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Scientific Update™

The Role of the Endocannabinoid System in Managing Cardiometabolic Risk (Part II): The Cardiovascular Consequences of Abdominal Adiposity and Cannabinoid-1 Receptor Blockade

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Review of a Presentation at a Satellite Symposium and the Clinical Trial Update Session at the World Congress of Cardiology 2006

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By: Gordon Moe, MD

The current global health threat posed by abdominal obesity is largely attributed to an excess of intra-abdominal adipose tissue. Recognized now as an important endocrine organ, intra-abdominal adipose tissue is highly metabolically active and correlates closely with metabolic abnormalities and cardiovascular (CV) disease. In a previous issue of *Cardiology Scientific Update*, the role of the endocannabinoid system in the management of cardiometabolic risk was reviewed. This issue reviews additional data supporting the role of the endocannabinoid system in the management of patients with cardiometabolic risk, type-1 cannabinoid receptor blockade, as well as new data on global CV disease prevalence and the relationship with waist circumference (WC).

The cardiovascular consequences of abdominal adiposity

Despite significant advances in the primary and secondary prevention of CV disease over the past two decades, the increasing prevalence of overweight and obesity will continue to pose a significant CV threat in the future. One of the most alarming features of this epidemic is the marked increase in overweight and obesity amongst young people. Abdominal obesity 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."[1] Traditionally, one tends to regard the CV risk imposed by obesity as being related to dyslipidemia and hypertension; however, obesity by itself – *independent* of these "conventional risk factors" – can induce structural and functional abnormalities in both the heart and vasculature.[2-4] Indeed, in young obese individuals, reduced arterial compliance, increased cardiac mass, and mechanical abnormalities of the left ventricle (LV) occur well before any observed changes in risk parameters or the onset of symptoms.[2,5,6] In the Bogalusa Heart Study, increased subclinical atherosclerosis was observed in young adults with metabolic syndrome and their carotid artery intima-media thickness increased as the number of components of the metabolic syndrome increased.[7] The superimposition of environmental and coronary risk factors (eg, smoking, dyslipidemia, hypertension, and glucose intolerance) on obesity-related CV disease acquired during youth consequently results in progressive and accelerated atherosclerosis and LV dysfunction.[1,2,8]

As reviewed in Part I of this topic, in a previous issue of *Cardiology Scientific Update*, the mechanisms by which obesity induces perturbations in the CV system are complex but, nevertheless, primarily related to visceral fat, which produces a pro-inflammatory and pro-thrombotic CV environment. Individuals with increased visceral, hepatic, epicardial, and/or perivascular fat have elevated levels of C-reactive

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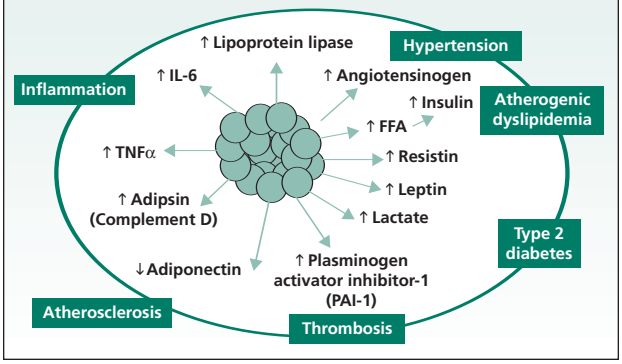
Figure 1: Cardiometabolic effects of bioactive substances secreted by visceral adipocytes



protein (CRP), in addition to abnormalities in other cytokines related to the future risk of coronary events (Figure 1).[9-12] Thus, obesity is not only a risk factor for a first CV event, it may also impact the outcome of patients following a coronary event.[6,13,14] The recently lowered targets for the management of dyslipidemia and hypertension will greatly reduce the risk of CV events; however, substantial risk remains in many patients who are overweight or obese due to the consequences of insulin resistance and/or the metabolic syndrome.[15-17] Clinicians should, therefore, also identify obesity as a target for intervention, after therapeutic lifestyle changes fail.

CV disease prevalence and the relationship with WC in Asians versus Europeans: the IDEA study

Surveys in several populations suggest that there is an epidemic of abdominal obesity if criteria similar to that used to define the metabolic syndrome by the National Cholesterol Educational Program (NCEP/ATP III) expert panel are used,[18,19] and the prevalence of abdominal obesity is increasing.[20] However, data about the prevalence of abdominal obesity are not available for all countries, either in population or clinical settings. Even in countries where prevalence data are available, the subjects studied may not be representative of the background population or the protocols used for measuring WC may differ. Thus, the comparability of studies in this setting is limited and, as a result, universal cut-off criteria for defining abdominal obesity cannot be ascertained.

The International Day for the Evaluation of Abdominal Obesity (IDEA) study was an international, noninterventional, epidemiological, cross-sectional study conducted in 63 countries across 5 continents and incorporating 177,345 subjects. The principal aim was to estimate the prevalence of abdominal obesity – as measured by WC – in an unselected population of consecutive patients consulting a randomly-selected sample of primary care physicians on 2 pre-specified half-days. The study also estimated the association between abdominal obesity, CV disease, and other cardiometabolic

Figure 2: The IDEA Study – Prevalence of abdominal obesity in Europe and Asia

Prevalence of abdominal obesity	NW Europe Men (%)	NW Europe Women (%)	South Asia Men (%)	South Asia Women (%)	East Asia Men (%)	East Asia Women (%)	SE Asia Men (%)	SE Asia Women (%)
Per NCEP ATP III criteria*	31	43	20	55	6	22	6	22
Per IDF criteria†	58	67	58	75	38	51	38	51

* Waist circumference >102 cm for men and >88 cm for women
† Waist circumference >90 cm for men and >80 cm for women in Asia and >94 cm for men, >80 cm for women in Europeans

risk factors. The main results of the IDEA study, presented at the American College of Cardiology (ACC) meeting in March 2006,[21] indicated that WC and body mass index (BMI) were both determinants of CV disease. However, the relationship between WC and the increased prevalence of CV disease was independent of the relationship between BMI and CV disease, regardless of age, gender, or geographic location.

In the current study, presented at the World Congress of Cardiology 2006,[22] 3 Asian regions were studied: South Asia (India and Pakistan), East Asia (China, Korea and Taiwan), and Southeast Asia (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam). Data from a total of 30,783 patients in these countries were compared with those of 29,582 individuals in Northwestern Europe (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, the Netherlands, Norway, Sweden, and Switzerland). The criteria studied included WC, height, body weight, demographic data, the presence or absence of classic CV disease risk factors (ie, smoking, dyslipidemia, hypertension, diabetes), and the presence of existing CV disease (coronary heart disease, stroke, or prior revascularization). The main results are shown in Figure 2. There was a higher prevalence of low WC in both East Asia and Southeast Asia, as compared to South Asia. The profile in South Asia was intermediate, between East/Southeast Asia, and Northwest Europe, in men. However, in women, there was a similar trend towards a higher prevalence of low WC in East and Southeast Asia, but the prevalence of high WC in India/Pakistan (South Asia) was particularly striking. The profile of the India/Pakistan female populations was very similar to the European populations. In Canada, the age-standardized prevalence of obesity and overweight are 36% and 39% respectively, for men, and 36% and 29% respectively, for women.

When considering the age-standardized prevalence of CV disease and risk factors, the prevalence of hypertension and diabetes in both men and women was particularly high in South Asia and Southeast Asia, as compared to the other 2 regions. The most striking result was that WC is an independent predictor of the prevalence of diabetes in men, whereas BMI was not; while in women, WC was an independent predictor of the presence of CV disease, and BMI was not.

The same was true for diabetes, where once again, WC was a predictor, but BMI was not. In summary, WC is a better predictor than BMI of the prevalence of diabetes in both men and women and a better predictor of the prevalence of CV disease in women.

Taking the main results presented at ACC 2006 into account, one can conclude that the prevalence of CV disease and its risk factors increases as WC increases. The prevalence of obesity in South Asia is similar to that observed in Western Europe, and there is a high prevalence of obesity in South Asia as compared to East and Southeast Asia. WC is closely associated with CV disease and even more so with diabetes, independent of BMI, in patients from primary care practices in Asia. Accordingly, there may be a need to redefine the thresholds for defining abdominal obesity in certain populations, since a unique threshold for all Asia populations appears to be inappropriate. More robust, prospective, epidemiological data are likely to be forthcoming to further define the optimal global management strategy.

Endocannabinoid system overactivity: its role in cardiometabolic risk

The endocannabinoids (ECs) are endogenous lipids that bind to, and activate, two specific receptors for the *Cannabis* psychoactive principle, delta^9-tetrahydrocannabinol. The best studied ECs are anandamide (AEA) and 2-arachidonoylglycerol (2-AG).[23,24] Of the 2 known cannabinoid receptors (CB), namely type 1 (CB1) and type 2 (CB2) receptors, CB1 is widely distributed in mammalian tissues, with the highest concentrations in areas in the brain, including the hypothalamic nuclei (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).[25] CB1 receptors are also expressed in peripheral tissues.[23,26] However, CB2 receptors are mainly expressed in immune cells and do not play a role in food intake,[26] although recent data suggest that CB2 receptors are also present in atherosclerotic plaque macrophages and their activation leads to inhibition of plaque accumulation. The presence of specific receptors and their endogenous ligands support the existence of an endogenous cannabinoid system. Endogenous cannabinoids are synthesized and released from neurons following Ca^{2+}-sensitive hydrolysis of lipid precursors and, hence, are not stored in neurons prior to their release, but are released "on demand" immediately after their *de novo* biosynthesis. Following their release, their rapid inactivation is induced by specific enzymes.[27] Recent studies have indicated that ECs are produced in response to stressful stimuli to help re-establish the homeostasis of neurotransmitters and cytokines. CB1 receptor stimulation is time- and space-limited, and terminates once the organism has recovered from its transient "unbalanced" condition. Therefore, the endocannabinoid system serves as a general stress-recovery system. However, some chronic pathological states may induce longer-lasting and possibly less specific activation of CB1 receptors that may then contribute to the manifestations of these cardiometabolic disorders.[28]

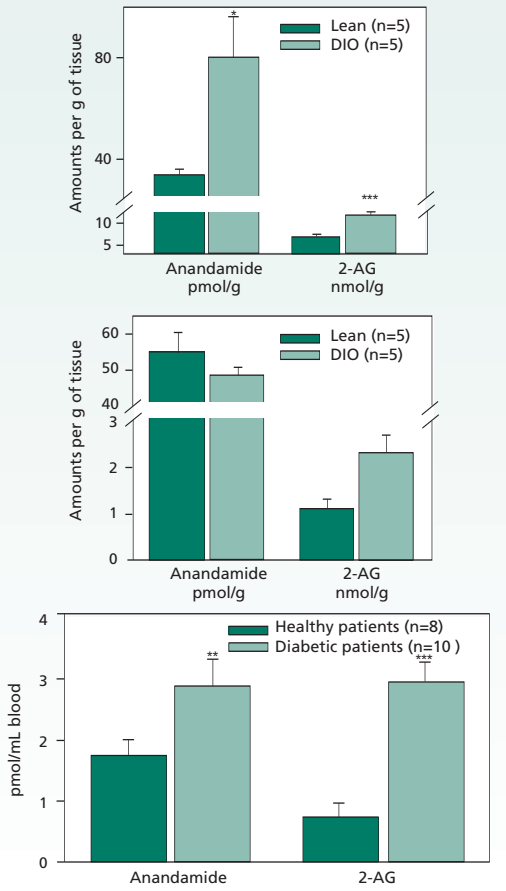
CB1 is present in the brain and in peripheral organs, including adipose tissue and the gastrointestinal (GI) system, major organs in the regulation of energy metabolism.[23,29,30] CB1 receptors appear to be necessary to induce food intake after a short period of food deprivation, to help accumulate fat into adipocytes, to induce lipogenesis in the liver, to prolong nutrient retention in the GI tract, and to reduce energy expenditure.[31] Some of the evidence supporting the role of CB1 receptors in hunger-induced food intake and energy balance was reviewed in Part I in a previous issue of *Cardiology Scientific Update*. Briefly, CB1 receptor activation restores feeding in satiated animals,[32] whereas CB1 receptor blockade decreases the rate of response to food.[33] CB1 blockade induces a transient reduction in food intake and a more lasting reduction in body weight in diet-induced obese mice, with no effect on CB1 receptor knockout mice.[34] Genetically-induced obesity is accompanied by chronic and intense activation of the EC system.[35] CB1 receptor-deficient mice have reduced body weight and activation of metabolic processes that are independent of reduced food intake[36] and resistant to diet-induced obesity.[37] CB1 receptor stimulation increases *de novo* fatty acid synthesis in the liver and in isolated hepatocytes that express CB1 receptors,[37] while stimulating adipocyte differentiation and lipogenesis.[38] In a model of established obesity, CB1 receptor blockade produces a sustained decrease in body weight associated with a reduction in leptin, insulin, glucose, triglyceride, and low-density lipoprotein (LDL) cholesterol.[39] CB1 blockade also increases insulin sensitivity of the skeletal muscle in Lep(ob)/Lep(ob) mice.[40]

Recently published data have shown that EC/CB1 signaling:

- participates in adipocyte differentiation and lipid accumulation and remains activated in mature adipocytes, where it causes depression of adiponectin expression;
- stimulates insulin secretion in pancreatic islet β-cells and, in turn, is stimulated by insulin under conditions mimicking hyperglycemia.[38]

Importantly, an overactive EC system, as evidenced by increased concentrations of AEA and 2-AG, is observed in the epididymal fat and pancreatic β-islet cells of mice with diet-induced obesity (DIO) as compared to those of the lean mice.[37,38] Increased concentrations are also observed in the visceral fat of obese patients and in the blood of obese women and patients with type-2 diabetes when compared to those of corresponding controls (Figure 3).[38,41] These data strongly suggest that a shift towards a permanent peripheral overactivation of CB1 receptors occurs following high-fat diets, as well as in patients with hyperglycemia and visceral obesity.

Figure 3: Overactive endocannabinoid system in experimental obesity and in diabetic patients



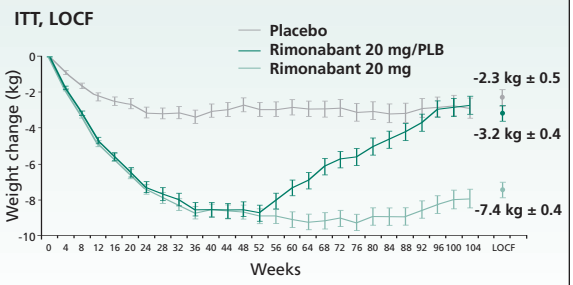
DIO = diet-induced obesity

This may explain the observed weight loss-independent reductions in lipogenesis, hypoadiponectinemia, and hypoinsulinemia following CB1 receptor blockade in obese animals and humans.[37]

The Rimonabant in Obesity (RIO) program

CB1 receptor blockade provides a novel pharmacotherapeutic approach for managing multiple cardiometabolic risk factors. Rimonabant (not yet approved in Canada),[42] is a specific CB1 receptor blocker that has made it possible to understand facets of the EC system. The RIO programme investigated the impact of rimonabant on cardiometabolic risk factors in an overweight/obese population; it comprised 4 trials: RIO-North America,[43] RIO-Europe,[44] RIO-Lipids,[45] and RIO-Diabetes. All utilized a 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 preceded randomization; the diet was maintained.

Figure 4: Prevention of weight regain by chronic therapy



Weight (kg) change from baseline over 2 years (mean ± SEM)

In RIO-Europe and RIO-North America, patients were randomised to placebo, rimonabant 5 mg, or rimonabant 20 mg in a 1:2:2 ratio. Patients in RIO-Lipids and RIO-Diabetes were stratified according to triglyceride levels and antidiabetic treatment, respectively. Randomization to the 3 treatment groups in these trials was carried out in a 1:1:1 ratio. Efficacy endpoints included weight change, WC, effects on lipids, glycemic parameters, and prevalence of metabolic syndrome.

Baseline characteristics were similar in all trials. The majority of patients were female in RIO-North America and RIO-Europe, while men and women were equally represented in RIO-Lipids and RIO-Diabetes. Close to 90% of all subjects had abdominal obesity (ie, WC >102 cm (40") in men and >88 cm (35") in women). RIO-Diabetes patients had an average HbA_{1c} of 7.5% at screening. Multiple cardiometabolic risk factors were common in all participants,[43] over half of the subjects in RIO-North America, RIO-Europe, and RIO-Diabetes had elevated lipids, and many had hypertension. A high proportion of the study population had NCEP/ATPIII-defined metabolic syndrome at baseline, indicating the presence of multiple cardiometabolic risk factors.

Results of RIO-North America, RIO-Europe, RIO-Lipids and RIO-Diabetes have been published,[43-45] and the primary results were reviewed in detail in Part I. The findings indicated that in obese subjects, CB1 receptor blockade with rimonabant results in:

- significant reductions in WC and body weight
- significant improvement in the metabolic profile (eg, increased HDL-C and decreased triglyceride levels, improved insulin sensitivity, and improved HbA_{1c} in type-2 diabetes)
- significant decreases in the percent of subjects with metabolic syndrome
- improvements in other metabolic and CV risk factors (increased adiponectin, decreased CRP, and improved small dense LDL particles).

Figure 5: RIO-Lipids: change in proportion of small and large LDL particles

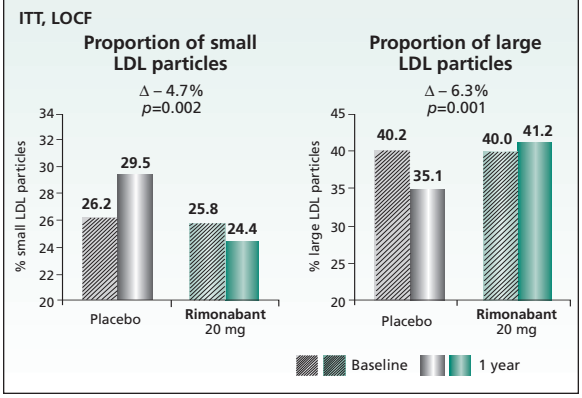
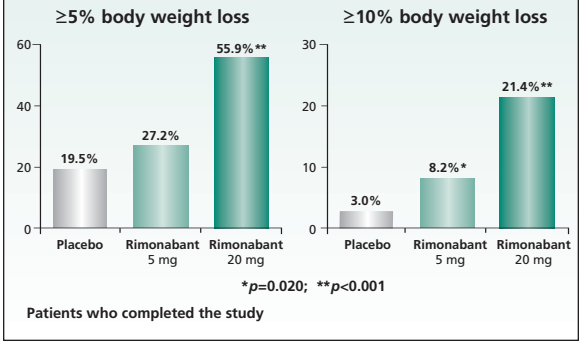


Figure 6: RIO-Diabetes: patients achieving pre-specified weight loss targets



In addition to the above findings, body weight loss and loss of abdominal fat achieved at 1-year were maintained over 2 years in the RIO-North America trial. In the intention-to-treat (ITT) analyses, changes in body weight during the period of re-randomization (52–104 weeks) paralleled changes in WC. As with WC, body weight in patients re-randomized to placebo did not reach the baseline value at the time of randomization (Figure 4). Further benefits from rimonabant (20 mg/day) were seen in the RIO-Lipids study, including an increase in LDL peak particle size and a decrease in the proportion of atherogenic small LDL particles (Figure 5).

These findings are of interest because the size, density of LDL particles, and the proportion of small, dense LDL have been known to provide additional information regarding the overall atherogenicity of the lipid profile,[46,47] and alterations in LDL particles are frequently observed in populations considered at "high cardiometabolic risk," such as those with abdominal obesity, insulin resistance, or type 2 diabetes.[48,49] In the RIO-Diabetes study,[50] a reduction in body weight occurred in all groups, consistent with the mild hypocaloric diet intervention received by all patients. Additional reductions in weight occurred in the rimonabant 20 mg group, relative to placebo, and these beneficial effects were maintained over the 52-week study period (Figure 6). More than half of the rimonabant 20 mg group lost more than 5% of their initial body weight and about one-fifth of this group lost more than 10% of their initial body weight ($p<0.001$ vs. placebo in each case). In addition, treatment with rimonabant 20 mg reduced HbA_{1c} by 0.7% vs. placebo ($p<0.001$) over the 52-week treatment period in the ITT analysis.

Similar effects were obtained when patients completing the study were analyzed. The changes in body weight may represent substantial treatment effects, given that patients with type 2 diabetes usually find it considerably more difficult to achieve sustained weight loss than their nondiabetic counterparts.[51] Indeed, the benefits of rimonabant on both body weight and HbA_{1C} were observed, regardless of concurrent antidiabetic therapies such as metformin or the sulfonylureas, agents that are sometimes associated with weight gain,[52,53] which might have counteracted the effect of rimonabant on overall improvement in cardiometabolic risk. Patients on background therapy with metformin lost 4.3 kg, while those on sulfonylureas lost 3.1 kg (mean for all was 3.9 kg). However, HbA_{1C} levels improved for 0.7% in both subgroups of patients treated with metformin and sulfonylureas.

Clinical implications

Results from the RIO program have thus far demonstrated that selective central and peripheral CB1 receptor blockade using rimonabant improves multiple cardiometabolic risk factors by countering the adverse effects of an overactive endocannabinoid system. CB1 receptor blockade could, therefore, be useful for the management of clustering CV disease risk factors in high-risk, abdominally-obese patients with/without type 2 diabetes, through its impact on both abdominal adiposity and related cardiometabolic risk factors.

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