

The investigation and management of obesity

M Labib

J Clin Pathol 2003;**56**:17–25

Obesity is a chronic condition characterised by an excess of body fat. It is a complex disorder of appetite regulation and energy metabolism controlled by specific biological factors. In the past 10 years, great progress has been made in the scientific understanding of the pathophysiology of obesity and the interactions between genetic predisposition to weight gain and the environment. This article will review the current understanding of the pathophysiology and the approach to the investigation and management of obesity.

obesity increases the risks of developing several of these diseases relative to the non-obese population.¹⁷

In addition to increasing the risk of ill health, obesity significantly increases the risk of mortality at any given age.^{18 19} Among women with a BMI of ≥ 32.0 kg/m² who had never smoked, the relative risk of death from cardiovascular disease and cancer was 4.1 and 2.1, respectively, as compared with the risk among women with BMI < 19 kg/m².²⁰ Although the relation between relative mortality risk and increasing BMI is strongest until the age of 50, the effect of overweight on mortality persists into the 9th decade of life.¹ In addition, the degree by which this risk is increased varies depending on physical fitness.²¹

The body mass index (BMI) is the most widely used method of measuring overweight and obesity. It gives a measure of relative weight, adjusted for height (BMI = weight kg/height m²), which allows comparisons both within and between populations. The World Health Organisation (WHO) classification of weight in adults is useful in identifying individuals at increased risk of morbidity and mortality from obesity (table 1).¹

The anatomical distribution of body fat also has a major influence on associated health risks, with central (visceral) adiposity carrying a greater health risk than peripheral adiposity.² For this reason, the measurement of the waist circumference in centimetres (table 2) can be a useful indicator of clinical risk, particularly for hypertension, diabetes, or dyslipidaemia.³

THE ECONOMIC COSTS OF OBESITY

Given the high prevalence of obesity and the significant associated health risks, the economic costs of obesity have been estimated to be 3–8% of total health care expenditure.²² It has recently been shown that BMI is associated with the annual rates of inpatient days, number and cost of outpatient visits, and costs of outpatient pharmacy and laboratory services.²³

“A rapid increase in the prevalence of obesity in children has also been seen in England”

PREVALENCE

In recent years, obesity has increased at an alarming rate in industrialised countries. In 1980, 6% of adult men and 8% of adult women in England were obese. By 1998, the figures had increased to 17% and 21%, respectively.⁴ A rapid increase in the prevalence of obesity in children has also been seen in England.⁵ Among 3 to 4 year old English children, there was a 60% increase in the prevalence of being overweight (BMI > 85 th centile) and a 70% increase in the prevalence of obesity (BMI > 95 th centile) between 1989 and 1998.⁶

HEALTH CONSEQUENCES OF OBESITY

Obesity is associated with increased risk of type 2 diabetes,⁷ coronary heart disease,⁸ stroke, congestive heart failure,⁹ hypertension,¹⁰ dyslipidaemia,¹¹ gall bladder disease,¹² osteoarthritis,¹³ sleep apnoea,¹⁴ and certain cancers, such as ovary, breast, and colon.^{15 16} Table 3 shows the extent to which

In England, the direct cost to the National Health Service (NHS) of obesity and its associated illnesses was estimated at £½ billion in 1998 (about 1.5% of NHS expenditure in that year). Of this total, the cost of treating obesity itself was only £9.5 million, because the bulk of the cost arose from treating hypertension, coronary heart disease, and type 2 diabetes. The estimated indirect cost, in terms of lost output in the economy as a result of sickness absence or premature death, was estimated at £2.1 billion.¹⁷

Abbreviations: BMI, body mass index; LCD, low calorie diet; LFD, low fat diet; NHS, National Health Service; PC1, prohormone convertase 1; POMC, pro-opiomelanocortin; PPAR γ , peroxisome proliferator activated receptor γ ; RMR, resting metabolic rate; WHO, World Health Organisation

Correspondence to:
Dr M Labib, Department of
Clinical Biochemistry,
Russells Hall Hospital,
Dudley, West Midlands
DY1 2HQ, UK;
mlabib5555@aol.com

Accepted for publication
23 September 2002

Table 1 WHO classification of weight and the risk of co-morbidities according to BMI values (BMI=weight in kg/height² in metres)

WHO classification	BMI (kg/m ²)	Risk of co-morbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal weight	18.5–24.9	Average
Overweight	25.0–29.9	Mildly increased
Obese	≥30.0	
Class I	30.0–34.9	Moderate
Class II	35.0–39.9	Severe
Class III	≥40.0	Very severe

BMI, body mass index; WHO, World Health Organisation.

Table 2 Waist circumference values for the prediction of risk of metabolic complications

Sex	Alerting zone	Action zone
Male	94–102 cm	>102 cm
Female	80–88 cm	>88 cm

THE BENEFITS OF WEIGHT LOSS

There is strong evidence to suggest that the risks of mortality and morbidity associated with obesity can be reduced with weight loss. A 10 kg weight loss was associated with a 20–25% fall in total mortality, 30–40% fall in diabetes related deaths, and 40–50% fall in obesity related cancer deaths.²⁴ A relatively modest weight loss of 5–10% of pretreatment body weight has been associated with significant improvements in concomitant medical disorders, such as type 2 diabetes, hypertension, and cardiovascular disease, in addition to an increase in life span.^{25–27} In severely obese patients who lost 20–30 kg following surgical banding gastroplasty, hypertension and diabetes were cured in 89% and 43% of patients, respectively.²⁸ Weight loss can also prevent the progression to type 2 diabetes. Two recent studies have shown that modest weight loss in overweight subjects with impaired glucose tolerance resulted in a 58% reduction in incident diabetes.^{29,30} The ongoing prospective Swedish obese subjects study has recently examined the effect of a large, longstanding and intentional weight reduction on the incidence of several cardiovascular risk factors.³¹ After two years, the incidence of diabetes was reduced 32 times and that of hypertension by 2.6 times in the surgically treated group compared with the control group. After eight years, there was still a fivefold reduction in diabetes incidence.³²

REGULATION OF ENERGY BALANCE

Energy stores are determined by the balance between energy intake and energy expenditure. Energy intake is determined by the intake of macronutrients. Different macronutrients have different properties in terms of their calorie content, energy density, thermic effect, storage capacity, autoregulation, and ability to suppress hunger (table 4). For example, any consumed alcohol is oxidised for energy and there is no storage capacity for it in the body. In addition, there is no storage capacity for protein and only a limited storage capacity for carbohydrate, in the form of glycogen in the liver and muscle.

There are two mechanisms by which the utilisation of ingested nutrients can affect energy balance: the efficiency of nutrient utilisation and the postingestive fuel selection. The efficiency of nutrient utilisation is inversely related to the nutrient induced thermogenesis, which is the energy cost of absorbing, processing, and storing nutrients. Based on these

Table 3 The relative risk of developing associated diseases in obese women and men

Disease	Relative risk in women	Relative risk in men
Type 2 diabetes	12.7	5.2
Hypertension	4.2	2.6
Myocardial infarction	3.2	1.5
Colon cancer	2.7	3.0
Angina	1.8	1.8
Gall bladder diseases	1.8	1.8
Ovarian cancer	1.7	–
Osteoarthritis	1.4	1.9
Stroke	1.3	1.3

thermic effects, fat is utilised with a very high efficiency (97–98%) compared with either carbohydrates (92–94%) or proteins (70–75%).³³ The postingestive fuel selection depends essentially on the plasma concentrations of glucose, insulin, and free fatty acids. Insulin promotes glucose uptake and oxidation and inhibits lipolysis and lipid oxidation. Thus, after a high carbohydrate meal, glucose oxidation is promoted, whereas fat oxidation is inhibited.³⁴ In contrast, dietary fats are primarily deposited in adipose tissue and lipid oxidation is not stimulated after a high fat meal.³⁵ Therefore, postingestive fuel selection favours the oxidation of dietary proteins and carbohydrates, whereas dietary fats are preferentially stored in adipose tissue. Alcohol, by inhibiting lipid oxidation, indirectly favours the storage of dietary fats. Therefore, fat intake seems to be particularly important in inducing weight gain compared with carbohydrates or proteins.

“A relatively modest weight loss of 5–10% of pretreatment body weight has been associated with significant improvements in concomitant medical disorders, such as type 2 diabetes, hypertension, and cardiovascular disease, in addition to an increase in life span”

The three major components of energy expenditure are resting metabolic rate (RMR), meal induced thermogenesis (see above), and energy cost of physical activity. The largest component of these is the RMR, which is the energy expended by the body to maintain basic physiological functions, and is approximately 1 kcal/minute (4.2 kJ/minute). Energy expenditure from physical activity is the most variable component of daily energy expenditure and can vary greatly within and between individuals.³⁶

MOLECULAR PATHWAYS TO OBESITY

New information regarding neural circuits that control food intake and their hormonal regulation has extended our understanding of energy homeostasis. Although most of the insights into the regulation of energy balance have been obtained in rodent models, there is sufficient evidence to suggest that several of these mechanisms are also important in humans. Obesity genes encode the molecular components of the physiological system that regulates body weight. A key element of this system is the hormone leptin, which is produced by adipose tissue and acts on nerve cells in the brain, modulating their function.³⁷ Key molecules in this neural network are the hypothalamic neurotransmitters neuropeptide Y, agouti related protein, and melanin concentrating hormone, which stimulate food intake (orexogenic); and proopiomelanocortin (POMC), α melanocyte stimulating hormone, and cocaine and amphetamine regulated transcript,

Table 4 Properties of macronutrients

Properties	Fat	Protein	Carbohydrate	Alcohol
kcal/g (kJ/g)	9 (38)	4 (17)	4 (17)	7 (29)
Energy density	High	Low	Low	High
Thermic effect (as % of energy content)	2–3%	25–30%	6–8%	15–20%
Storage capacity	High	None	Low	None
Autoregulation	Poor	Good	Good	Poor
Ability to suppress hunger	Low	High	High	Negative (stimulating)

which decrease food intake (anorexigenic).³⁸ These neural circuits also regulate energy expenditure by their effects on several key molecules, which include uncoupling proteins and peroxisome proliferator activated receptor γ (PPAR- γ) coactivator 1, a key regulator of the genes that control thermogenesis.³⁹ Genetic evidence indicates that leptin regulates energy balance by modulating the balance among these neuropeptides.⁴⁰ More recently, ghrelin, a novel endogenous ligand for the growth hormone secretagogue receptor, has been reported to have adipogenic actions and to induce weight gain.⁴¹ It is synthesised predominantly in the stomach and has been shown to stimulate food intake in humans.⁴¹ Plasma ghrelin concentrations normally increase after fasting and reduce after feeding.⁴² A recent study showed that obese subjects do not exhibit the expected decline in plasma ghrelin after a meal compared with lean controls, suggesting that ghrelin may be involved in the pathophysiology of obesity.⁴³

THE PATHOGENESIS OF OBESITY

Genetic factors

It has been estimated that between 25% and 70% of the variations in body weight can be attributable to genetic factors.^{44–46} Family studies have consistently demonstrated that BMI is highly correlated among first degree relatives^{47–48} and adoption studies have provided evidence of the contribution of genetics to BMI.^{46–49} Linkage studies have shown an association between several chromosomes and the obese phenotype.^{50–51} Although these studies suggest that the genetic background must affect one or more component of energy balance, the mechanism by which genes may contribute to differences in body weight is less clear. Studies have reported that a low RMR,⁵² a low thermic effect of food,⁵³ or an inability to oxidise fat with a high reliance on carbohydrate as a fuel may predispose to obesity.⁵⁴

In humans, autosomal recessive mutations in the genes for leptin,^{55–57} the leptin receptor,⁵⁸ prohormone convertase 1 (PC1),⁵⁹ and POMC,⁶⁰ have been shown to lead to early onset obesity. All of the mutations apparently lead to additional phenotypical manifestations including adrenal insufficiency (POMC), red hair (POMC), and reduced or impaired fertility (PC1, leptin, and leptin receptor). The first autosomal dominant form of human obesity resulting from a missense mutation in the gene encoding PPAR γ 2 was identified in four of 121 obese unrelated Germans.⁶¹ Prader-Willi syndrome is a complex multisystem disorder, which is associated with childhood onset obesity and is characterised by upper body obesity, short stature, mental retardation, and hypogonadism. It is caused by the absence of expression of the paternally active genomic material in the Prader-Willi chromosomal region 15q11–13.⁶²

Environmental factors

Two major changes in the environment seem to have directly contributed to the increasing prevalence of obesity. The first is the decline in energy expenditure caused by technological advances and sedentary behaviour and the second is the increased consumption of low cost, high fat, energy dense food.

There is no doubt that the amount of energy expenditure required for daily living has declined over the past few decades

as a result of the increased use of computers, remote control devices, microwave ovens, and cars. Sedentary behaviour is another factor that has contributed to the recent increase in obesity. For example, it has been shown that the prevalence of obesity increases proportionally with the daily time spent watching television⁶³ and that television viewing is inversely associated with the time spent outdoors.⁶⁴

There is some evidence that the consumption of high fat diets is associated with an increased risk of obesity.⁶⁵ However, dietary studies have failed to show a consistent relation between nutritional factors and relative weights, and available data suggest that there has been either a slight increase or a modest decrease in total energy intake over the past two to three decades.⁶⁶ Interestingly, a study combining data on energy intake and physical activity in relation to the secular increase in adult obesity showed no relation between total energy intake or fat consumption and the prevalence of obesity, but a close relation between proxy measures of physical activity (television viewing and car ownership) and obesity.⁶⁷

Overall, the above data suggest that the increased prevalence in obesity over the past two or three decades may have resulted from a decline in energy expenditure that was not matched by an equivalent reduction in energy intake.

THE CLINICAL ASSESSMENT OF THE OBESE PATIENT

The clinical assessment of the obese patient should not be different from the assessment applied to other patients with chronic conditions. Patients referred to a specialist obesity clinic must have a detailed history taken, a clinical examination performed, and appropriate investigations done. The clinic must be suitably equipped for obese patients with larger chairs and couches, large blood pressure cuffs, and appropriate weighing scales, at least up to 200 kg (approximately 31.5 stones).

Obesity focused history

It is important to establish from the outset the patient's perspective of his/her problem because although obesity may have been clearly stated as the reason for the referral, often the patient may state a different reason, indicating unreadiness to enter obesity treatment. A thorough chronological history of weight gain is essential and may provide clues to possible aetiological or precipitating factors, such as cessation of smoking, stress, bereavement, or low mobility. A history of previous attempts at weight loss and their nature, duration, and degree of success should be documented. Many obese patients give a history of having lost weight in the past, often on "fad" diets, but that they had put the weight back on when they returned to their "normal" diet. Total weight lost with each attempt and time to regain weight should be noted. Occasionally, patients claim that they were unable to lose weight even on a starvation diet.

"The increased prevalence in obesity over the past two or three decades may have resulted from a decline in energy expenditure that was not matched by an equivalent reduction in energy intake"

Table 5 Comorbidities associated with obesity

System	Symptom, sign, or disease
Cardiovascular	Hypertension, coronary heart disease, congestive heart failure, ankle oedema, varicose veins
Respiratory	Shortness of breath, sleep apnoea, pickwickian syndrome
Gastrointestinal	Indigestion, reflux oesophagitis, gallstones, fatty liver
Musculoskeletal	Arthritis, back pain
Skin	Venous stasis of legs, intertrigo, acanthosis nigricans
Endocrine and metabolic	Glucose intolerance, type 2 diabetes, dyslipidaemia, polycystic ovary syndrome, amenorrhoea, lipodystrophy

A detailed family history is important and often suggests a genetic predisposition. A familial predisposition should be considered if at least one first degree relative is also obese. The risk for developing obesity related complications, such as type 2 diabetes, should also be ascertained. The weight of the partner and children may give an indication about shared dietary habits and lifestyle. The level of activity and exercise should be recorded because most obese patients blame their inactivity on their excess weight and claim that if they lose weight they will be able to be more active.

Drug history should be taken to identify possible drugs that may be contributing to weight gain, such as steroid hormones, antidepressants (tricyclics), antipsychotics (phenothiazines and butyrophenones), anticonvulsants (valproate and carbamazepine), lithium, and antidiabetics (insulin, sulfonylurea, and thiazolidinediones).⁶⁸

The psychological aspects of eating behaviour should be explored, such as loneliness, boredom, or stress. Often obese patients express feelings of low self esteem and depression. Eating disorders should be particularly sought in young women. Binge eating is characterised by recurrent loss of control over eating, eating large amounts of food rapidly, and then feeling guilty or disgusted after a binge. Bulimia nervosa is characterised by binge eating together with purging and excessive concern about shape or weight.

Finally, a thorough review of systems must be taken to assess any co-morbidities that are directly or indirectly related to obesity, to identify any evidence of endocrine disease as an occult aetiology of obesity (for example, Cushing's disease or hypothyroidism), and also to identify any systemic disease that might affect the treatment programme (such as arthritis or heart disease).

Dietary assessment

A detailed dietary history of the patient's current diet is paramount. This should be done by a dietitian with a special interest, and experience, in obesity and should include an assessment of the total daily calorie intake and the percentage of calories derived from fat. Although obese patients tend to underestimate their food intake, this assessment provides a good indication of the patient's current dietary habits. Different methods have been suggested for the assessment of dietary intake, including the diet history and the seven day unweighed diet diary.⁶⁹

Clinical examination

A physical examination with attention to details specific to obesity and complications of obesity is essential (table 5). Evidence of Cushing's disease or hypothyroidism should be sought. Visual inspection of the skin (intertrigo, acanthosis nigricans, bruising, or thinning) and fat distribution (lipodystrophy) is important. Weight, height, and waist circumference should be accurately measured. Blood pressure should be measured with an appropriately sized cuff. Examination of the heart may reveal left ventricular hypertrophy. Evidence of varicose veins, peripheral oedema, or venous stasis should be

Table 6 The investigation of the obese patient

Baseline
Biochemical profile
Full blood count
Fasting lipid profile
Fasting plasma glucose
Serum uric acid
Serum FT4 and TSH
Further investigations depending on clinical picture
24 hour urine free cortisol
ECG and chest x ray
Respiratory function tests
Plasma leptin
ECG, electrocardiogram; FT4, serum free thyroxine; TSH, thyroid stimulating hormone.

sought. The presence of acanthosis nigricans (hyperpigmented velvety plaques of body folds) in obese adolescents is frequently associated with hyperinsulinaemia and insulin resistance. Severe lipodystrophy (loss of fat in the legs, arms, face with central obesity and dorsal fat pads) is also a manifestation of insulin resistance and is associated with hypertriglyceridaemia and hepatic steatosis. In young patients, features of monogenic forms of obesity (such as adrenal insufficiency or disturbances of the hypothalamic–pituitary–gonadal axis) should be sought.

Investigations

The role of laboratory and other investigations is to exclude possible underlying causes of obesity and its complications (table 6). A biochemical profile (renal, bone, and liver) and a full blood count are useful as a baseline. Fasting plasma glucose and lipid profile should be done to exclude diabetes and dyslipidaemia and serum free thyroxine and thyroid stimulating hormone to exclude hypothyroidism. An electrocardiogram should be done in view of the high prevalence of hypertension and cardiovascular disease in obesity. Further investigations will depend on the degree of clinical suspicion of underlying (for example, Cushing's disease) or coexisting pathology (for example, polycystic ovary syndrome). The measurement of plasma leptin is not routinely indicated but may be useful in suspected cases of leptin deficiency (morbid obesity, increased appetite and hyperphagia, and hypogonadotropic hypogonadism) or in severe lipodystrophy. Young patients with features of monogenic forms of obesity should be referred to a specialist centre for further investigations.

Assessment of risk status

The patient's risk status should be assessed by determining the degree of obesity (BMI), the presence of abdominal obesity (waist circumference), and the presence of co-morbidities. The presence of established coronary heart disease, peripheral arterial disease, type 2 diabetes, and sleep apnoea indicates a high absolute risk that necessitates the need for intense management. The presence of three or more of the following risk

factors also indicates a high absolute risk: hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg), smoking, low density lipoprotein-cholesterol ≥ 4.1 mmol/litre, high density lipoprotein-cholesterol ≤ 0.9 mmol/litre, impaired fasting plasma glucose (6.1–6.9 mmol/litre), or a family history of premature coronary heart disease.⁷⁰

Assessment of patient motivation, readiness for change, and expectation

Patient motivation is a key component for success in a weight loss programme. Therefore, it is important to establish that the patient is ready to make changes before initiating treatment. Factors that must be evaluated are: reasons for wanting to lose weight, the extent of family support, the patient's understanding of the problem, attitude towards physical activity, time availability for outpatient visits, any barriers or financial considerations.

“Patient motivation is a key component for success in a weight loss programme”

When counselling patients who are ready to embark on a weight reducing programme, it is essential to accommodate their individual needs and to consider their ethnic backgrounds, age, and circumstances. It is also important to explain to obese patients that obesity is a chronic condition (similar to hypertension and diabetes), which although not curable, requires life long treatment and that, if treatment is stopped, weight will be regained.

Most obese patients have unrealistic expectations of weight loss. Therefore, it is important to discuss with patients what is a realistic target for them. An initial target of 5–15% weight loss can be achieved by most patients and is a reasonable starting point. It is also important at this stage to explain to patients that more weight loss could be achieved and that once they reach their first target, a lower target can be set.

THE MANAGEMENT OF THE OBESE PATIENT

The principle aims of weight management are: first, to induce a negative energy balance to reduce body weight and, second, to maintain a lower body weight over the longer term. The new criterion for success, which has been proposed by the WHO,¹ is a 5–15% reduction in initial weight. Therefore, the initial goal of weight loss treatment should be to reduce body weight by approximately 10% over six months. If this target is achieved, consideration can be given to further weight loss. However, it is difficult for most patients to continue to lose weight after a period of six months and the challenge for the patient should be to maintain the lower body weight. This can only be achieved if the patient continues to adhere to a programme consisting of diet, physical activity, and behavioural treatment, indefinitely.

Several approaches have been described for the management of obesity, namely: diet, physical activity, behavioural treatment, drugs, and surgery. In practice, a combination of these is used depending on the patient weight, co-morbidities, and expected targets.

Dietary approaches

The aims of the dietary approaches are twofold: first, to achieve a deficit in energy balance of 500–600 kcal/day (2100–2520 kJ/day), which would result in a weight loss of 0.5–1.0 kg/week, and second, to ensure that obese people are following a healthy balanced diet that is low in saturated fat and high in complex carbohydrate. It is important that the advice is designed on an individual basis, taking into consideration the patient's energy requirements. The dietary history should provide the basis for discussion of what changes can be

made with each individual patient. Any changes must be acceptable to the patient so that they are likely to be maintained in the long term.

The conventional approach has been to tell patients to “go on a diet” or to give them “a diet sheet”. This is no longer appropriate in that it suggests that changes are needed on a temporary basis only. It is now clear that long term changes in food choice, eating behaviour, and lifestyle are needed. There are two main dietary options, namely: low calorie diets (LCDs) and low fat diets (LFDs).

Low calorie diets

LCDs put more emphasis on restricting the total energy intake and less on the macronutrient composition—for the patient it means eating less. Several studies have found that weight loss on calorie restricted diets was related to energy intake and not nutrient composition.^{71–73} Based on 34 randomised controlled trials assessing the impact of LCDs in obese patients, it was concluded that LCDs produced weight loss regardless of the duration of treatment, and body weight was reduced by an average of 8% over three to 12 months compared with controls.⁷⁰ However, there was a large variation in mean weight loss between the studies. In addition, it is difficult to separate the impact of the dietary treatment because most trials included some elements of behavioural modification. Nevertheless, LCDs are suitable for most patients irrespective of their financial and time constraints or cultural backgrounds. Very low calorie diets, providing about 400–500 kcal/day (1680–2100 kJ/day), produce greater initial weight loss than LCDs, but the long term (> 1 year) weight loss is not different from that of LCDs.

Low fat diets

There is no doubt that a high fat diet, because of its high energy density, promotes weight gain and obesity, particularly in sedentary people who have a genetic predisposition to obesity. Therefore, restricting fat intake should be seen as a means of reducing the diet's energy density and total energy intake. Unfortunately, the ability of low fat diets to induce weight loss is less pronounced than LCDs. A systematic review of 28 low fat randomised controlled trials showed that a weight loss of 1.6 g/day was achieved for each percentage point reduction in energy from fat.⁶⁵

In unselected obese patients, LFDs generally produce a rate of weight loss of 100–200 g/week compared with 300–700 g/week for LCDs. Four randomised controlled trials have compared LCDs with ad libitum LFDs. Taken together, these trials show that the impact of LFDs on weight loss is increased if some restrictions are put on total energy intake.^{74–77}

Based on the above, it would appear that a decrease in energy intake is the most important component of weight loss and that reducing fat as part of a lower calorie diet is a practical way to reduce energy intake.

Physical activity

In general, cross sectional studies have shown that physical activity is inversely related to body weight^{78–79} and rate of weight gain with age.⁸⁰ An increase in physical activity can create an energy deficit and is an important component of weight loss treatments. In addition, there is strong evidence that increased physical activity in overweight and obese adults increases cardiorespiratory fitness and reduces the risk of cardiovascular disease, independent of weight loss.⁸¹ However, it is difficult to achieve a significant weight loss through physical activity alone. For example, a 75 kg person requires 100 kcal (420 kJ) to walk a mile. If each kilogram of body fat contains about 7000 kcal, one would have to walk about 70 miles to expend the energy contained in 1 kg of fat. For patients who may be 30–40 kg overweight, it is an extraordinary challenge to lose that much fat by exercise. In addition,

many overweight individuals are unfit and therefore the effort required is even greater. Despite this, increased physical activity is a useful adjunct to dietary treatment in promoting weight reduction and in maintaining weight loss.⁸²

For most obese patients, physical activity should be initiated slowly (for example, walking or swimming at a slow pace). The patient can start walking for 10 minutes, three days a week. With time, and depending on progress and capacity, the intensity of exercise could be increased to 30 to 45 minutes at least five days a week. With this regimen, an additional 100–200 kcal/day (840 kJ/day) of energy can be expended.

Behavioural treatment

The assumptions of behavioural treatment are that patterns of eating and physical activity are learned behaviours and can be modified. Therefore, the goal of behavioural treatment for weight control is to help obese patients identify their eating and activity patterns and thinking habits that contribute to their excess weight. Unless the patient acquires a new set of eating and physical activity habits, long term weight reduction is unlikely to succeed.

“Increased physical activity is a useful adjunct to dietary treatment in promoting weight reduction and in maintaining weight loss”

The cornerstone of behavioural treatment is self monitoring and studies have shown that self monitoring of intake correlates with successful long term weight control.⁸³ Initially, patients are asked to keep daily records of their food intake, including the type and amount of food, information about times and places of eating, and feelings associated with eating. These records can then be analysed to provide targets for intervention. For example, patients who tend to snack on high calorie foods (such as crisps, biscuits, chocolates) can be advised to substitute these for foods which are as filling but lower in calories (such as fruits, yoghurt, breakfast cereals). At breakfast, patients can be encouraged to have a cereal or porridge, which is both filling and nutritious, rather than having a couple of slices of toast with butter and marmalade. Patients who tend to snack in the evening, often while watching television, generally do so because of boredom and not hunger. They can be advised to control their snacking by drinking low calorie drinks. The behavioural approach to physical activity is that any activity is better than none. The principal goal is to increase energy expenditure, without concern for the intensity of activity. Patients should be advised to use the stairs whenever they can, to stand while on the telephone, park further away from entrances, etc.

Short term trials show that patients treated by a comprehensive group behavioural approach lose approximately 9% of their initial body weight in 20 weeks of treatment.⁸⁴ However, long term results show that these patients typically regain about 30–35% of their weight loss in the year after treatment. However, several studies have shown that greater weight loss could be maintained if patients continue to attend regular (weekly or fortnightly) follow up sessions.^{85–86} Therefore, it would appear that maintenance sessions provide patients with the support and motivation needed to continue to practise their weight control skills.

Drugs

Drugs should be used only as part of a comprehensive programme that includes dietary modification, physical activity, and behavioural treatment.⁸⁷ They should be considered for patients with a BMI ≥ 30 kg/m², who are at increased risk of developing obesity related complications, and for those with a BMI ≥ 27 kg/m² who have co-morbidities, such as diabetes, hypertension, sleep apnoea, and dyslipidaemia, where dietary and lifestyle modifications have been unsuccessful in achiev-

ing a 10% weight reduction after at least three months of supervised care. Drugs should not be used for “cosmetic” reasons.

Continuous assessment of drug treatment for efficacy is necessary because the response is variable. If a patient does not lose 2.0 kg (4.4 lb) in the first four weeks after initiating treatment, the likelihood of a long term response is very low and the doctor should reassess the patient to determine adherence to the diet. If the patient continues to be unresponsive, the medication should be discontinued. If weight is lost in the initial six months of treatment or is maintained after the initial phase of weight loss, this should be considered a success, and the drug may be continued as long as adverse effects are mild.

The only two drugs that are currently approved by NICE (National Institute of Clinical Excellence) are orlistat (a pancreatic lipase inhibitor) and sibutramine (a serotonin-noradrenaline reuptake inhibitor). At present, using more than one drug in a combination is not recommended.

Orlistat

Orlistat (Xenical) is a potent inhibitor of pancreatic/intestinal lipase and therefore increases faecal fat loss. The effect is dose related but reaches a plateau with doses above 400–600 mg/day. Less than 1% of an oral dose is absorbed and pharmacodynamic studies suggest that orlistat does not affect the pharmacokinetic properties of digoxin, phenytoin, warfarin, oral contraceptives, alcohol, frusemide, captopril, nifedipine, or atenolol. However, the absorption of fat soluble vitamins A and E and β carotene may be slightly reduced, so that some patients may require vitamin supplements.

Double blind, randomised, placebo controlled trials showed a weight loss of 8.5–10.2% at one year with orlistat compared with 5.5–6.6% with placebo.^{88–90} Using a criterion of > 10% weight loss, these trials showed that 38.8–43% of patients treated with orlistat reached that target compared with 17.7–25% of placebo treated patients. However, studies lasting two years showed that a quarter to a third of the weight lost during the first year was regained during the second year of treatment, although overall weight loss was still significantly greater than that seen with placebo.^{89–90} Improvements in serum lipid and plasma glucose concentrations were also significantly greater in patients taking orlistat compared with those taking placebo.⁸⁹ In patients with type 2 diabetes, orlistat led to improvement in glycated haemoglobin and a decreased requirement for sulfonylurea drugs.⁹¹

Treatment with orlistat should only be started if diet alone has previously produced a total weight loss of at least 2.5 kg over a period of four consecutive weeks. Treatment should be discontinued after 12 weeks if patients have been unable to lose at least 5% of their initial body weight. Treatment should not usually be continued beyond 12 months, and never beyond 24 months.

Orlistat is generally well tolerated and side effects are mainly related to gastrointestinal symptoms. These are usually mild and occur within the first few weeks of treatment and they include abdominal pain, borborygmi, flatus, and oily spotting.

Sibutramine

Sibutramine is a noradrenergic and a serotonin reuptake inhibitor, which is thought to act principally by enhancing satiety. Another proposed mechanism of action is stimulation of fasting and postprandial thermogenesis, but the effect appears to be relatively small, approximately 3–5% of RMR six hours after ingestion.⁹²

Randomised controlled trials found that sibutramine produced a dose related weight loss when given in the range 5–30 mg/day, with an optimal dose of 10–15 mg/day.^{93–95} Over a six month period, subjects who received sibutramine lost

5–8% of preintervention body weight, as compared with 1–4% among subjects who received placebo.^{93–96–98}

In a two year study, although weight was regained in both the sibutramine and placebo groups during the second year of follow up, weight losses were significantly greater among those who received sibutramine for the full two years of the study.⁹⁴

The starting dose of sibutramine should normally be 10 mg/day. The continuation of treatment beyond three months should be supported by evidence of a loss of at least 5% of initial body weight. Treatment with sibutramine is not recommended beyond 12 months. The most common side effects seen during treatment with sibutramine are headache, dry mouth, constipation, and insomnia. Sibutramine has the tendency to raise blood pressure, and this effect is dose related. The mean increase in blood pressure is about 2 mm Hg systolic and diastolic at the 15 mg dose. Although this increase may seem modest, it has been estimated that a 2 mm Hg change in diastolic blood pressure changes the risk of coronary heart disease by 6% and the risk of stroke by 15%.⁹⁹ Therefore, treatment with sibutramine is not recommended for patients whose blood pressure before the start of treatment is above 145/90 mm Hg. Patients started on sibutramine should have their blood pressure monitored closely and treatment should be discontinued if blood pressure rises above 145/90 mm Hg or by more than 10 mm Hg (systolic or diastolic), or if resting pulse rate rises by more than 10 beats/minute.

“Sibutramine has the tendency to raise blood pressure, and this effect is dose related”

Sibutramine should not be used to treat patients with a history of coronary artery disease, congestive cardiac failure, cardiac arrhythmia, stroke, major eating disorders, or psychiatric disorders. Sibutramine should not be used with drugs such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors. In addition, because sibutramine is metabolised by cytochrome P450 CYP3A4, it may interfere with the metabolism of many common drugs.

Surgery

Surgical interventions are occasionally used to treat morbidly obese patients, when other treatments have failed. Many procedures have been described but three operations, gastric bypass, vertical banded gastroplasty, and gastric banding have produced the best results to date. These procedures are designed primarily to reduce food consumption and can result in substantial weight loss. Compared with other interventions, surgery has produced the longest period of sustained weight loss. Defining success as a weight loss of more than 50% of excess weight, the Adelaide study showed that, at three years, the success rate was 48% for vertical banded gastroplasty and 67% for gastric bypass.¹⁰⁰

In experienced centres, the mortality from these procedures is usually 1.5% or less. The incidence of complications varies depending on the severity of obesity and co-morbidities. Apart from intraoperative incidents, early postoperative complications include anastomotic leaks, wound infections, dehiscence, ileus, cardiopulmonary failure, pulmonary embolism, pneumonia, and myocardial infarction. The rapid postoperative weight loss is associated with a high rate of cholelithiasis in the form of cholesterol stones. Incisional hernias are relatively common and are usually repaired 12–18 months postoperatively. Other general complications include B12 deficiency, anaemia, depression, cholecystitis, and gastritis. Therefore, after these procedures, patients require life long medical supervision to monitor potential complications and to correct micronutrient deficiencies.

Take home messages

- Obesity is increasing at alarming rates in industrialised countries because of (1) a reduction in daily energy expenditure, as a result of technological improvements, and (2) an increase in energy intake resulting from the increasing availability of palatable, low cost, high fat, energy dense food
- Obesity is a complex disorder of appetite regulation and energy metabolism controlled by specific biological factors
- The major health problems related to obesity are increased risk of type 2 diabetes, coronary heart disease, stroke, congestive heart failure, hypertension, dyslipidaemia, gall bladder disease, osteoarthritis, sleep apnoea, and certain cancers, such as ovary, breast, and colon
- Health benefits can be seen after moderate but sustained weight loss
- A combination of energy restriction, exercise, behavioural modification, drugs and, occasionally, surgery should help in the management of the current obesity problem
- However, for any significant progress to be made in the prevention of obesity, a public health approach is urgently needed

CONCLUSION

Obesity is increasing at alarming rates in industrialised countries. Two changes in the environment seem to have directly contributed to this increase. The first is a reduction in the energy expenditure required for daily living, as a result of technological improvements, and the second is an increase in energy intake resulting from the increasing availability of palatable, low cost, high fat, energy dense food.

Health problems related to obesity are becoming more widely recognised and have major consequences on overall health care costs. Health benefits can be seen after moderate but sustained weight loss. Weight normalisation should no longer be the ultimate goal of treatment and new definitions of success should be adopted and applied by health professionals. A combination of energy restriction, exercise, behavioural modification, drugs and, occasionally, surgery should help in the management of the current obesity problem. However, for any significant progress to be made in the prevention of obesity, a public health approach is urgently needed. This would not only involve clinicians but would also require input from the Department of Health, the Education Authority, public health specialists, and the food industry.

REFERENCES

- 1 **World Health Organisation.** *Obesity: preventing and managing the global epidemic.* Report of a World Health Organisation consultation on obesity. Geneva: World Health Organisation, 1998.
- 2 **McKeigue PM,** Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;**337**:382–6.
- 3 **Han TS,** van Leer EM, Seidell JC, *et al.* Waist circumference action levels in identification of cardiovascular risk factors: prevalence study in a random sample. *BMJ* 1995;**311**:1401–5.
- 4 **Erens B,** Primates P. *Health survey for England: cardiovascular disease.* London: The Stationery Office, 1998.
- 5 **Rudolf M,** Sahota P, Barth J, *et al.* Increasing prevalence of obesity in primary school children: cohort study. *BMJ* 2001;**322**:1094–5.
- 6 **Bundred P,** Kitchiner D, Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. *BMJ* 2001;**322**:326–8.
- 7 **Colditz G,** Willett W, Roinitzky A, *et al.* Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995;**122**:481–6.
- 8 **Donahue R,** Abbot R. Central obesity and coronary heart disease. *Lancet* 1987;**2**:1215.
- 9 **Savage M,** Krolewski A, Kenien G, *et al.* Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. *Am J Cardiol* 1998;**62**:665–9.
- 10 **Havlik R,** Hubert H, Fabsitz R, *et al.* Weight and hypertension. *Ann Intern Med* 1983;**98**:855–9.
- 11 **Denke M,** Sempos C, Grundy S. Excess body weight: an underrecognised contributor to high blood cholesterol levels in white American men. *Arch Intern Med* 1993;**153**:1093–103.

- 12 **Stampfer M**, Maclure K, Colditz G, *et al*. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr* 1992;**55**:652-8.
- 13 **Cicuttini F**, Baker J, Spector T. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *J Rheumatol* 1996;**23**:1221-6.
- 14 **Shepard J**. Hypertension, cardiac arrhythmias, myocardial infarction and stroke in relation to obstructive sleep apnea. *Clin Chest Med* 1992;**13**:437-58.
- 15 **French S**, Folsom A, Jeffery R, *et al*. Weight variability and incident disease in older women: the Iowa women's health study. *Int J Obes Relat Metab Disord* 1997;**21**:217-23.
- 16 **Giovannucci E**, Ascherio A, Rimm E, *et al*. Physical activity, obesity and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995;**122**:327-34.
- 17 **National Audit Office Report**. *Tackling obesity in England*. Report of the Comptroller and Auditor General (HC220), 2001. London, The Stationary Office, 2001.
- 18 **Andres R**. Beautiful hypotheses and ugly facts. The BMI-mortality association. *Obes Res* 1999;**7**:417-19.
- 19 **Sempos C**, Durazo-Arvizu R, McGee D, *et al*. The influence of cigarette smoking on the association between body weight and mortality: the Framingham heart study revisited. *Ann Epidemiol* 1998;**8**:286-8.
- 20 **Manson J**, Willett W, Stampfer M, *et al*. Body weight and mortality among women. *N Engl J Med* 1995;**333**:677-85.
- 21 **Wei M**, Kampert J, Barlow C, *et al*. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight and obese men. *JAMA* 1999;**282**:1547-53.
- 22 **Wolf A**, Colditz G. Current estimates of the economic cost of obesity in the United States. *Obes Res* 1998;**6**:97-106.
- 23 **Quesenberry C, Jr**, Caan B, Jacobson A. Obesity, health services use, and health care costs among members of a health maintenance organization. *Arch Intern Med* 1998;**158**:466-72.
- 24 **Jung R**. Obesity as a disease. *Br Med Bull* 1997;**53**:307-21.
- 25 **Goldstein D**. Beneficial health effects of modest weight loss. *Int J Obes* 1992;**16**:397-415.
- 26 **Wing R**, Koeske R, Epstein L, *et al*. Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med* 1987;**147**:1749-53.
- 27 **Datilo A**, Kris-Etherton P. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;**56**:320-8.
- 28 **SIGN**. Obesity in Scotland: integrating prevention with weight management. Scottish Intercollegiate Guidelines Network. Edinburgh: SIGN Secretariat, 1996.
- 29 **Tuomilehto J**, Lindstrom J, Eriksson J, *et al*. Finnish diabetes prevention study group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;**344**:1343-50.
- 30 **Diabetes Prevention Program Research Group**. Reduction of the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393-403.
- 31 **Sjostrom C**, Lissner L, Wedel H, *et al*. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. *Obes Res* 1999;**7**:477-84.
- 32 **Torgerson J**, Sjostrom L. The Swedish obese subjects (SOS) study: rationale and results. *Int J Obes Relat Metab Disord* 2001;**25**(suppl 1):S2-4.
- 33 **Jequier E**. Nutrient effects: post-absorptive interactions. *Proc Nutr Soc* 1995;**54**:253-65.
- 34 **Flatt J**. Importance of nutrient balance in body weight regulation. *Diabetes Metab Rev* 1988;**4**:571-81.
- 35 **Schutz Y**, Flatt J, Jequier E. Failure of dietary fat to promote fat oxidation: a factor favoring the development of obesity. *Am J Clin Nutr* 1989;**50**:307-14.
- 36 **Goran M**. Variation in total energy expenditure in humans. *Obes Res* 1995;**3**:59-66.
- 37 **Friedman J**, Halaas J. Leptin and the regulation of body weight in mammals. *Nature* 1998;**395**:763-70.
- 38 **Woods S**, Seeley R, Porte D, *et al*. Signals that regulate food intake and energy homeostasis. *Science* 1998;**280**:1378-83.
- 39 **Puigserver P**, Adelmant G, Wu Z, *et al*. Activation of PPARgamma coactivator-1 through transcription factor docking. *Science* 1999;**286**:1368-71.
- 40 **Elias C**, Aschkenasi C, Lee C, *et al*. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron* 1999;**23**:775-86.
- 41 **Wren A**, Seal L, Cohen M, *et al*. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001;**86**:5992.
- 42 **Ariyasu H**, Takaya K, Tagami T, *et al*. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab* 2001;**86**:4753-8.
- 43 **English P**, Ghatel M, Malik I, *et al*. Food fails to suppress ghrelin levels in obese humans. *J Clin Endocrinol Metab* 2002;**87**:2984.
- 44 **Bouchard C**, Perusse L. Genetic aspects of obesity. *Ann N Y Acad Sci* 1993;**699**:26-35.
- 45 **Bouchard C**, Tremblay A, Despres J, *et al*. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990;**322**:1477-82.
- 46 **Stunkard A**, Foch T, Hrubec Z. A twin study of human obesity. *J Am Med Assoc* 1986;**256**:51-4.
- 47 **Bouchard C**, Perusse L, Leblanc C, *et al*. Inheritance of the amount and distribution of body fat. *Int J Obes* 1988;**12**:205-15.
- 48 **Tambis K**, Mow T, Eaves L, *et al*. Genetic and environmental contributions to the variance of the body mass index in a Norwegian sample of first- and second-degree relatives. *Am J Hum Biol* 1991;**3**:257-67.
- 49 **Sorensen T**, Holst C, Stunkard A, *et al*. Correlations of body mass index of adult adoptees and their biological and adoptive relatives. *Int J Obes Relat Metab Disord* 1992;**16**:227-36.
- 50 **Chagnon Y**, Perusse L, Bouchard C. Familial aggregation of obesity, candidate genes and quantitative trait loci. *Curr Opin Lipidol* 1997;**8**:205-11.
- 51 **Chagnon Y**, Chung W, Perusse L, *et al*. Linkages and associations between the leptin receptor (LEPR) gene and human body composition in the Quebec family study. *Int J Obes Relat Metab Disord* 1999;**23**:278-86.
- 52 **Segal K**, Lacayanga I, Dunaif A, *et al*. Impact of body fat mass and percent fat on metabolic rate and thermogenesis in men. *Am J Physiol* 1989;**256**:E573-9.
- 53 **Segal K**, Gutin B, Nyman A, *et al*. Thermic effect of food at rest, during exercise, and after exercise in lean and obese men of similar body weight. *J Clin Invest* 1985;**76**:1107-12.
- 54 **Zurlo F**, Lillioja S, Esposito-Del Puente A, *et al*. Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. *Am J Physiol* 1990;**259**:E650-7.
- 55 **Montague C**, Farooqi I, Whitehead J, *et al*. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997;**387**:903-8.
- 56 **Strobel A**, Issat T, Camoin L, *et al*. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat Genet* 1998;**18**:213-15.
- 57 **Ozata M**, Ozdemir I, Licinio J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. *J Clin Endocrinol Metab* 1999;**84**:3686-95.
- 58 **Clement K**, Vaisse C, Lahlou N, *et al*. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998;**392**:398-401.
- 59 **Jackson R**, Creemers J, Ohagi S, *et al*. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet* 1997;**16**:303-6.
- 60 **Krude H**, Biebermann H, Luck W, *et al*. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 1998;**19**:155-7.
- 61 **Ristow M**, Muller-Wieland D, Pfeiffer A, *et al*. Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. *N Engl J Med* 1998;**339**:953-9.
- 62 **Dittrich B**, Robinson W, Knoblauch H, *et al*. Molecular diagnosis of the Prader-Willi and Angelman syndromes by detection of parent-of-origin-specific DNA methylation in 15q11-13. *Hum Genet* 1992;**90**:301-5.
- 63 **Gortmaker S**, Must A, Sobol A, *et al*. Television viewing as a cause of increasing obesity among children in the United States, 1986-1990. *Arch Pediatr Adolesc Med* 1996;**150**:356-62.
- 64 **Maffeis C**, Zaffanello M, Schutz Y. Relationship between physical inactivity and adiposity in prepubertal boys. *J Pediatr* 1997;**131**:288-92.
- 65 **Bray G**, Popkin B. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998;**68**:1157-73.
- 66 **Ernst N**, Sempos C, Briefel R, *et al*. Consistency between US dietary fat intake and serum total cholesterol concentrations: the National Health and Nutrition Examination Surveys. *Am J Clin Nutr* 1997;**66**:965S-72S.
- 67 **Prentice A**, Jebbs S. Obesity in Britain: gluttony or sloth? *BMJ* 1995;**311**:437-9.
- 68 **Pijil H**, Meinders E. Bodyweight change as an adverse effect of drug treatment: mechanisms and management. *Drug Safe* 1996;**14**:329-42.
- 69 **Bingham S**. The dietary assessment of individuals; methods, accuracy, new techniques and recommendations. *Nutr Abstr Rev* 1987;**57**:705-42.
- 70 **Expert Panel**. *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report*. Bethesda, MD: National Institutes of Health, National, Heart, Lung, and Blood Institute, Public Health Service, US Department of Health and Human Services, 1998.
- 71 **Golay A**, Allaz A, Morel Y, *et al*. Similar weight loss with low- or high-carbohydrate diets. *Am J Clin Nutr* 1996;**63**:174-8.
- 72 **Roust L**, Hammel K, Jensen M. Effects of isoenergetic, low-fat diets on energy metabolism in lean and obese women. *Am J Clin Nutr* 1994;**60**:470-5.
- 73 **Peterson C**, Jovanovic-Peterson L. Randomised crossover study of 40% vs. 55% carbohydrate weight loss strategies in women with previous gestational diabetes mellitus and non-diabetic women of 130-200% ideal body weight. *J Am Coll Nutr* 1995;**14**:369-75.
- 74 **Hammer R**, Barrier C, Roundy E, *et al*. Calorie-restricted low-fat diet and exercise in obese women. *Am J Clin Nutr* 1989;**49**:77-85.
- 75 **Jeffery R**, Hellerstedt W, French S, *et al*. A randomised controlled trial of counselling for fat restriction versus calorie restriction in the treatment of obesity. *Int J Obes Relat Metab Disord* 1995;**19**:132-7.
- 76 **Schlundt D**, Hill J, Pope-Cordle J, *et al*. Randomised evaluation of a low fat ad libitum carbohydrate diet for weight reduction. *Int J Obes Relat Metab Disord* 1993;**17**:623-9.
- 77 **Shah M**, McGovern P, French S, *et al*. Comparison of a low-fat, ad libitum complex-carbohydrate diet with low-energy diet in moderately obese women. *Am J Clin Nutr* 1994;**59**:980-4.

- 78 **Miller W**, Lindeman A, Wallace J, *et al*. Diet composition, energy intake and exercise in relation to body fat in men and women. *Am J Clin Nutr* 1990;**52**:426–30.
- 79 **French A**, Jeffery R, Foster J, *et al*. Predictors of weight change over two years among a population of working adults: the health worker project. *Int J Obes Relat Metab Disord* 1994;**18**:145–54.
- 80 **Williams P**. Evidence for the incompatibility of age-neutral overweight and age-neutral physical activity standards from runners. *Am J Clin Nutr* 1997;**65**:1391–6.
- 81 **Lee C**, Blair S, Jackson A. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 1999;**69**:373–80.
- 82 **McGuire M**, Wing R, Klem M, *et al*. Long-term maintenance of weight loss: do people who lose weight through various weight loss methods use different behaviors to maintain their weight? *Int J Obes Relat Metab Disord* 1998;**22**:572–7.
- 83 **Wadden T**. Characteristics of successful weight loss maintainers. In: Allison DB, Pi-Suynier FX, eds. *Obesity treatment: establishing goals, improving outcomes, and reviewing the research agenda*. New York: Plenum Press, 1995:103–11.
- 84 **Wadden T**. New goals of obesity treatment: a healthier weight and other ideals. *Primary Psychiatry* 1998;**5**:45–54.
- 85 **Perri M**, McAllister D, Gange J, *et al*. Effects of four maintenance programs on the long-term management of obesity. *J Consult Clin Psychol* 1988;**56**:529–34.
- 86 **Wadden T**, Foster G, Letizia K. One-year behavioural treatment of obesity: comparison of moderate and severe calorie restriction and the effects of weight maintenance therapy. *J Consult Clin Psychol* 1994;**62**:165–71.
- 87 *Clinical management of overweight and obese patients*. A report of the Royal College of Physicians. London: Royal College of Physicians, 1998.
- 88 **Hill J**, Hauptman J, Anderson J, *et al*. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* 1999;**69**:1108–16.
- 89 **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**:167–72.
- 90 **Davidson M**, Hauptman J, DiGirolamo M, *et al*. Long-term weight control and risk factor reduction in obese subjects treated with orlistat, a lipase inhibitor. *JAMA* 1998;**281**:235–42.
- 91 **Hollander P**, Elbein S, Hirsch I, *et al*. Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomised double-blind study. *Diabetes Care* 1998;**21**:1288–94.
- 92 **Hansen D**, Toubro S, Stock M, *et al*. Thermogenic effects of sibutramine in humans. *Am J Clin Nutr* 1998;**68**:1180–6.
- 93 **Bray G**, Blackburn G, Ferguson J, *et al*. Sibutramine produces dose-related weight loss. *Obes Res* 1996;**4**:263–70.
- 94 **James W**, 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**:2119–25.
- 95 **Smith J**, Goulder M. Randomised placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. *J Fam Pract* 2001;**50**:505–12.
- 96 **Fanghanel G**, Cortinas L, Sanchez-Reyes L, *et al*. A clinical trial of the use of sibutramine for the treatment of patients suffering essential obesity. *Int J Obes Relat Metab Disord* 2000;**24**:144–50.
- 97 **Fujioka K**, Seaton T, Rowe E, *et al*. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2000;**2**:175–87.
- 98 **Ryan D**. Use of sibutramine and other noradrenergic and serotonergic drugs in the management of obesity. *Endocrine* 2000;**13**:193–9.
- 99 **Cook N**, Cohen J, Hebert P, *et al*. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med* 1995;**155**:701–9.
- 100 **Hall J**, Waits J, O'Brien P, *et al*. Gastric surgery for morbid obesity. The Adelaide study. *Ann Surg* 1990;**211**:419–27.

New JCP online submission and review system

We are pleased to inform authors and reviewers of the new online submission and review system at JCP. Developed by High-Wire Press (CA, USA), Bench Press is a fully integrated electronic system that utilises the web to allow rapid and efficient submission of manuscripts. It also allows the peer review process to be conducted entirely online. We are one of the first journals in the BMJ Special Journals group to go online in this way. The aim, apart from saving trees, is to speed up the often frustratingly slow process (for both authors and editors) from submission to publication. Many reviewers might appreciate this too. Authors may submit their manuscript in any standard word processing software. Acceptable standard graphic formats include: jpeg, tiff, gif, and eps. The text and graphic files are automatically converted to PDF for ease of distribution and reviewing purposes. Authors are asked to approve their submission before it formally enters the reviewing process. On approval by the authors, the submission is passed to the editor and/or reviewers via the web. All transactions are secure.

To access the system click on "SUBMIT YOUR MANUSCRIPT HERE" on the JCP homepage: [HYPERLINK http://www.jclinpath.com](http://www.jclinpath.com), or you can access Bench Press directly at [HYPERLINK http://submit-jcp.bmjournals.com](http://submit-jcp.bmjournals.com).

We are very excited with this new development and would encourage authors and reviewers to use the online system whenever possible. As editors, we will use it all the time, the up side being lack of need to travel to the editorial office to deal with papers, the down side having no more excuses to postpone decisions on papers because we are "at a meeting"!

The system is very easy to use and should be a big improvement on the current peer review process. Full instructions can be found on Bench Press <http://submit-jcp.bmjournals.com> and JCP online at <http://www.jclinpath.com>. Please contact Natalie Davies, Project Manager, [HYPERLINK mailto:ndavies@bmjgroup.com](mailto:ndavies@bmjgroup.com) for any further information.

H Holzel, P van Diest