ROBERT GORDON UNIVERSITY · ABERDEEN

OpenAIR@RGU

The Open Access Institutional Repository at Robert Gordon University

http://openair.rgu.ac.uk

This is an author produced version of a paper published in

British Journal of Diabetes and Vascular Disease (ISSN 1474-6514)

This version may not include final proof corrections and does not include published layout or pagination.

Citation Details

Citation for the version of the work held in 'OpenAIR@RGU':

BROOM, I., 2006. Thinking around abdominal obesity and cardiovascular risk. Available from *OpenAIR@RGU*. [online]. Available from: http://openair.rgu.ac.uk

Citation for the publisher's version:

BROOM, I., 2006. Thinking around abdominal obesity and cardiovascular risk. British Journal of Diabetes and Vascular Disease, 6 (2), pp. 58-61.

Current thinking around abdominal obesity and cardiovascular risk

IAIN BROOM*

*Professor Iain Broom, BSc, MBCHB, FRCP (Glas), FRCPath

Research Professor in Clinical Biochemistry & Metabolic Medicine

Robert Gordon University and NHS Grampian

St Andrew Street

Aberdeen

AB25 1HG

Scotland

Tel   [01224 262895]

Fax   [01224 262828]

E-mail d.skinner@rgu.ac.uk

Abstract

Obesity, particularly abdominal (visceral) obesity, is a burden on healthcare systems worldwide and is a leading cause of cardiovascular disease (CVD), insulin resistance, Type 2 diabetes, dyslipidaemia, metabolic syndrome, inflammation and thrombosis. Excess visceral fat is associated with an increased risk of CVD. A reliable indicator for visceral fat is waist circumference (WC), which is strongly associated with all-cause mortality. One of the central debates is how does obesity cause CVD. A key hypothesis is that pro-inflammatory adipokines released by adipocytes play a causal role in the development of the pathologies that are associated with insulin resistance, Type 2 diabetes and CVD. Although current drug therapies for the treatment of obesity induce weight loss, there is still a need for new therapeutic approaches for the treatment of abdominal obesity. A new class of compounds, cannabinoid receptor 1 (CB_1) blockers, is currently under development for the treatment of obesity and shows promising preliminary clinical results.

Introduction

Obesity is a global public health concern, with over 50 percent of the adult population in England being overweight or obese.[1] In particular, it is the presence of abdominal obesity, due to excess visceral fat (also known as intra-abdominal fat, i.e. fat surrounding the organs within the peritoneal cavity), that is associated with an increased risk of developing cardiovascular disease (CVD).[2-3] However, excess visceral fat is also linked to an increased risk of metabolic syndrome, which is in turn linked to a greater risk of developing Type 2 diabetes[4] and its attendant cardiometabolic consequences.[5]

Patients with metabolic syndrome are defined as individuals who are abdominally obese (i.e. Europid men and women with waist circumference [WC] >94 cm and >80 cm, respectively), and who also present with any two of the following.[6-7]

- Elevated triglyceride levels, i.e. ≥150 mg/dL (≥1.7 mmol/L), or receiving specific treatment for this lipid abnormality

- Reduced HDL-cholesterol, i.e. <40 mg/dL (<1.03 mmol/L) in men or <50 mg/dL (<1.29 mmol/L) in women, or receiving specific treatment for this lipid abnormality

- Raised blood pressure (BP), i.e. systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or receiving treatment for previously diagnosed hypertension

- Raised fasting plasma glucose levels, i.e. ≥100 mg/dL (≥5.6 mmol/L), or previously diagnosed with Type 2 diabetes

However, there are other definitions for metabolic syndrome, and there is ongoing debate with regards to the acceptance of these guidelines worldwide.[8]

In the clinical setting, WC, as opposed to body mass index (BMI), is becoming more commonly used as a surrogate marker of abdominal fat.[9] WC measurements are more practical than BMI and WC has been found to correlate closely with total abdominal fat mass.[10] In addition, WC is now known to be strongly associated with all-cause mortality in middle-aged adults.[11]

Abdominal obesity and cardiovascular risk

An early literature review reported an increased risk for CVD in patients with increased visceral fat, compared with fat that was largely confined to the gluteofemoral area.[2] This contradicted previous suggestions that general fat deposits and visceral fat deposits played equal roles in the development of CVD.[12] In addition, a more recent review has highlighted the importance of excess visceral fat and its association with insulin resistance and other metabolic risk factors for CVD.[9]

Yusuf *et al* have also demonstrated the importance of abdominal obesity as a risk factor for increased CVD.[13] The INTERHEART study was a large, international, standardised, case-controlled study, where 12,461 cases and 14,637 controls were analysed. It was designed to assess the importance of nine easily measurable, protective or risk factors for coronary heart disease, as measured by a first episode of myocardial infarction.[13] These factors were current or former smoking, history of diabetes or hypertension, abdominal obesity, combined psychosocial stressors, irregular consumption of fruits and vegetables, no alcohol intake, avoidance of any regular exercise and raised plasma lipids. All nine risk factors represented a population attributable risk (PAR) of 90.4%, accounting for most of the risk of acute myocardial infarction in the study population. After adjustment for age, sex and geographic region, abnormal lipids had the highest PAR in both men (49.5%) and women (47.1%). Abdominal obesity was found to contribute 19.7% (men) and 18.7% (women) to this risk. Furthermore, abdominal obesity was found to have a similar

odds ratio as hypertension, especially in men, i.e. odds ratios of 2.24 and 2.32, respectively.[13]

One of the central debates is how may obesity cause CVD. Although the overall picture is far from clear, it is gradually becoming evident that dysfunction of the vascular endothelium is associated with obesity, insulin resistance and Type 2 diabetes.[14] It is known that insulin sensitivity is regulated in part by adipokines, secreted from adipose tissue, levels of which are adversely altered in obese individuals.[14] The possibility of a direct link between endothelial dysfunction and insulin resistance, mediated via adipokine action on the vascular endothelium, is currently a topic of significant research.[14]

Abdominal obesity, adipokines and the risk of CVD

Adipose tissue is an important active endocrine and paracrine organ. It is divided into several distinct anatomic depots, the two main ones being subcutaneous fat and visceral fat. Excess visceral fat has been hypothesised to be more harmful than subcutaneous fat because of its association with an increased risk of CVD.[3] It is well known that adipose tissue releases cytokines and other bioactive mediators, collectively known as adipokines (adipocytokines), which in turn influence bodyweight homeostasis.[15] Under normal physiological conditions, the expression and secretion of adipokines are intricately regulated.[16] However, in individuals with abdominal obesity, certain adipokines are up-regulated, whilst others are down-regulated (table 1).[17-18]

Table 1: The regulation of the expression of adipokines in abdominal obesity

Adipokine	Regulation in abdominal obesity
TNF-α	↑
IL-6	↑
Adiponectin	↓
Leptin	↑
Resistin	↓↑ (i.e. controversial findings)

TNF-α: tumour necrosis factor alpha

IL-6: interleukin-6

The role of these adipokines in the pathogenesis of obesity, in particular abdominal obesity and insulin resistance, has been reviewed extensively.[16-18] A recent review postulates that pro-inflammatory adipokines play a causal role in the development of insulin resistance and associated pathologies of obesity (i.e. metabolic syndrome).[19] Obesity has also been linked with chronic low-grade inflammation,[14,19] as mediated by interleukin-6 (IL-6) and tumour necrosis alpha (TNF-α). In addition, there is an increasing body of evidence to suggest that the pro-inflammatory adipokines (i.e. TNF-α and IL-6) may also contribute to the atherosclerotic process.[20] Furthermore, IL-6 has been suggested to increase the secretion of hepatic triglycerides, causing hypertriglyceridaemia associated with abdominal obesity, which in turn may lead to insulin resistance.[17]

Given this body of evidence, it has become clear that the management of abdominal obesity is an important target for directly reducing the cardiovascular and metabolic (cardiometabolic) risk profile of obese individuals.

Current management of abdominal obesity

Interventions such as exercise and diet have been shown to reduce total body and abdominal fat, and produce favourable changes in risk factors for CVD and diabetes.[21-22] However, lifestyle and dietary changes alone may not be sufficient to achieve significant weight loss, especially in the abdominal area.[23-25] Therefore, several UK guidelines recommend pharmacological intervention in conjunction with a low-fat diet and exercise as second-line treatment for abdominal obesity.[26-28]

The most extensively studied and widely used pharmacological agents for obesity are the pancreatic lipase inhibitor, orlistat, and the centrally acting agent, sibutramine.[29-30] The European Multicentre Orlistat Study adopted a double-blind, randomised, placebo-controlled and parallel-group design to examine the efficacy and tolerability of orlistat in promoting weight loss and preventing weight regain.[31] A total of 743 obese patients were recruited, of whom 688 patients completed the run-in and were randomised to receive double-blind treatment with orlistat or placebo, in addition to a hypocaloric diet in the first year. In the second year, completers were reassigned orlistat or placebo with a weight maintenance (eucaloric) diet. At 2 years, orlistat produced significant improvement in weight reduction compared with placebo $(p<0.001)$.[31] In addition, improvements were found for total and LDL-cholesterol and glucose and insulin concentrations in the orlistat group, compared with the placebo group. However, no beneficial effects on HDL-cholesterol levels were shown.[31]

Unlike orlistat, which exerts its anti-obesity effects by acting on the gastrointestinal system, promoting malabsorption of triglycerides,[29] sibutramine induces premature satiety centrally and enhances the effects of diet and exercise on weight loss.[32] The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) trial was a randomised, double-blind trial, conducted at eight European centres; it recruited 605 obese patients on individualised 600 kcal/day deficit programmes, to assess the

usefulness of sibutramine in maintaining weight loss over 2 years.[33] This study found that 43% of sibutramine-treated patients who completed the trial maintained 80% of more of their original weight loss compared with 16% of patients receiving placebo (p<0.001).[33]

However, in a recent meta-analysis, Li *et al* have suggested that sibutramine and orlistat promote only modest weight loss when given with dietary recommendations, and highlight the relative lack of long-term (i.e. longer than 12 months) data on any of the currently available therapies.[30] Pagotto and Pasquali also advocate the need for new therapeutic approaches for the treatment of abdominal obesity.[25]

A new therapeutic target for the potential treatment of abdominal obesity

The endocannabinoid system (ECS) comprises the cannabinoid receptors, CB_1 and CB_2, and their endogenous ligands (e.g. anandamide). The ECS has been reported to play a key role in the regulation of energy balance and in glucose and lipid metabolism.[34] Overactivation of the ECS, both centrally and peripherally, may result in elevated levels of endogenous ligands[35] and up-regulation of adipocyte CB_1 receptors.[36] This in turn may disrupt the feedback mechanism inherent in steady state homeostasis, impacting on food intake, lipid parameters, fat accumulation and lipid and glucose metabolism.[34]

Early studies suggesting a role for CB_1-receptor blockade in the reduction of food intake fuelled the search for selective CB_1-receptor antagonists. SR141716A (also known as rimonabant) is the first selective and most widely researched orally active antagonist to be developed.[37] Studies in diet-induced obese mice and in CB_1 knock-out mice confirmed the hypophagic action of rimonabant and the role of the ECS as an essential regulator of energy homeostasis.[39-40]

Mice with established diet-induced obesity, treated chronically with rimonabant, exhibited a marked and sustained decrease in bodyweight (p<0.001).[41] In addition, serum leptin, insulin and glucose levels were all significantly reduced with rimonabant treatment (p<0.001).[41]

Similar findings have been reported in human studies. Data from a 1-year, phase III clinical trial with rimonabant (Rimonabant in Obesity [RIO] Europe) showed promising potential in the treatment of abdominal obesity.[42] This large, multicentre, multinational, randomised, placebo-controlled trial was undertaken to assess the efficacy and safety of rimonabant versus placebo in reducing bodyweight and WC, and in improving cardiovascular risk factors in overweight and obese patients who were put on low-fat diets.[42] A total of 1507 patients with BMI $\geq$30 kg/m^2, or BMI $\geq$27 kg/m^2 with treated or untreated dyslipidaemia or hypertension or both, were recruited.

The higher dose of rimonabant used in the study (i.e. 20 mg) induced significant weight loss and reduction in WC (p<0.001).[42] This study also demonstrated significant improvements in several other known cardiovascular and metabolic risk factors, including HDL-cholesterol levels, triglyceride concentrations and HOMA-IR (homeostasis model assessment for insulin resistance; all p$\leq$0.005).[42]

A number of other phase III clinical trials with rimonabant are currently underway including those that extend over 2 years. Preliminary 2-year data have been presented at the American Heart Association Annual Scientific Sessions 2004[43] and at the American College of Cardiology Annual Scientific Session earlier this year. Data from these studies show that the weight loss benefit observed in the rimonabant-treated patients was maintained over a period of 2 years.[43]

Summary

In summary, abdominal obesity, particularly that due to excess visceral fat, is a major and growing public health concern, and is associated with an increased risk of developing insulin resistance, Type 2 diabetes, dyslipidaemia, metabolic syndrome, inflammation and thrombosis. Waist circumference is a good measure of abdominal obesity and may be used in clinical settings to identify those patients most at risk of CVD. Once identified, patients considered to be 'at risk' can be managed with lifestyle modifications and, if necessary, pharmacotherapy. A new class of drugs, the CB_1 blockers, shows promising preliminary results, producing significant weight loss and improvements in various metabolic parameters. Therefore, if abdominal obesity is targeted, this may lead to a reduced risk of developing cardiometabolic disease.

Key messages

- Abdominal obesity, due to excess visceral fat, is associated with an increased risk of cardiovascular disease
- Abdominal obesity, measured by waist circumference, is a reliable predictor of cardiovascular and metabolic (cardiometabolic) risk
- Waist circumference measurement should be included as standard whenever cardiometabolic risk factors are assessed
- A new class of drugs, known as CB_1 blockers, shows potential in the treatment of abdominal obesity

References

1. York DA, Rossner S, Caterson I *et al.* Obesity, a worldwide epidemic related to heart disease and stroke group I: worldwide demographics of obesity. *Circulation* 2004;**110**:e463–70.

2. Emery EM, Schmid TL, Kahn HS *et al.* A review of the association between abdominal fat distribution, health outcome measures, and modifiable risk factors. *Am J Health Promot* 1993;**7**(5):342–53.

3. Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001;**322**(7288):716–20.

4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;**365**(9468):1415–28.

5. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;**365**(9467):1333–46.

6. International Diabetes Federation. The IDF worldwide definition of the metabolic syndrome. Launched 14 April 2005. Accessible via http://www.idf.org/home/index.cfm?unode=32EF2063-B966-468F-928C-A5682A4E3910 (accessed Sept 2005).

7. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;**366**(9491):1059–62.

8. Reaven GM. The metabolic syndrome: requiescat in pace. *Clin Chem* 2005; **51**(6):931–8.

9. Klein S. The case of visceral fat: argument for the defense. *J Clin Invest* 2004;**113**(11):1530–32.

10. Pouliot MC, Despres JP, Lemieux S *et al.* Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of

abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;**73**(7):460–8.

11. Bigaard J, Frederiksen K, Tjonneland A *et al.* Waist and hip circumferences and all-cause mortality: usefulness of the waist-to-hip ratio? *Int J Obes Relat Metab Disord* 2004;**28**(6):741–7.

12. Kannel WB, Cupples LA, Ramaswami R *et al.* Regional obesity and risk of cardiovascular disease: the Framingham Study. *J Clin Epidemiol* 1991;**44**(2):183–90.

13. Yusuf S, Hawken S, Ounpuu S *et al.* INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**(9438):937–52.

14. Ritchie SA, Ewart MA, Perry CG *et al.* The role of insulin and the adipocytokines in regulation of vascular endothelial function. *Clin Sci (Lond)* 2004;**107**(6):519–32.

15. Lau DC, Dhillon B, Yan H *et al.* Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol* 2005;**288**(5):H2031–41.

16. Arner P. Insulin resistance in Type 2 diabetes – role of the adipokines. *Curr Mol Med* 2005;**5**(3):333–9.

17. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 2000;**21**(6):697–738.

18. Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. *Diabetologia* 2003;**46**(12):1594–1603.

19. Trayhurn P. The biology of obesity. *Proc Nutr Soc* 2005;**64**(1):31–8.

20. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *NEJM* 2005;**352**(16):1685–95.

21. Stewart KJ, Bacher AC, Turner K *et al*. Exercise and risk factors associated with metabolic syndrome in older adults. *Am J Prev Med* 2005;**28**(1):9–18.

22. McAuley KA, Hopkins CM, Smith KJ *et al*. Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia* 2005;**48**(1):8–16.

23. Pirozzo S, Summerbell C, Cameron C *et al*. Advice on low-fat diets for obesity. *Cochrane Database Syst Rev* 2002;**2**:CD003640.

24. Norris SL, Zhang X, Avenell A *et al*. Long-term non-pharmacologic weight loss interventions for adults with Type 2 diabetes. *Cochrane Database Syst Rev* 2005;**2**:CD004095.

25. Pagotto U, Pasquali R. Fighting obesity and associated risk factors by antagonising cannabinoid Type 1 receptors. *Lancet* 2005;**365**(9468):1363–4.

26. National Obesity Forum (NOF) Guidelines: Appendix 2 – Accessible via www.nationalobesityforum.org.uk (accessed Sept 2005).

27. NICE Technology Appraisal Guidance – No. 22: Guidance on the use of orlistat for the treatment of obesity in adults. March 2001.

28. NICE Technology Appraisal Guidance – No. 31: Guidance on the use of sibutramine for the treatment of obesity in adults. October 2001.

29. Halpern A, Mancini MC. Treatment of obesity: an update on anti-obesity medications. *Obes Rev* 2003;**4**(1):25–42.

30. Li Z, Maglione M, Tu W *et al*. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005;**142**(7):532–46.

31. Sjostrom L, Rissanen A, Andersen T *et al*. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;**352**(9123):167–72.

32. Day C, Bailey DJ. Sibutramine update. *Br J Diabet Vasc Dis* 2002;**2**:392–7.

33. James WP, Astrup A, Finer N *et al*. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;**356**(9248):2119–25.

34. Finer N, Pagotto U. The endocannabinoid system: a new therapeutic target for cardiovascular risk factor management. *Br J Diabet Vasc Dis* 2005;**5**:121–4.

35. Di Marzo V, Goparaju SK, Wang L *et al*. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 2001;**410**(6830):822–5.

36. Bensaid M, Gary-Bobo M, Esclangon A *et al*. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* 2003;**63**(4):908–14.

37. Rinaldi-Carmona M, Barth F, Heaulme M *et al*. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett* 1994;**350**(2–3):240–4.

38. Ravinet Trillou C, Arnone M, Delgorge C *et al*. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol* 2003;**284**(2):R345–53.

39. 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**(3):423–31.

40. Ravinet Trillou C, Delgorge C, Menet C *et al*. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obes Relat Metab Disord* 2004;**28**(4):640–8.

41. Poirier B, Bidouard JP, Cadrouvele C *et al*. The anti-obesity effect of rimonabant is associated with an improved serum lipid profile. *Diabetes Obes Metab* 2005;**7**(1):65–72.

42. Van Gaal LF, Rissanen AM, Scheen AJ *et al*. RIO-Europe Study Group. 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* 2005;**365**(9468):1389–97.

43. Pi-Sunyer FX. Effect of rimonabant on weight reduction and weight maintenance: RIO North America (RIO-NA) trial. *Circulation* 2005;**111**:1727.