Ample intake of vegetables, whole grains, and fruits should be encouraged.

Along with making lifestyle changes, all patients should be closely monitored for the development of the risk factors that comprise this condition. Published guidelines for the management of hypertension, diabetes, and dyslipidemia should be followed and drug therapy initiated as indicated.

Future research and therapies targeting the metabolic syndrome

There is an ongoing search for potential new molecular drug targets treating the metabolic syndrome and its components. At the present time, there is insufficient evidence to recommend any pharmacotherapy specifically for individuals with the metabolic syndrome. Drugs targeting obesity and insulin insensitivity have been considered to be the most promising candidate therapies for this syndrome. A couple of such drugs that have been publicized as potential therapies are reviewed below.

It is well-recognized that the endocannabinoid system plays a central role in the regulation of body metabolism and composition by enhancing the central orexigenic drive and increasing lipogenesis.[41] Rimonabant is an antiobesity drug that acts as an endocannabinoid receptor antagonist that may be a candidate drug for patients with the metabolic syndrome. There have been 4 large randomized trials in humans published to date studying this drug.[42-45] Collectively known as the Rimonabant in obesity (RIO) trials, these studies have reported significant reductions in body weight and waist circumference with continued therapy with rimonabant compared to placebo.[46] In addition, favourable changes in the cardiometabolic risk profile have also been seen, including improvement in lipid profiles, improved glycemic control, and an overall decrease in the prevalence of the metabolic syndrome. While these results appear promising, further, long-term studies are needed to examine CV endpoints. As with other obesity trials, high drop-out rates were seen in these studies, which raises concerns regarding compliance and long-term use.

Drugs that improve insulin sensitivity are also felt to be candidate drugs for patients with the metabolic syndrome. Peroxisome proliferator activated receptor gamma (PPAR γ), which is a nuclear receptor that is expressed at high levels in adipose tissue, has been shown to play an important role in adipocyte differentiation, lipid storage, and glucose homeostasis.[47] The thiazolidinedione class of insulin sensitizers mediate their effects through activation of this receptor and improve insulin responsiveness. A recent study in diabetic patients found that pioglitazone, a PPAR γ agonist, significantly reduced a composite of death, MI, and stroke compared to placebo.[48] While this class of drugs is currently prescribed to patients with diabetes, its mechanism of action and potential impact on CV outcomes make it a potentially attractive therapeutic for patients with the metabolic syndrome. There is also interest in PPARΔ agonists, which have been shown to stimulate fat burning and, therefore, may have potential for treating obesity.[49]

Several other new drugs are in development by the pharmaceutical industry that target the treatment of obesity and the metabolic syndrome.[50] However, it is beyond the scope of this review to discuss these potential treatments in any detail. Given the current obesity epidemic, there is no doubt this will continue to be an active area of research.

Summary

The metabolic syndrome is prevalent worldwide and associated with an increased risk of developing diabetes and atherosclerotic heart disease. While the pathophysiology linking the components of the syndrome is not well-understood, it is strongly associated with the presence of abdominal obesity. Lifestyle interventions are the initial steps in the treatment of this condition. At the present time, there is no evidence for the primary use of drugs targeting the underlying causes of this syndrome. Hopefully, with further research in this field, there will be a better understanding of this syndrome and appropriate therapies.

Dr. Allard is a cardiology trainee at St. Michael's Hospital, Toronto.

References

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782-87.
2. Iribarren C, Go A, Husson G, et al. Metabolic syndrome and early-onset coronary artery disease. *J Am Coll Cardiol* 2006;48(9):1799-1807.
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607.
4. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-94.
5. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small dense LDL) in men? *Circulation* 2000;102:179-184.
6. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia and hypertension. *Arch Intern Med* 1989;149:1514-20.
7. Kylin E. Studien über das Hypertooni-Hyperglycemi-Hyperurikemi syndrome. *Zentralblatt für Innere Medizin* 1923;44:105-112.
8. Vague J. The degree of masculine differentiation of obesities. A factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *Am J Clin Nutr* 1956;4:20-34.

9. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, Part 1: diagnosis and classification of diabetes mellitus- provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.
10. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999;16:442-443.
11. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract* 2003;9:237-252.
12. National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the national cholesterol education program expert panel on detection evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
13. International Diabetes Federation. Worldwide definition of the metabolic syndrome. Available at: http://www.idf.org/webdata/docs/MetSyndrome_FINAL. pdf. Accessed January 7, 2007.
14. 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;112:2735-2752.
15. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004;33:351-75.
16. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. Finding from the third national health and nutrition examination survey. *JAMA* 2002;287:356-359.
17. Brien SE, Katzmarzyk PT. Physical activity and the metabolic syndrome in Canada. *Appl Physiol Nutr Metab* 2006;31(1):40-7.
18. Pollex RL, Hanley AJ, Zinman B, Harris SB, Khan HM, Hegele RA. Metabolic syndrome in aboriginal Canadians: prevalence and genetic associations. *Atherosclerosis* 2006;184(1):121-9.
19. World Health Organization. Global Strategy on Diet, Physical Activity and Health. Online publication: http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/. Accessed January 7, 2007.
20. Flegal KM, Carroll MD, Kuczmarki RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obes Relat Metab Disord* 1998;22(1):39-47.
21. Katzmarzyk PT. The Canadian Obesity Epidemic, 1985-1998. *CMAJ* 2002;166:1039-1040.
22. Tjepkema M. Measured Obesity. Adult obesity in Canada: Measured height and weight. Nutrition: Findings from the Canadian Community Health Survey. Component of Statistics Canada Catalogue no. 82-620-MWE2005001. Online www.statcan.ca/english/research/82-620-MIE/2005001/pdf/aobesity.pdf
23. Shields M. Overweight Canadian children and adolescents. Nutrition: Findings from the Canadian Community Health Survey Issue no 1. Component of Statistic Canada Cataloque no. 82-620-MWE2005001. Online: www.statcan.ca/english/ research/82-620-MIE/2005001/pdf/aobesity .pdf
24. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415-28.
25. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996;45:633-638.
26. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 2003;24:278-301.
27. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004;92:347-55.
28. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004;24:29-33.
29. Sutherland J, McKinnley B, Eckel RH. The metabolic syndrome and inflammation. *Metabolic Syndr Rel Disord* 2004;27:2057-66.
30. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total cardiovascular disease mortality in middle-aged men. *JAMA* 2002;228:2709-2716.
31. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease and all causes in United States adults. *Circulation* 2004;110:1245-1250.
32. Ninomiya JK, L'Italien G, Criqui MH, WHyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 2004;109:42-46.
33. Bonora E. The metabolic syndrome and cardiovascular disease. *Ann Med* 2006;38:64-80.
34. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome versus Framingham Risk Score for prediction of coronary heart disease, stroke and type 2 diabetes mellitus. *Arch Intern Med* 2005;165:2644-2650.
35. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 2004;27:2676-2681.
36. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11 year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities study. *Diabetes Care* 2005;28:385-390.
37. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for Diabetes. *Diabetologia* 2005;48:1684-1699.
38. American Diabetes Association. The Cardiometabolic Risk Initiative. Online http://www.diabetes.org/for-health-professionals-and-scientists/cardiometabolic-risk.jsp. Accessed January 9, 2007.
39. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation Technical Report Series 894, Geneva, Switzerland; 2000.
40. Franklin BA, Kahn JK, Gordon NF, Bonow RO. A cardioprotective "polypill"? Independent and additive benefits of lifestyle modification. *Am J Cardiol* 2004; 94:162-166.
41. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003;112:423-31.
42. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005;353:2121-34.
43. VanGaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; 365:1389-97.
44. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized control trial. *JAMA* 2006;295: 761-75.
45. Scheen AJ. Effects of rimonabant in patients with type 2 diabetes mellitus. Results of the RIO-DIABETES trial. Presented at: American Diabetes Association Scientific Sessions; San Diego, CA: 2005.
46. Gelfand EV, Cannon CP. Rimonabant: A cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol* 2006;47: 1919-26.
47. Takahashi S, Tanaka T, Kodama T, Sakai J. Peroxisome proliferators-activated receptor delta, a novel target site for drug discovery in metabolic syndrome. *Pharmacol Res* 2006;53:501-507.
48. Dormandy JA, Charbonnel B, Eckland D et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzsone Clinical Trial in macroVascular Events). *Lancet* 2005;366:1279-90.
49. Wang YX, Lee CH, Tiep S, et al. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* 2003;113(2):159-170.
50. Nisoli E, Carruba MO. Emerging aspects of pharmacotherapy for obesity and metabolic syndrome. *Pharmacol Res* 2004;50:453-469.

Upcoming meetings

11-15 March 2007
23rd Annual Cardiovascular Conference Lake Louise
Fairmont Chateau Lake Louise Hotel,
Lake Louise, Alberta, Canada
Contact: www.acclakelouise.com

24-27 March 2007
56th Annual Scientific Session of the American College of Cardiology (ACC.07)
New Orleans, Louisiana
Contact: www.acc.org

Disclosure Statement: *Dr. Allard and Dr. Moe have no disclosures to announce in association with the contents of this issue.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.