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MANAGEMENT OF OBESITY & METABOLIC SYNDROME

- **Obesity is a major preventable cause of morbidity and mortality worldwide; lifestyle intervention is the cornerstone of management**
- **Drug treatment should be considered where lifestyle intervention has failed and for those with BMI ≥30kg/m² or ≥27kg/m² with a co-morbidity**
- **Drug treatment may be of limited efficacy (2-5 kg loss) and may have adverse effects in individual patients**
- **Metabolic syndrome may also require therapy to reduce cardiovascular risk**

INTRODUCTION

Obesity is defined as a disease where excess body fat has accumulated to an extent that health is adversely affected.[1,2] It is an escalating problem: the World Health Organisation (WHO) has estimated there were 300 million obese adults globally in 2000, increasing to an estimated 400 million in 2005 and to 700 million in 2015.[2] It is thought that currently the number of overweight individuals in the world equals the number of underweight people.[3] Once considered a problem only in high-income countries, the number of overweight and obese people is increasing in low- and middle-income countries, particularly in urban settings.[2] It is a major public health concern for Ireland, where in 2001 it was estimated that 39% of adults were overweight and 18% were obese.[4]

Childhood obesity – There is increasing concern about the rise in childhood obesity; figures from Ireland in 2005 estimated that there were >300,000 overweight and obese children.[4] On a global level the WHO estimated 20 million children < 5 yrs were overweight in 2005.[2] In the US excess weight has been associated with a dramatic rise in type 2 diabetes mellitus (DM) amongst children.[5]

This bulletin will review the management of obesity and also review one of the conditions associated with obesity – the metabolic syndrome. This bulletin is an update on a previous bulletin on obesity [NMIC 2002 Vol 8, No. 2].

CAUSES OF OBESITY

While genetic factors have a clear role in obesity,[6] evidence suggests that the marked rise is due to behavioural and environmental changes,[2,7-9] as the increase is occurring in a relatively constant gene pool.[7] Dietary habits have changed with increased intake of energy-dense foods that are high in fat and sugars.[2,6,8,10] In addition, physical activity has decreased due to the sedentary nature of many forms of work, changing modes of transportation and urbanisation.[2]

Effects on health - Obesity is a risk factor for major causes of death, including cardiovascular disease (CVD), DM, cancer, and it is also associated with diminished life expectancy.[5,6,11-13] The decrease in life expectancy associated with obesity is similar to that seen with smoking [1,12] and the relationship of obesity to DM and heart disease has been compared to that of smoking and lung cancer.[14] The risk of developing hypertension (HTN) is 5 times higher in obese than non-obese people. Osteoarthritis, gall bladder disease, sleep apnoea, respiratory impairment and diminished mobility are also associated with this condition.[5,11]

In addition to health, obesity has an economic impact, and is estimated to be responsible for 2-8% of health costs in Europe.[15] The Irish National Task Force on Obesity, estimated in 2005, that the 2,000 premature deaths attributed to obesity annually, cost an estimated 4 billion. [4]

MANAGEMENT OF OBESITY

Obesity should be managed like any other chronic disease.[16] The prevention of obesity requires a population health approach for adults and children. Even if preventive measures against obesity were successful immediately there would still be an epidemic of diabetes and its complications in 10-20 years. The treatment of obesity must therefore be prioritised alongside prevention.[1]

Many obese people have poor motivation as well as a lack of awareness of the relationship between obesity and disease.[6,16] This results in high relapse rates and hence management should be tailored to the individual.[9] Assessment of success must take account of the age of the patient, the baseline weight, the presence of indicators of associated risk or complications, and previous attempts at weight control.[9] Evidence shows that a weight loss of 5% of the initial body weight will result in some improvement in health, and a 10% weight loss is of major benefit, resulting in clinically useful changes. Such changes include reduction in blood pressure, reduction in plasma total cholesterol and triglycerides, an increase in HDL cholesterol and a significant improvement in diabetic control.[5,9,11,17,18]

Assessment - Identifying people who are overweight and obese is essential for directing future intervention. BMI and waist circumference are well-validated measurements.[19] The WHO defines overweight as a BMI ≥25 (kg/m²) and obesity as ≥30 (kg/m²).[2] BMI may not be appropriate for all ethnic groups and individuals as it does not distinguish fat from other sources of weight, [2] therefore waist circumference (WC) is considered a better assessor of metabolic risk.[1,19] WC should be measured midway between the lower rib margin and iliac crest, with a horizontal tape at the end of gentle expiration.[19] There is an increased risk of metabolic complications for caucasian men with WC ≥102cm, and women ≥88cm. A measurement of waist to hip ratio (WHR) is another method of identifying patients with abdominal fat accumulation.[7] Table 1 shows the classification of overweight and obesity by BMI and WC.

Patients should be assessed for conditions associated with obesity including CVD, type 2 DM, sleep apnoea, osteoarthritis and gallstones; and also assessed for characteristics of the metabolic syndrome, which is defined later. [9]

Table 1: Classification of overweight and obesity in caucasian adults according to BMI, waist circumference and associated disease risk for type 2 DM, HTN and CVD [19]

Classification	BMI (kg/m²)	Risk relative to normal weight and waist circumference	
		Men <102cm (40in) Women <88cm (35in)	Men ≥102cm (40in) Women ≥88cm (35in)
Underweight	<18.5	Not increased	Not increased
Normal range	18.5-24.9	Not increased	Increased
Overweight	25.0-29.9	Increased	High
Obese class I	30.0-34.9	High	Very high
Obese class II	35.0-39.9	Very high	Extremely high
Obese class III	≥40.0	Extremely high	Extremely high

NON-PHARMACOLOGICAL MANAGEMENT

The primary intervention for the management of obesity and the overweight patient is a combination of dietary restriction and lifestyle change lasting at least three months.[9] Studies show that psychological intervention combined with dietary and exercise strategies enhance weight reduction by up to 5kg,[20,21] and prevent the development of type 2 DM among high-risk individuals.[5]

Dietary management – control of diet is the cornerstone of the management of overweight and obese patients [9] and can be more effective than exercise alone in facilitating weight loss.[22] Long-term changes in food choices, eating behaviour and lifestyle are more beneficial than a temporary restriction of specific foods.[9] A recent Cochrane review concluded that overweight/obese people on low glycaemic index diets (e.g. lentils, brown rice) lose weight more than those (i) on high glycaemic index diets (e.g. white rice, baked potato) or (ii) conventional energy restricted weight loss diets.[23] Table 2 gives principles of a successful diet.

Table 2: Key principles for a successful diet [5,16]

- Aim to have a diet with a deficit of 500-600 kcal/day below the current requirements
- Follow a structured meal plan that starts with breakfast
- Include a variety of foods from the main food groups and limit portion size
- Reduce the proportion of fat and partially replace saturated fat with monounsaturated fat
- Increase intake of fruit and vegetables to at least five portions a day
- Ensure that meals include wholegrain and high fibre foods and foods with a low glycaemic index

Physical activity – It is recommended that overweight people should exercise 30-60 minutes a day.[25,26] A Cochrane review supports the use of exercise as a weight loss intervention particularly when combined with dietary change.[22] The combination also has beneficial effects on cardiovascular risk factors, insulin resistance and depression.[9,16] Although some people join gyms other suggestions to increase physical activity include: taking the stairs whenever possible; walking on lunch break; trying to park in spaces far away from work or the shops; getting off a stop earlier and walking to your destination when using public transportation.[5]

PHARMACOTHERAPY FOR OBESITY

Anti-obesity drug treatment should be considered only as an adjunct to intensive lifestyle intervention, for patients with a BMI of ≥30kg/m² or a BMI 27-29 kg/m² with a major obesity related co-morbidity (e.g. HTN, DM, obstructive sleep apnoea).[17] Treatment should be discontinued if clinically significant weight loss (5-10% initial body weight) does not occur within the first 3 months.[9,17] There are three drugs currently licensed for the treatment of obesity and the initial choice should be based on the adverse effect profiles, patient's associated cardiovascular risk factors and psychiatric history.[17] Studies of all anti-obesity drugs are notable for their high attrition rates and lack of long-term data on major obesity-related morbidity and mortality.[17,26]

Orlistat is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by about 30%.[17,27] The dose is typically 120mg three times daily with meals.[28] It has a low bioavailability of <1% and most of the drug is excreted in the faeces unchanged.[17]

Efficacy – attrition rates average 33%.[17] Studies have shown that orlistat reduces weight by an average of 3.2 kg more than placebo.[28] Orlistat is also associated with a small reduction in blood pressure, LDL cholesterol and fasting glucose in diabetic patients.[17]

Adverse effects – the major adverse effect is gastrointestinal including fatty and oily stools, faecal urgency and occasionally faecal incontinence. Patients should be advised to eat a low fat diet, which also helps to reduce the risk of loose stools. Prescription of a daily multivitamin is recommended (taken 2 hours after administration of orlistat or at bedtime[28]) to prevent possible deficiencies of fat-soluble vitamins. Systemic adverse effects are minimal because of the lack of systemic absorption. Orlistat may reduce the absorption of certain drugs e.g. amiodarone and ciclosporin, and potentiate the effect of warfarin.[17] (See Summary of Product Characteristics (SPC) for full prescribing details).

Sibutramine is a centrally acting monoamine-reuptake inhibitor, which mainly acts by increasing satiety.[9,17] It undergoes extensive first pass metabolism by cytochrome P450 3A4 to active primary and secondary amine metabolites, which are more potent than the parent compound. Most of the drug and its active metabolites are renally excreted.[17] The recommended dose is 10-15mg for up to one year and it should only be given as adjunctive therapy under the care of a physician experienced in the treatment of obesity.[29]

Efficacy – attrition rates average 48%.[17] Studies have shown that sibutramine reduces weight by 4.3 kg more than with placebo.[17,26] Long-term studies have shown little effect on LDL cholesterol and glycaemic control.[17] Data on the use of sibutramine over one year is limited.[29]

Adverse effects – common side effects include insomnia, nausea, dry mouth and constipation. Concomitant treatment with monoamine-oxidase inhibitors or serotonergic drugs is not recommended because of the potential risk of serotonin syndrome.[17] Exercise caution with other drugs metabolised by CYP3A4.[29] Sibutramine has been associated with small increases in blood pressure and it is not recommended in patients with uncontrolled hypertension, pre-existing CVD or tachycardia.[22,30]

Blood pressure and pulse rate should be monitored in all patients on sibutramine. Other contraindications include: psychiatric illness, hyperthyroidism, severe hepatic and renal disease. (See SPC for full prescribing details.)

Rimonabant inhibits cannabinoid (CB1) receptors, which are located in the brain, gastrointestinal tract, adipose tissues, skeletal muscle and the liver.[29] It is thought to improve energy balance by reducing appetite, decreasing lipogenesis in adipose tissue and increasing glucose uptake in muscles.[29] The recommended dose is 20mg daily in the morning before breakfast.[31] It is metabolised mainly in the liver and excreted predominantly in the faeces.[29, 22]
Efficacy – attrition rates average 40-50%.[17] Trials have shown that rimonabant significantly reduces weight by up to 4.9 kg more than placebo, reduces WC and improves triglyceride and HDL cholesterol profiles.[17,31,32] The safety and efficacy of rimonabant has not been evaluated beyond 2 years. Clinical trials have suggested that rimonabant significantly reduces the incidence of metabolic syndrome.[17]
Adverse effects – the most frequent side-effects are nausea, dizziness, diarrhoea and insomnia.[17] A recent review by the European Medicines Agency (EMEA) concluded that rimonabant's benefits outweigh the risks, but that patients with ongoing major depression or patients receiving antidepressants should not be prescribed rimonabant.[33] (See SPC for full prescribing details.)

Summary: Table 3 outlines a plan for the medical management of a patient with obesity.

Table 3: Medical management pathway for obesity [9]

Primary intervention

- Diet, physical activity and behavioural management

Failure to achieve 5-10% weight loss

- Consider drug treatment if:
  - BMI ≥30
  - BMI ≥27 with risk factors
  - Fulfils medical criteria

Drug treatment

< 5% weight loss after 12 weeks
- Discontinue drug treatment
- Reinforce advice
- Other treatment options considered

≥5% weight loss after 12 weeks
- Continue drug treatment
- Regular monitoring of weight
- Duration of treatment determined by success and product licence

Cost of 28 day's therapy *

Preparation	Cost ()
Orlistat 120mg tid	65.14
Sibutramine 10mg od	59.17
Sibutramine 15mg od	66.09
Rimonabant 20mg od	79.05

* Costings from HSE-Primary Care Reimbursement Services Database (April 2007)

SURGERY

Surgery is an option used increasingly, for those patients with a BMI >40kg/m^2 and those with a BMI >35kg/m^2 and severe comorbidity[6]. In this group of patients surgery has been shown to improve morbidity and mortality.[34,35] Surgical treatment (including gastric bypass and gastroplasty) may result in greater weight loss than lifestyle intervention and pharmacotherapy, but it also results in complications including wound infections, heartburn and postoperative mortality.[36] Liposuction removes only subcutaneous fat, which carries little metabolic risk and energy intake is unaffected, with body weight subsequently rising.[27]

THE METABOLIC SYNDROME

The metabolic syndrome is a condition that results from a cluster of risk factors occurring in an individual and is associated with an increased risk of developing CVD and type 2 DM.[37-42] These risk factors include dyslipidaemia, disturbed insulin and glucose metabolism, elevated blood pressure, obesity, a pro-thrombotic state and a pro-inflammatory state.[37,43,44] Prospective studies show that those who are diagnosed with metabolic syndrome have twice the risk of developing CVD, and five times the risk of developing DM compared to those without the syndrome.[37,45] The development of CVD and type 2 DM in individuals with obesity is related to the site of deposition of excess fat; people with greater deposits of visceral fat (ie. a greater waist circumference) have a higher risk than those with a lower waist circumference. Patients with metabolic syndrome have a higher prevalence of microalbuminuria, left ventricular hypertrophy and arterial stiffness than those without, and are also prone to developing steatohepatosis and obstructive sleep-apnoea.
Metabolic syndrome also known as Syndrome X or insulin resistance syndrome, has been recognised for many years but was first labelled in 1988.[46] It is becoming increasingly prevalent due to the increasing incidence of obesity [40,47,48] and is estimated to occur in 20-25% of adults in the world population.[49] Studies from the USA identify metabolic syndrome in up to 12% of adolescents [50] and the prevalence in Ireland is estimated at 20-25% of the adult population.[51]
There has been a lot of controversy as to whether metabolic syndrome is indeed a syndrome,[52,53] however all experts do agree it is important to identify and treat risk factors to prevent DM and CVD.[54] Advocates of metabolic syndrome believe that in diagnosing metabolic syndrome it is useful to get patients to address their emerging risk factors before the development of frank DM or CVD.[40,53] Metabolic syndrome is not a reliable tool for CVD risk in the short term (e.g. 10 year risk) and all patients diagnosed with metabolic syndrome should have a cardiovascular risk assessment to assess their short term risk.[45]
Definition - Controversy continues about the best way of defining metabolic syndrome. There have been several definitions proposed by different expert groups including the WHO, the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adults Treatment Panel III (NCEP ATP III).[52,55] The NCEP ATP III definition is thought to be more useful for clinical practice while the WHO definition is felt to be better suited as a research tool.[47] The newer IDF definition takes into account different criteria for various ethnic backgrounds. Table 4 shows the NCEP ATP III criteria.

Table 4: Definition of Metabolic Syndrome by NCEP ATP III [56]

Risk factor	Defining level
Obesity	**Three of the following** WC ≥ 102cm (40in) in men WC ≥ 88cm (35in) in women
Triglycerides	≥ 1.7mmol/L
HDL cholesterol	< 1.03mmol/L (men) < 1.29mmol/L (women)
Blood pressure	≥ 130/85mm/Hg
Fasting blood glucose	≥ 6.1mmol/L *

*a threshold of 5.6 mmol/L is used by the American Diabetes Association

Pathogenesis – the underlying cause of metabolic syndrome is unclear, however, lifestyle factors including physical inactivity, and a high calorie diet appear to be principle triggers.[44] Other associated risk factors include ageing, menopause, and ethnic predisposition.[37,48]

Obesity leads to insulin resistance with compensatory hyperinsulinaemia.[14] Genetic factors have an influence as many individuals with insulin resistance have hyperinsulinaemia without impaired glucose tolerance, while others develop impaired glucose tolerance or type 2 DM.[14] Individuals with insulin resistance are predisposed to dyslipidaemia with elevated triglycerides, low HDL cholesterol and small dense LDL cholesterol particles. In addition, the insulin resistant state promotes the development of hypertension.[14] Abdominal obesity is associated with a greater amount of visceral fat, which produces free fatty acids and inflammatory cytokines. In summary, abdominal obesity in association with other lifestyle factors (including physical inactivity and smoking) and genetic predisposition are associated with an increased risk of the development of metabolic syndrome.[14]

MANAGEMENT OF METABOLIC SYNDROME

The greatest benefit for those with the metabolic syndrome is derived from lifestyle intervention such as weight loss and physical activity.[37,52,57] The risk of developing metabolic syndrome increases with weight gain, whereas insulin sensitivity is improved by weight loss and eating less saturated fat.[46] The Finnish Diabetes Prevention Study showed that individuals with metabolic syndrome were less likely to develop type 2 DM with lifestyle intervention than controls.[52,57] Research shows that cardiorespiratory fitness provides a protective effect against all-cause and CVD mortality in healthy men and women with metabolic syndrome.[38] Diets which exchange polyunsaturated fats for saturated and trans fatty acids, and diets with a high amount of fibre could appreciably reduce the risk of type 2 DM.[58]

The aim is to reduce body weight by 7-10% during the first year of therapy and to maintain an agreed target weight thereafter. Patients should be encouraged to take moderate-intensity regular physical activity (e.g brisk walking) for 30-60 minutes per day.[37] It is essential that therapy is also directed at reducing the major risk factors: stop smoking, reduce LDL-C, blood pressure and glucose levels to the recommended goals.[37]

Management of risk factors

In patients with metabolic syndrome, additional administration of antihypertensive, antidiabetic or lipid lowering drugs are required when HTN, DM or dyslipidaemia is present. Recommendations for treatment are based on current guidelines for each condition.

Hypertension – guidelines recommend the reduction of BP to <140/90 mm/Hg or to <130/80mm/Hg if DM or other high risk factors are present (including stroke, renal dysfunction, proteinuria).[59] There is controversy regarding the use of antihypertensives in all metabolic syndrome patients with a high normal blood pressure.[59] Intensive lifestyle intervention should be adopted in all patients prior to starting pharmacotherapy. Pharmacotherapy should start with a drug unlikely to increase the risk of developing DM. ACE inhibitors/angiotensin receptor blockers are suggested followed by, if required, the addition of a calcium channel blocker or a low-dose thiazide diuretic. [59]

Elevated blood glucose – for patients with impaired blood glucose the aim is to prevent the progression to type 2 DM, which can be achieved by diet and exercise.[56,60] For those patients with DM, drug therapy is often required to reduce the HbA1c to <7%. The use of metformin and thiazolidinediones improve insulin sensitivity but metformin reduces weight while thiazolidinediones increase it.[37] See the NMIC bulletin 2007 Vol 13, No. 3 for detailed information on the management of type 2 DM.

Dyslipidaemia – Metabolic syndrome is associated with increased triglycerides, apo-B, small LDL particles and low HDL cholesterol. Lipid lowering therapy may be required as an adjunct to lifestyle intervention in the management of dyslipidaemia. Statins are considered the standard LDL-C lowering drugs.[61,62] Nicotinic acid and fibrates produce moderate reductions in LDL-C and also increase HDL-C and may be the drug of choice for patients with severe hypertriglyceridaemia. Fibrates have been used in combination with statins, although there is an increased risk of myopathy, particularly with gemfibrozil.[47] The combination of a statin and nicotinic acid can also be used for patients with metabolic syndrome. For further information on lipid lowering therapy see the NMIC bulletin 2006 Vol 12, No.4.

SUMMARY

Obesity is an increasing health problem associated with morbidity and mortality. The relationship of obesity as a risk factor for type 2 DM and CVD has been compared to that of smoking and lung cancer. Lifestyle intervention is the cornerstone of management of obesity while the use of anti-obesity drugs can also be used as adjunctive treatment. Due to the high relapse rate associated with the management of obesity, patients require an individual management plan.

Metabolic syndrome is increasing in prevalence due to the global epidemic of obesity. Even though there is controversy amongst experts about metabolic syndrome, the importance of metabolic syndrome is that it helps identify individuals at high risk of both type 2 DM and CVD. Even modest changes towards a healthy lifestyle result in significant improvement and may be the most direct route to treating the metabolic syndrome and preventing the development of type 2 DM and CVD.

List of references available on request. Date of preparation: August 2007

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