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Scientific Update™

Medical Crossfire – Managing Global Cardiometabolic Risk: How Can We Disrupt the Pathological Process?

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A Review of Presentations at a Satellite Symposium at the 56th Annual Scientific Session of the American College of Cardiology 2007

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By GORDON MOE, MD, FRCPC

The worldwide epidemic of obesity and diabetes has been accompanied by an increase in the prevalence of cardiovascular disease (CVD). Even with considerable research and the development of new approaches for managing cardiometabolic risk, the residual risk remaining in treated patients is still associated with a high rate of cardiovascular events. This may be due, in part, to the fact that many pharmacologic options treat the downstream consequences of CV and metabolic processes that are distal to the point in the pathogenic cascade at which classic CVD risks develop. This issue of *Cardiology Scientific Update* discusses new data on the factors driving global CVD risk, potential new therapeutic targets, as well as therapy that may influence multiple risk factors by targeting upstream causes, such as those associated with abdominal obesity.

Cardiometabolic risk assessment: identifying patients for treatment

The pattern of CVD risk factors in adults has gradually changed over the past 40 years. While the prevalence of traditional risk factors such as hypertension, smoking, and dyslipidemia has declined, the prevalence for overweight and obesity has actually increased (Figure 1). It is now well-known that overweight and obesity increase the risk of CVD mortality.[1-3] Indeed, the risk of death from all causes, CVD, cancer, or other diseases increases throughout the range of moderate and severe overweight for both men and women in all age groups.[1] The metabolic syndrome is a term used to describe a clustering of metabolic risk factors that are found to occur in an individual more often than by chance alone, and obesity is an important component. Although there is controversy as to whether metabolic syndrome is a distinct scientific concept,[4] most authorities generally recognize it as a key risk factor for CVD.[4-6] The 5 current criteria and cut-off values proposed by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP–ATP III)[5,7] and endorsed by the International Diabetes Federation (IDF)[8] to diagnose the likely presence of metabolic syndrome are shown in Table 1. Given that many of the syndrome components are also recognized CVD risk factors, it is not surprising that individuals with the metabolic syndrome have up to a 2-fold increased risk of developing CVD and a 4-fold increased risk of developing diabetes,[6,9,10] hence, the term cardiometabolic risk.

Accordingly, ATP III recommends that obesity be the primary target of intervention and that first-line therapy should be weight reduction reinforced with increased physical activity.[6] Indeed, when obesity and body fat distribution are targeted by therapy, the resulting benefits include:

- lower cholesterol and triglycerides
- higher high-density lipoprotein (HDL) cholesterol
- lower blood pressure (BP) and glucose
- less insulin resistance
- lower serum C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1)

In general, regardless of the diagnostic criteria used, there is little disagreement that therapeutic lifestyle changes, with an emphasis on weight reduction, constitute first-line therapy for metabolic syndrome. Drug treatment to directly reduce insulin resistance is promising, but clinical trial data proving reductions in CVD are still lacking. In patients for whom lifestyle changes fail to reverse metabolic risk factors, consideration should be given to treating specific risk factor abnormalities with pharmacologic agents. However, the use of these agents to target risk factors should be in accordance with current treatment guidelines.

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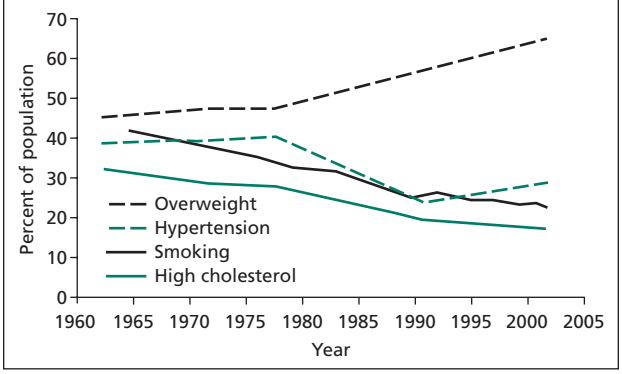
Figure 1: Prevalence of CVD risk factors in adults in the US: 1961-2001



National Institute of Health, NHLBI Fact Book, Fiscal Year 2005 (www.nhlbi.gov/about/factbook/chapter4.htm, accessed June 12, 2007)

Pathological mechanisms in cardiometabolic risk: emerging treatment for intervention

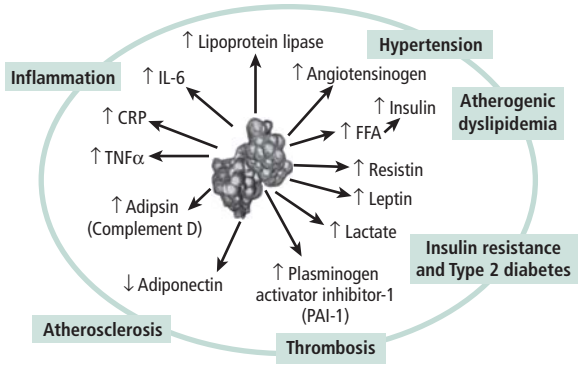
The pathological mechanisms in cardiometabolic risk were reviewed in a recent issue of *Cardiology Scientific Update*. The pathophysiology of metabolic syndrome seems to be largely attributable to insulin resistance with an implicated excessive flux of fatty acids.[11,12] In addition, a proinflammatory state likely contributes to the syndrome. The adverse cardiometabolic effects of visceral adipocytes are summarized in Figure 2.[12-14] Adipose tissue is a dynamic endocrine organ secreting a number of factors that are increasingly recognized as contributors to systemic and vascular inflammation. Several of these factors, collectively referred to as adipokines, have now been shown to regulate, directly or indirectly, a number of processes that contribute to the development of atherosclerosis, including hypertension, endothelial dysfunction, insulin resistance, and vascular remodeling.[13] The adipokinome, together with released lipid moieties (eg, fatty acids and prostaglandins), constitute the secretome of fat cells and includes proteins involved in lipid metabolism, insulin sensitivity, the alternative complement system, vascular hemostasis, BP regulation, angiogenesis, and the regulation of energy balance. In addition, there is a growing list of adipokines involved in inflammation including tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-10, transforming growth factor-beta, nerve growth factor, and factors involved in the acute-phase response, such as PAI-1, haptoglobin, and serum amyloid A. Production of these proteins by adipose tissue has been demonstrated to increase in obesity.[14] The possible integration of the metabolic syndrome and multiple CVD risk factors are depicted in Figure 3.[15] This implies that therapeutic intervention targeting excess/abnormal adiposity may modulate cardiometabolic risk by reducing the progression of diabetes and its associated CVD risk, either by disrupting the pathological cascade prior to clinical manifestations of conventional risk factors, and/or reducing the residual risk that remains with current treatment modalities.

The endocannabinoid system (ECS) represents a novel metabolic regulatory system that integrates the intake, transport, metabolism, and storage of nutrients in the brain, gut, liver, adipose tissue, and muscle. The endocannabinoids bind 2

Table 1: AHA/ATP III clinical criteria for the identification of metabolic syndrome

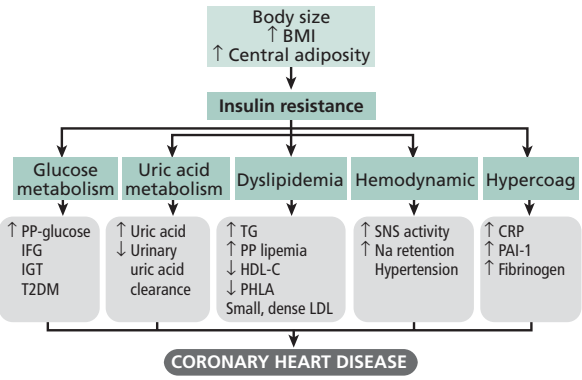
Measure (any 3 of 5 constitutes diagnosis of metabolic syndrome)	Categorical cutpoints
Elevated waist circumference	≥102 cm (≥40 inches) in men ≥ 88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (≥1.7 mmol/L) or on drug treatment for elevated TG
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <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

Figure 2: Adverse cardiometabolic effects of the visceral adipocytes



FFA = free fatty acid; CRP = C-reactive protein

Figure 3: Integration of the metabolic syndrome and multiple CVD risk factors



PP = postprandial; IFG = increased fasting sugar; IGT = impaired glucose tolerance; SNS = sympathetic nervous system; PHLA = post-heparin lipase activity

cannabinoid receptors (CBs), CB1 and CB2. These receptors belong to the G protein-coupled superfamily and were discovered during investigations of the mode of action of Δ^9-tetrahydrocannabinol, an exogenous cannabinoid and an important component of *Cannabis sativa*, which the receptors bind with high affinity.[16] CB1 is widely distributed in the central nervous system (CNS), including the hypothalamic nuclei, which are involved in the control of energy balance and body weight, and in neurons of the mesolimbic system believed to mediate the incentive value of food;[17] it is also expressed in peripheral tissues.[16,18] As a result, CB1-receptor blockade provides a novel approach to the management of multiple cardiometabolic risk factors by addressing abdominal obesity, directly improving lipid and glucose metabolism and insulin resistance.

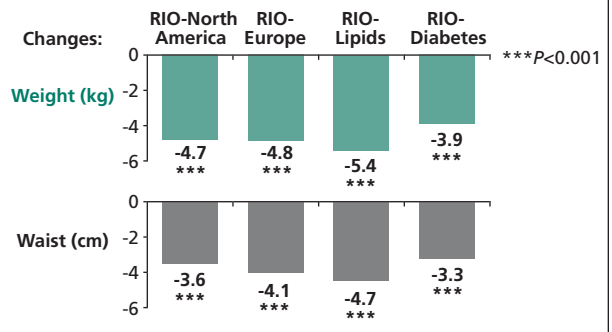
The discovery of rimonabant (not yet approved in Canada),[19] the first specific CB1-receptor blocker, sets the stage for the development of novel pharmacotherapeutic approaches to treat obesity. The Rimonabant in Obesity (RIO) program enrolled over 6,600 subjects in an investigation of the impact of rimonabant on cardiometabolic risk factors in an overweight/obese population. RIO-North America[20] and RIO-Europe[21] were 2-year studies that enrolled patients with body mass index (BMI) ≥30 kg/m^2, or BMI >27 kg/m^2 with comorbid factors, such as hypertension and dyslipidemia. RIO-Lipids was a 1-year study designed to evaluate rimonabant in patients with untreated dyslipidemia.[22] In addition, RIO-Lipids included measurements of additional parameters related to atherosclerotic risk, ie, adiponectin levels, low-density lipoprotein (LDL) particle size and density, and CRP levels. RIO-Diabetes was a 1-year study conducted in patients with type-2 diabetes mellitus (DM) receiving metformin or sulfonylurea treatment.[23] Results from studies in the RIO program have been discussed in a previous issue of *Cardiology Scientific Update*. The primary results can be summarized as follow (Figure 4).

In obese subjects, CB1-receptor blockade with rimonabant resulted in:

- significant reductions in waist circumference and body weight
- significant improvements in the metabolic profile, including increased HDL-C and decreased triglyceride levels, improved insulin sensitivity, and improvements in glycosylated hemoglobin (HbA_{1c}) in type-2 DM
- significant decreases in the percentage of subjects with metabolic syndrome
- improvements in other metabolic and cardiovascular risk factors, including increased adiponectin, decreased CRP, and an improved small dense LDL particles profile.

Manipulation of the ECS via CB1-receptor blockade, therefore, represents a novel mechanism through which central adiposity and other downstream risk factors may be targeted. Clinical trials to date demonstrate that the use of rimonabant produces consistent and sustained effects on body weight, waist circumference, lipid profiles, glycemic control, and levels of adipokines and inflammatory markers.

Figure 4: Placebo-subtracted weight and waist reductions in the RIO Program



Rimonabant 20 mg minus placebo (ITT LOCF).

ITT = intention-to-treat; LOCF = last observation carried forward

Cardiometabolic risk: current research and future therapies

Atherothrombosis is now the leading cause of CV morbidity and mortality around the globe. Until recently, no single international database characterized the atherosclerosis risk factor profile or treatment intensity of individuals with atherothrombosis globally. The recently-published Reduction of Atherothrombosis for Continued Health (REACH) Registry collected data on atherosclerosis risk factors and treatment in 67,888 patients aged ≥45 years from 5,473 physician practices in 44 countries.[24] These patients either had established arterial disease (coronary artery disease [CAD], n=40,258; cerebrovascular disease, n=18,843; peripheral arterial disease, n=8,273) or ≥3 risk factors for atherothrombosis (n=12,389), between 2003 and 2004.

The regional prevalence of overweight and obesity is shown in Figure 5. The prevalence of overweight (39.8%), obesity (26.6%), and morbid obesity (3.6%) were similar in most geographic locales, but prevalence was highest in North America (overweight: 37.1%, obese: 36.5%, and morbidly obese: 5.8%; P<0.001 versus other regions). In addition, there is undertreatment of conventional risk factors worldwide (Figure 6). In

Figure 5: Prevalence of overweight and obesity in geographic regions

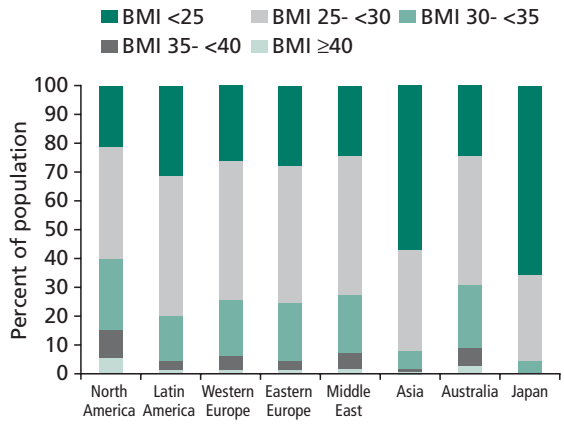
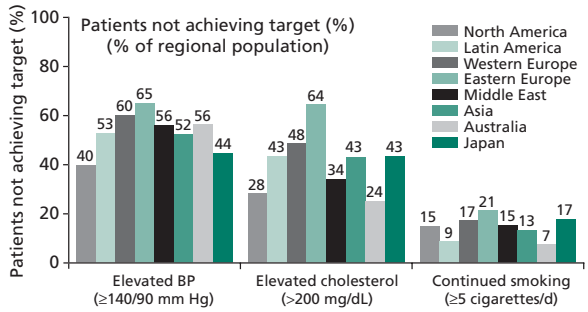


Figure 6: Treatment of conventional risk factors worldwide



general, patients were undertreated with statins (69.4% overall; range: 56.4% for cerebrovascular disease to 76.2% for CAD), antiplatelet agents (78.6% overall; range: 53.9% for ≥3 risk factors to 85.6% for CAD), as well as, other evidence-based risk-reduction therapies. Current smoking in patients with established vascular disease was substantial (14.4%). Undertreated hypertension (50.0% with elevated BP at baseline), undiagnosed hyperglycemia (4.9%), and impaired fasting glucose (36.5% in those not known to be diabetic) were particularly common. Among those with symptomatic atherothrombosis, 15.9% had symptomatic disease in multiple vascular territories.

These contemporary data demonstrate that conventional risk factors for CVD are prevalent worldwide and yet, remain undertreated. Established therapies or therapies under investigation that target specific and conventional cardiometabolic risk factors include intense LDL-reduction,[25,26] HDL-raising strategies, antiplatelet therapy beyond acetylsalicylic acid (ASA) alone, and novel antiglycemic approaches. Targeting abdominal obesity will likely be an important strategy, using intensive lifestyle intervention with or without CB1-receptor blockade. In this regard, the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial is an ongoing multinational, randomized, multicentre, double-blind, placebo-controlled trial of rimonabant (20 mg daily) for reducing the risk of major CV events in abdominally obese patients with clustering risk factors, (*www.clinicaltrials.gov*).

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