Obesity

Rimonabant: A golden bullet for 'diabesity'?

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Although a pivotal complication of obesity is the development of type 2 diabetes and the benefits of a modest 5–10 % weight loss are, at last, increasingly understood, there is a pressing need for more effective treatments that will promote greater weight loss in a higher proportion of people with type 2 diabetes – the vast majority of whom are overweight or obese. The drug rimonabant is expected to receive a licence for the treatment of obesity in 2006. Uniquely, rimonabant exerts its effects by blocking cannabinoid (CB_1) receptors (the sites at which the drug cannabis acts in the brain) thereby suppressing addictive behaviours such as eating.

In the RIO-Europe study (abstracted on right) a daily dose of 20 mg of rimonabant significantly enhanced weight loss, reduced weight circumference and improved metabolic syndrome risk factors. While there are responders and non-responders to all anti-obesity drugs, many people appear to achieve greater than 10 % weight loss with rimonabant. Rimonabant is well tolerated and reduces appetite, but also preferentially reduces visceral fat and insulin resistance. Rimonabant also possesses another important attribute that will be helpful for many overweight people with diabetes: promoting smoking cessation.

Therefore, this drug holds the promise of promoting weight loss and producing important reductions in cardiovascular disease risk. Studies on people with type 2 diabetes are well advanced and preliminary results are promising. While time will tell, rimonabant looks set to become an important new tool in the treatment of overweight people with type 2 diabetes.

DIABETES

Moderate weight loss reduces FPG

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓

1 It has previously been observed that moderate weight loss in obese people can lead to a clinically significant reduction in fasting plasma glucose (FPG), although the mechanism for this has not been elucidated.

2 Eight obese people with type 2 diabetes were assessed using magnetic resonance spectroscopy (MSR) for intrahepatic and intramyocellular lipid (IHL and IMCL, respectively) content. All eight people were studied before and after weight normalisation using a hypocaloric and very low fat diet.

3 A moderate weight loss of approximately 8 kg (8 % of total initial weight) resulted in a clinically significant reduction of FPG by 2.4 mmol/l (P=0.00037).

4 IHL levels were also significantly reduced, by 81 % (P=0.009) to nearly normal levels. In contrast, there were no relevant changes in IMCL levels with weight reduction.

5 The mechanism by which hepatic steatosis induces liver-specific insulin resistance is still unclear, yet these data indicate that a moderate loss in weight via a calorie controlled and a very low fat diet could lead to the reversal of hepatic steatosis in patients with type 2 diabetes.

6 The authors conclude that, as no effect was observed in peripheral insulin resistance or IMCL content, IHL could be responsible for dysregulated hepatic glucose metabolism in people with type 2 diabetes.

Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI (2005) Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* **54**(3): 603–8

LANCET

CB_1 receptor blocker shown to reduce weight

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 The cannabinoid receptor system was discovered in the early 1980s and has recently been shown to be involved in the regulation of body weight. CB_1 is one of two receptors discovered in this system.

2 The RIO-Europe (Rimonabant In Obesity Europe) trial assessed the effectiveness of rimonabant, a CB_1 blocker, in aiding weight loss for overweight and obese people (classified by a body mass index of >27 kg/m^2 or >30 kg/m^2, respectively).

3 A total of 1507 people were enrolled for this randomised double-blind trial, with the primary endpoint being weight change from baseline after 1 year in this intention-to-treat group. The participants were divided into three groups: placebo; treated with 5 mg rimonabant; and treated with 20 mg rimonabant.

4 Those treated with rimonabant showed significant weight loss (5 mg: mean weight loss of 3.4 kg, P=0.002 vs placebo; 20 mg: mean weight loss of 6.6 kg, P<0.001 vs placebo). Significantly more people treated with 20 mg rimonabant achieved weight loss of 10 % or greater compared with those treated with 5 mg.

5 In conclusion, Van Gaal et al state that 20 mg rimonabant combined with a hypocaloric diet benefits overweight and obese people with clinically significant weight loss over 1 year, and that modulating the endocannabinoid system holds promise for the treatment of obesity.

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, RIO-Europe study group (2005) Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* **365**(9468): 1389–97

ANNALS OF INTERNAL MEDICINE

Lifestyle changes benefit metabolic syndrome

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Little is known about the prevalence of the metabolic syndrome (MS) in people with impaired glucose tolerance. This secondary analysis of the Diabetes Prevention Program Randomized Trial (DPPRT) studied the effect of metformin and intensive lifestyle changes on the prevalence of MS in 3234 participants of the DPPRT.

2 The main inclusion criterion for this study was impaired glucose tolerance (by World Health Organization criteria and fasting blood glucose level ≥5.3 mmol/l).

3 The interventions analysed were 850 mg metformin twice daily or an intensive lifestyle change, designed to sustain a 7 % weight loss, and 150 minutes of exercise per week.

4 At baseline, 53 % of participants had MS and incidence did not vary with age. The younger participants were found to have lower HDL-cholesterol levels than others, while high blood pressure predominated in the older participants.

5 In conclusion, compared with the placebo group, the incidence of MS was reduced by 41 % in the lifestyle group (P<0.001) and by 17 % in the metformin group (P=0.03). Both lifestyle intervention and treatment with metformin can reduce the incidence of MS in high-risk subjects.

Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S, Diabetes Prevention Program Research Group (2005) The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: The Diabetes Prevention Program Randomized Trial. *Annals of Internal Medicine* **142**(8): 611–9

THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM

Sibutramine safe for use in adolescents

Readability	✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Currently, drug therapy is not indicated for the treatment of adolescent obesity and it remains at the investigational stage.

2 This study aimed to evaluate the safety and efficacy of sibutramine for adolescents aged 14–17 years with a body mass index range of 30–45 kg/m^2.

3 Contraindications for inclusion into the study included diabetes, severe hyperlipidaemia, uncontrolled hypertension or other cardiovascular risk factors.

4 The trial lasted 6 months including a 4-week run-in period.

5 All participants (n=60; with no participant being removed due to non-adherence) received placebo, and instruction on a hypocaloric diet and an exercise regimen during the run-in period, after which they were randomised to receive placebo or sibutramine (10 mg/day).

6 During the 6-month trial all participants were seen, whenever possible, by the same doctor every 4 weeks. During these visits routine blood tests were carried out for measurements of lipids, serum glucose and insulin.

7 At 6 months, the sibutramine group had lost an average of 10.3 kg and those in the placebo group had lost an average of 2.4 kg (P<0.001). Both groups had received advice on hypocaloric diets and aerobic exercises prior to the start of the study. No safety issues were raised during the trial.

Godoy-Matos A, Carraro L, Vieira A, Oliveiri J, Guedes EP, Mattos L et al (2005) Treatment of obese adolescents with sibutramine: A randomized, double-blind, controlled study. *The Journal of Endocrinology and Metabolism* **90**(3): 1460–5

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Cardiovascular risk factors lower now than in 1960 in obese adults in USA

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓

1 Five health surveys, ranging from 1960–2000, were analysed for the prevalence of cardiovascular disease (CVD) risk factors; these included high cholesterol levels, high blood pressure, smoking status and diabetes.

2 All risk factors were analysed according to body mass index (BMI) group: <25 kg/m^2, lean; 25–29 kg/m^2, overweight; ≥30 kg/m^2, obese.

3 Between 1960 and 2000 levels of all CVD risk factors, except diabetes, decreased significantly across all BMI groups. There was a non-significant increase of diabetes.

4 Of those surveyed, obese persons had a 21 % lower incidence of high cholesterol levels (39 % vs 18 %), an 18 % lower prevalence of high blood pressure (42 % vs 24 %) and a 12 % lower prevalence of smoking (32 % vs 20 %) in 2000 than in 1960.

5 The prevalence of diabetes saw a non-significant increase of 1–2 % from one of the surveys in 1976–1980 to 1999–2000.

6 In summary, although most risk factors for heart disease have declined over the last 40 years in overweight and obese people, diabetes has not declined. Obesity probably has a disproportionate effect on the risk of diabetes.

Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM et al (2005) Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *Journal of the American Medical Association* **293**(15): 1868–74

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