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Scientific Update™

The Role of the Endocannabinoid System in the Management of Cardiometabolic Risk

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The obesity epidemic has been accompanied by a parallel rise in the prevalence of insulin resistance and the metabolic syndrome that increases the risk for cardiovascular disease and type 2 diabetes. Early and aggressive management of the constellation of risk factors associated with obesity, including hyperglycemia, dyslipidemia, hypertension, and chronic inflammation, is of major importance in improving patient outcomes. In addition to conventional management strategies aimed at reducing risk, a novel physiological target, known as the endocannabinoid system, has recently emerged. In this issue of *Cardiology Scientific Update,* the importance of recognizing cardiometabolic risk and the role of the endocannabinoid system in the management of cardiometabolic risk is reviewed.

Intra-abdominal adiposity: A key contributor to cardiovascular risk

The increasing prevalence of obesity is accompanied by a parallel increase in the prevalence of insulin resistance and the metabolic syndrome.[1] Patients with insulin resistance and metabolic syndrome have a greater risk for acute coronary syndrome (ACS), a higher likelihood of ACS at a younger age, as well as a worse prognosis following a coronary event.[2,3] Indeed, autopsy studies have demonstrated that atherosclerosis in youth is strongly linked to obesity and "early" insulin resistance.[2] Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries[4] and the coronary circulation is dysfunctional in obesity-related insulin-resistant syndromes.[5]

Abdominal obesity (waist circumference >102 cm in men and >88 cm in women)[6] plays a major role in the development of multiple metabolic disorders, including dyslipidemia, insulin resistance, type 2 diabetes (T2DM), and metabolic syndrome.[6-8] Indeed, 86% of abdominally obese subjects have ≥1 cardiovascular (CV) risk factors, and 24% have at least 2 additional CV risk factors that identify them as having the metabolic syndrome. Abdominal obesity, therefore, signifies a marked increase in overall CV risk that is often driven by the progression of multiple risk factors and, hence, the term "cardiometabolic risk" has been put into practice.[1] Surveys in various countries suggest that if criteria similar to those used for the metabolic syndrome, as defined by the National Cholesterol Educational Program (NCEP/ATP III) expert panel,[9,10] are used, there is an epidemic proportion of abdominal obesity and its prevalence is increasing.[11]

Why is abdominal obesity harmful? Abdominal obesity, driven by intra-abdominal adiposity, is not only often associated with other risk factors, but is also an *independent* and powerful predictor of adverse cardiovascular outcomes.[12] This is largely due to the highly active intra-abdominal adipocytes that secrete bioactive substances ("adipokines"), including the proinflammatory cytokines and procoagulant factors that would unfavourably impact on insulin sensitivity and cardiometabolic risk and, subsequently, increase the risk of adverse clinical events (Figure 1).[13-15] On the other hand, the adipocytes also elaborate adiponectin, an "adipokine" that exerts antiatherosclerotic, anti-inflammatory and antidiabetic effects.[15] In the case-control Health Professionals

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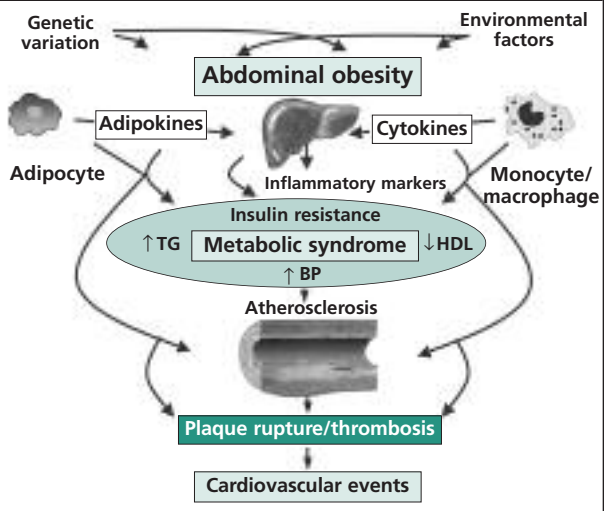
Figure 1: Abdominal obesity, cardiometabolic risk, atherosclerosis and cardiovascular events



Follow-up Study, low adiponectin levels were associated with a higher risk of myocardial infarction (MI) that remained significant even after adjustment for other risk variables.[16]

The association of visceral adipose tissue with incident MI in older men and women was evaluated in the Health, Aging, and Body Composition Study.[17] In the 1,116 men and 1,387 women aged 70-79 years who were followed, there were 116 MI events. No association was found between incident MI and the adiposity or fat distribution variables for men. For women, visceral adipose tissue was an independent predictor of MI, hazard ratio (HR) 1.67, 95% confidence interval (CI), 1.28-2.17. No association was found between body mass index (BMI) or total fat mass and MI events in women. Furthermore, the association between visceral adipose tissue and MI in women was independent of high-density lipoprotein (HDL) cholesterol, interleukin-6 concentration, hypertension, and diabetes.

In summary, the adverse effects of classical risk factors such as hypercholesterolemia, hypertension, and smoking are well-understood. Increased understanding of the pathophysiology of cardiovascular disease (CVD) identifies new CV risk factors. Among these, abdominal obesity, low HDL-C, hypertriglyceridemia, and the hyperglycemia associated with insulin resistance are all recognized criteria for the diagnosis of the metabolic syndrome. However, a range of important novel risk factors or risk markers for CVD are also associated with the metabolic syndrome, although not yet included within its definition. These include chronic, low-grade inflammation and disturbances in the secretion of bioactive substances from adipocytes ('adipokines') that influence CV structure and function. The CV risk factors associated with the metabolic syndrome, whether included within its diagnostic criteria or not, contribute to increased cardiometabolic risk and progression of atherosclerosis, and represent an important clinical need inadequately addressed by current therapies. Therefore, clinicians need to extend their routine systematic assessment from CV risk to cardiometabolic risk – that is, the risk for developing CVD and/or diabetes – and increase their understanding of the basic mechanisms that regulate energy balance and metabolic risk factors.

Physiology of the endocannabinoid system: Central and peripheral mediators of adiposity and insulin resistance

The endocannabinoids are endogenous lipids capable of binding to 2 cannabinoid (CB) receptors: CB1 and CB2. These receptors belong to the G protein-coupled superfamily and were discovered during investigation of the mode of action of Δ-tetrahydrocannabinol[9] – an exogenous cannabinoid and an important component of *Cannabis sativa* – which they bind to with high affinity.[18]

- CB1 is widely distributed in the central nervous system (CNS), including the hypothalamic nuclei that are involved in the control of energy balance and body weight, as well as in neurons of the mesolimbic system believed to mediate the incentive value of food;[19] CB1 is also expressed in peripheral tissues.[18,20]
- CB2, on the other hand, is mainly expressed in immune cells and does not appear to play a role in food intake.[20] Around the same time that CB1and CB2 were cloned, CB1 endogenous ligands (the so-called "endocannabinoids") were identified and synthesized. The most important are anandamide and 2-arachidonoylglycerol (2-AG).[21]

The discovery of specific receptors and their endogenous ligands, therefore, support the existence of an endogenous cannabinoid system. Endogenous cannabinoids are lipids synthesized and released from the neurons in response to membrane depolarization. Following their release, their rapid inactivation is induced by specific enzymes.[22] Therefore, the endocannabinoid system serves as a general stress-recovery system.

Strong evidence exists that has helped establish the role of CB1 receptors in hunger-induced food intake and energy balance. For example, CB1 activation may restore feeding in satiated animals,[23] whereas CB1 receptor blockade decreases the rate of responding to food.[24] CB1 blockade induces a transient reduction in food intake and a more long-lasting reduction in body weight in diet-induced obese mice, but has no effect on CB1 receptor knockout mice.[25]

Recent data from animal models have provided solid evidence that genetically-induced obesity is accompanied by chronic and intense activation of the endocannabinoid system.[26] Moreover, CB1 is also present in peripheral organs, including adipose tissue and the gastrointestinal system, major organs in the regulation of energy metabolism.[18,23] Indeed, CB1 receptor-deficient mice have reduced body weight, fat mass, and activation of metabolic processes that are independent of reduced food intake.[27] Furthermore, these CB1 receptor-deficient mice are resistant to diet-induced obesity and the development of what, in

Figure 2: Sites of CB1 receptor and potential effects of CB1 blockade

	Site of action	Mechanisms	Effects
	**Hypothalamus / Nucleus accumbens**	⇓ Food intake	Body weight Intra-abdominal adiposity
	**Adipose tissue**	⇑ Adiponectin ⇓ Lipogenesis	Dyslipidemia Insulin resistance
	**Muscle**	⇑ Glucose uptake	Insulin resistance
	**Liver**	⇓ Lipogenesis	Dyslipidemia Insulin resistance
	**GI tract**	⇑ Satiety signals	Body weight Intra-abdominal adiposity

humans, would be regarded as metabolic syndrome.[28] Treatment with a CB1 agonist increases *de novo* fatty acid synthesis in the liver and in isolated hepatocytes that express CB1 receptors.[28]

On the other hand, in a model of established obesity, chronic CB1 receptor blockade using rimonabant, – an investigational drug not yet approved in Canada – produced several beneficial effects. These included a marked and sustained decrease in body weight (equivalent to that achieved by dietary change) that was associated with favourable modifications in serum biochemical and lipid profiles, including a reduction in leptin, insulin, glucose, triglycerides, and low-density lipoprotein cholesterol (LDL-C).[29] CB1 blockade also increased insulin sensitivity of the skeletal muscle in Lep(ob)/Lep(ob) mice.[30] Finally, *in vitro*, CB1 blockade with rimonabant stimulated adiponectin production in the adipocytes of obese rats.[31]

The sites of the appetite-related and metabolic actions of the endocannabinoids and the possible sites of action of CB1 blockade are shown in Figure 2. The aforementioned experimental data, therefore, suggest that CB1 receptor blockade can reduce obesity via a dual mechanism of action that includes a central action of reducing appetite and a peripheral action of inducing favourable changes in energy storage and expenditure. Selective CB1 receptor blockade, particularly by rimonabant, may help to regulate overactivation of the endocannabinoid system. The end result is reduced body weight and adiposity and improved glucose and lipid metabolism, as demonstrated in animals with diet-induced obesity and associated metabolic abnormalities.

The effects of CB1 blockade on CV Risk: What the clinical trials tell us

CB1 receptor blockade provides a novel approach to the management of multiple cardiometabolic risk factors by addressing abdominal obesity and directly improving lipid and glucose metabolism and insulin resistance. The discovery of rimonabant,[32] the first specific CB1 receptor blocker, made it possible to understand the many facets of the endocannabinoid system and set the stage for the development of novel pharmacotherapeutic approaches to treat obesity.

Figure 3: The RIO study programme

Study	Population	N=6627	Design
RIO-North America	Obese or overweight with/without comorbidities (excluding diabetes)	3040	1+1 year Re-randomized
RIO-Europe	Obese or overweight with/without comorbidities (excluding diabetes)	1507	2 years
RIO-Lipids	Obese or overweight with untreated dyslipidemia (excluding diabetes)	1036	1 year
RIO-Diabetes	Obese or overweight with type 2 diabetes	1045	1 year

The rimonabant in obesity (RIO) study programme

A large phase III trial, the RIO programme, was initiated in August 2001 and enrolled >6,600 subjects to investigate the impact of rimonabant on cardiometabolic risk factors in an overweight/obese population (Figure 3).

- RIO-North America[33] and RIO-Europe[34] were 2-year studies that enrolled patients with a BMI ≥ 30 kg/m^2 or a BMI >27 kg/m^2 in the presence of comorbid factors, ie, treated or untreated hypertension, and/or treated or untreated dyslipidemia.
- RIO-Lipids was a 1-year study designed to specifically evaluate rimonabant in patients with untreated dyslipidemia; this cardiometabolic risk factor was, therefore, included in the inclusion criteria.[35] In addition, RIO-Lipids included measurement of additional parameters related to atherosclerotic risk, including adiponectin levels, LDL particle size and density, and C-reactive protein (CRP) levels.
- RIO-Diabetes was a 1-year study conducted in T2DM patients treated with metformin or sulfonylurea.

Design

The design of RIO-North America differed from the other RIO trials in that a second randomization was included after year 1, with patients subsequently randomly allocated to continue their original study therapy or switch to placebo. In this way, this trial evaluated the effects of rimonabant on the changes in cardiometabolic factors at 1 year, the maintenance of these effects in the second year, and the impact of discontinuing the drug.

All 4 trials in the RIO program utilized a multicentre, randomized, double-blind, placebo-controlled, parallel group, fixed-dose design. A single-blind placebo run-in of 4 weeks, accompanied by a mild hypocaloric diet (600 kcal/day energy deficit diet), preceded randomization. The diet intervention was maintained throughout the randomized phases of the studies. Patients were stratified before randomization based on weight loss during the run-in period (≤2 kg or >2 kg).

In RIO-Europe and RIO-North America, patients were randomized to receive placebo, rimonabant 5 mg, or rimonabant 20 mg in 1:2:2 ratios. Patients in RIO-Lipids and RIO-Diabetes

were also stratified before randomization according to their triglyceride levels and antidiabetic treatment, respectively. Randomization to the 3 treatment groups in these trials was carried out in a 1:1:1 ratio. As mentioned earlier, RIO-North America included a second randomization of rimonabant-treated patients to continue rimonabant or switch to placebo. Efficacy endpoints included weight change (primary endpoint for RIO-North America and RIO-Europe), waist circumference (a marker of intra-abdominal adiposity), effects on lipids (HDL-C, triglycerides), glycemic parameters, and prevalence of metabolic syndrome as defined by NCEP/ATP III criteria.

Patient characteristics

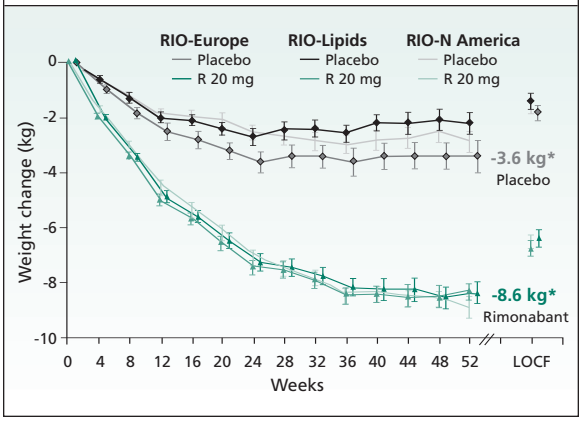
Baseline characteristics were similar across the treatment groups in all trials. The majority were female in RIO-North America and RIO-Europe, while men and women were equally represented in RIO-Lipids and RIO-Diabetes. Nearly 70% of patients were North American, 30% were European, and >80% were Caucasian. Close to 90% of patients in the 4 studies had abdominal obesity, defined as a waist circumference >102 cm (40") for men and >88 cm (35") in women, ie, the diagnostic criterion for abdominal obesity as defined by the NCEP/ATP III. In addition, in RIO-Diabetes, patients had an average HbA_{1c} of 7.5% at screening and the average time since diabetes diagnosis was 5 years. The mean age in the 4 studies was 45 years in RIO-North America and RIO-Europe, 48 years in RIO-Lipids, and 56 years in RIO-Diabetes. The number of patients completing 12 months of the study varied between 53%-66%.

The presence of multiple cardiometabolic risk factors was common at baseline in participants in the RIO programme.[33] Over half of the populations of RIO-North America, RIO-Europe, and RIO-Diabetes had elevated lipids at baseline. One-quarter to two-thirds of the patient populations had hypertension. A high proportion of the overall study population had NCEP/ATP III-defined metabolic syndrome at baseline (nearly 35% in RIO-North America to nearly 80% in the RIO-Diabetes population), indicating the presence of multiple comorbid cardiometabolic risk factors. Patients in RIO-Diabetes had a higher incidence of CV risk factors, which would be expected in a T2DM patient population. About 10%–20% of patients were smokers at baseline.

Results

Results of RIO-North America, RIO-Europe, and RIO-Lipids were recently published.[33-35] Data on changes in body weight of the 3 trials are summarized in Figure 4. Consistent reductions in body weight were seen across the 3 studies. In all cases, body weight declined continuously over the 12-month study period and weight loss in the rimonabant

Figure 4: Effect of rimonabant on body weight

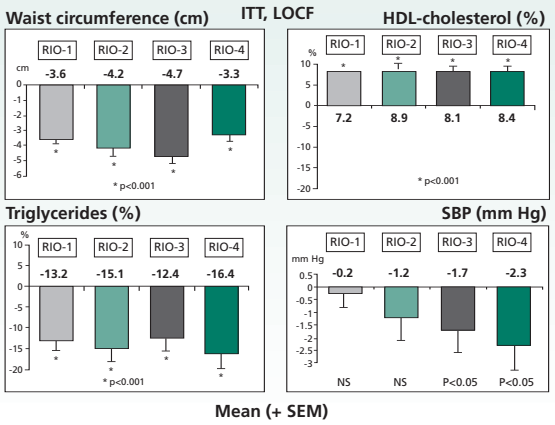


LOCF = last observed carried forward; R = rimonabant

20 mg group was significantly greater than in the placebo group in all 3 trials (p<0.001). Patients completing 12 months of treatment with rimonabant 20 mg benefited from an average weight loss from baseline of approximately 8.5 kg. A similar weight loss (mean change of -6.5 kg from baseline) was observed in the rimonabant 20 mg group in the intention-to-treat (ITT) analysis. Patients already lost, on average, approximately 2 kg body weight during the placebo/diet run-in period. Thus, the average total weight loss between enrolment and trial completion after 1 year of treatment with rimonabant 20 mg exceeded 10 kg. The average weight loss in the rimonabant 20 mg group in the RIO-Diabetes study (results not yet published) was 5.3 kg versus 1.4 kg for placebo (p<0.001, ITT; last observed carried forward, LOCF), whereas, it was 6.1 kg compared to 1.9 kg for placebo (p<0.001). For those who completed the studies, the proportion achieving weight loss of >5% and >10% was significantly greater in the rimonabant 5 mg and 20 mg groups, respectively, in the 3 trials.

The effects of rimonabant on waist circumference in RIO-Lipids, RIO-North America, and RIO-Europe were highly consistent, with an overall mean reduction from baseline of approximately 8.5 cm in patients receiving rimonabant 20 mg for 1 year (p<0.001 versus placebo for all 3 trials). An ITT analysis at 1 year or last prior measurement yielded similar results, with a mean reduction from baseline in waist circumference of approximately 6.5 cm for rimonabant 20 mg (p<0001 vs. placebo for all 3 trials). The average waist circumference reduction in the rimonabant 20 mg group in the RIO-Diabetes study was 5.2 cm (p<0.001 vs. placebo, ITT LOCF analysis). The placebo-subtracted effect was similar to the one observed in other RIO trials. In RIO-North America, after 1 year, the reduction in body weight and waist circumference persisted to 2 years in the group randomized to continue to receive rimonabant as compared to placebo.

Figure 5: Placebo-subtracted changes for metabolic syndrome parameters



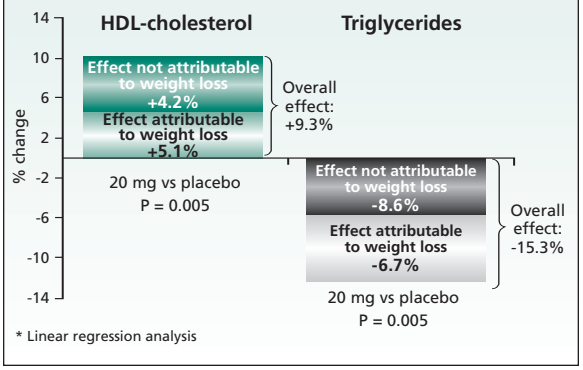
RIO-1 = RIO-North America
RIO-2 = RIO-Europe
RIO-3 = RIO-Lipids
RIO-4 = RIO-Diabetes

Other findings

The prevalence of the individual components that constitute the diagnostic criteria for the metabolic syndrome was also evaluated before and after treatment in a pooled analysis of the 4 trials. A consistent marked improvement in waist circumference, HDL-cholesterol, and triglycerides was seen vs placebo ($p<0.001$ in all cases) in the 4 trials. The placebo-subtracted changes for these parameters are shown in Figure 5. The effects of rimonabant on systolic blood pressure were largest in the RIO-Diabetes and RIO-Lipids trials, where the changes achieved statistical significance relative to placebo ($p<0.05$). The differences in the effect of rimonabant on blood pressure between the trials likely reflect differences in the hypertensive status of the trial populations at baseline. In general, rimonabant exerted larger effects on blood pressure in populations with high pressure before treatment (BP>140/90 mm Hg).

Overall, these data demonstrate that rimonabant consistently improved indices of cardiometabolic risk associated with the metabolic syndrome. A multivariate analysis (analysis of covariance) was used to identify the proportion of the effect of rimonabant 20 mg on HDL-cholesterol or triglycerides that arose via a direct effect of the drug and occurred secondary to the reduction in body weight with rimonabant treatment. Data from RIO-Europe are shown in Figure 6. The adjustment for weight loss revealed that about 50% of the effect of rimonabant 20 mg on these parameters was attributed to the direct effect of the drug. These findings were replicated in the other RIO studies where the improvements in HDL-cholesterol and triglycerides exceeded those expected from the degree of weight loss achieved, suggesting additional beneficial effects through the peripheral action of rimonabant. These data reveal that rimonabant

Figure 6: Improvement in lipids adjusted for weight loss*



* Linear regression analysis

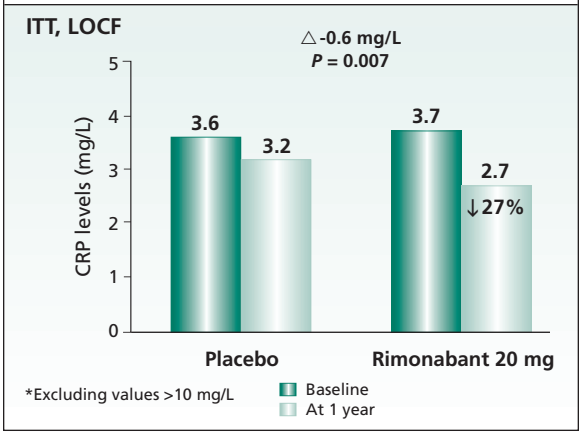
exerts potentially beneficial effects on cardiometabolic risk factors that arise both secondary to weight loss and also as a direct effect not attributable to weight loss.

Among the atherosclerosis risk factors, rimonabant 20 mg:

- significantly decreased the proportion of small LDL particles
- increased the proportion of large LDL particles (RIO-Lipids, ITT LOCF)[35]
- reduced insulin resistance as measured by HOMA (RIO-Europe, completers)[34]
- reduced leptin
- increased adiponectin (RIO-Europe)
- reduced CRP (Figure 7) at one year.[34]

Side effects were mainly mild and transient and most frequently involved the gastrointestinal tract, eg, nausea and diarrhea (related to CB1 blockade in the gut), CNS (dizziness), and psychiatric disorders (anxiety). They generally occurred in the first months of treatment and with the higher 20 mg dose. Most adverse events were generally mild and transient and did not lead to drug discontinuation. This safety profile was consistent across the 4 RIO studies and over the 1- and 2-year follow-up.

Figure 7: Effect of rimonabant on C-reactive protein from RIO-Lipids after 1 year



Summary

Clinical studies to date suggest that, in obese subjects, CB1 receptor blockade with rimonabant results in:

- significant reductions in waist circumference and weight
- significant improvements in the metabolic profile, including increased HDL-C, decreased triglycerides, improved insulin sensitivity; and improved HbA_{1c} in T2DM
- a significant decrease in the percentage of subjects with metabolic syndrome
- improvements in other metabolic and CV risk factors, including increased adiponectin, decreased CRP, and improved small, dense LDL particles profile.

Although rimonabant is not yet approved for use in Canada, specific CB1 blockade offers a new and promising approach to reduce multiple cardiometabolic risk factors in a population at high risk for CV events.

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