INVITED ARTICLE

CURRENT MANAGEMENT OF OBESITY

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ABSTRACT

Obesity is common and its prevalence is rising. In Singapore, a national health survey in 1992 showed that 5% of the adult population were obese and 21% were overweight. Obesity causes much morbidity and mortality and treatment is desirable. The majority of obese patients have no known cause but it is essential to exclude any underlying cause before treatment. Antiobesity drugs should be used as an adjunct to an adequate programme of dietary restriction, exercise and behavior modification. Serotonergic drugs and adrenergic agents are available in the treatment of obesity. The short-term efficacy and safety of antiobesity drugs such as fenfluramine and d-fenfluramine are proven. The long-term use of antiobesity drugs used singly or in combination remains to be established. Many peptides (cholecystokinin, glucagon, bombesin, neurotensin, etc) with weight reduction properties are undergoing extensive studies: their clinical applications are experimental. The treatment of obesity is difficult and frustrating and antiobesity drugs have an established short-term role. In morbid obesity where the life of the patient is in danger, surgery such as gastric plication may be life-saving. The recent discovery of leptin (1994) and neuropeptide Y (1995) are important breakthrough in obesity research; hopefully further research may produce more effective treatment of obesity in man.

Keywords: *obesity, management, antiobesity drugs, aetiology, leptin, neuropeptide Y*

SINGAPORE MED J 1996; Vol 37: 299-303

INTRODUCTION

The term 'obesity' implies an excess of adipose tissue (fat) and excess adiposity is a health risk[1,2]. In most cases it develops in the absence of any underlying disease process. It is always due to greater calorie intake than is expended; the mystery lies in the cause of the energy imbalance[2]. Recently there has been a tremendous surge of interest in understanding the mechanisms controlling energy homeostasis following the identification of the ob gene and its protein product (termed "leptin' from the Greek word "leptos", meaning thin) by Zhang, Proenca, Maffei et al in 1994[3].

DEFINITIONS OF OBESITY

All definitions of obesity are arbitary because the distribution of weight in the population is a curve; the division between the obese and non-obese groups is not clearcut. Many methods for measuring the fat content of the body directly are available: densitometry, estimates of total body water or potassium, neutron activation techniques, computed tomographic (CT) and magnetic resonance imaging (MRI) scans, electrical methods measuring impedance and conductivity, etc[2]. The gold standard for measuring body fat is densitometry; it involves weighing the subject in air and totally immersed in water. This method is cumbersome, tedious and time consuming and is not practical for clinical practice.

In practice, indirect methods for estimating body fat are used: skinfold measurements, weight/height ratios, waist/hip ratios, standard tables, actuarial data etc. The most widely used measurement in clinical practice is the Body Mass Index (BMI); defined as the ratio of the body weight (in kilograms) divided by the square of the height (in metres). In the adult, the normal range of the BMI is about 20-25; a BMI of 25.1 to 29.9 is overweight and a BMI of 30 and above is obese.

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All fat is not good but some are worse. In recent years, a large number of studies showed that the complications of obesity correlate with abdominal fat (android, central, or beer belly obesity) and less with lower body fat (gynaecoid obesity)[4]. A waist/hip ratio of greater than 0.72 is considered abnormal; complications rates increase substantially at ratios higher than 1.0 for men and 0.9 for women[5].

PREVALENCE OF OBESITY

As society becomes more developed and affluent, the prevalence of obesity increases. In Singapore, a national health survey (1992)[6] of the adult population showed that 5% of Singaporeans were obese (Body Mass Index or BMI $\geq$ 30) and 21% were overweight (25$\leq$ BMI < 30). A higher proportion of men (23%) were overweight compared with women (19%) whereas more women (6%) than men (4%) were obese. Among men, Indians had the highest proportion of obese persons (10%), followed by Malays (6%) and Chinese (3%). Among women, Malays had the highest proportion of obese persons (17%), followed by Indians (13%) and Chinese (4%)[6]. In contrast, in the USA 20%-30% of adult men and 30%-40% of adult women are obese[1].

OBESITY IS A HEALTH RISK AND REQUIRES TREATMENT

Obesity is a health risk and even mild obesity increases the risk of premature death, diabetes mellitus, hypertension, hyperlipidaemia, atherosclerosis, coronary artery disease, gout, gall bladder disease, respiratory disease, arthritis and certain types of cancer[1,7]. Obesity is a chronic disease and a major health problem[8].

A further reason to treat obesity is that it is often not a desirable aesthetic, social and cultural trait.

SECONDARY OBESITY

Almost every obese patient believes that there is an underlying "glandular" disorder: hence, obese patients are often referred to the endocrinologist[2]. In fact, secondary obesities are rare; in our Obesity Clinic about 5%-10% of the patients have an underlying cause. In adults, hypothyroidism, Cushing's syndrome, hypogonadism, pituitary disorders, depression, insulinoma, etc have to be excluded. In children hypothalamic

lesions (craniopharyngioma, other tumours, infections, trauma, etc) are the commonest. Obesity is present in many genetic syndromes (Prader -Willi, Alstrom, Laurence - Moon - Biedl, Cohen, Blount etc)[1,2].

MANAGEMENT OF OBESITY

A team approach is required for the successful management of obesity. The physician/endocrinologist requires the help of the dietician, behavioural therapist/psychiatrist, exercise therapist, surgeon, etc. Managing an obese patient often requires the full cooperation of the family and often it involves managing the whole family as well.

An underlying cause of the obesity has to be carefully excluded; although secondary obesity is rare, the differential diagnosis is very long (see above).

The complications and associated disorders of obesity (diabetes mellitus, hypertension, ischaemic heart disease, oesteoarthritis, sleep-apnoea syndrome and other respiratory disorders, etc) require evaluation; their presence would indicate a more aggressive approach to the treatment of obesity.

Diet

Caloric restriction is the cornerstone of weight reduction. If energy intake is less than energy expenditure, weight loss will occur. Any adult truly eating 1,000 calories or less daily will lose weight.

A dietician is required to educate the patient and family on the most appropriate diet for the patient to lose weight. Dietary restriction can range from near total starvation to mild caloric deprivation. Schemes for weight reduction have become profitable business and there are as many diets as there are therapists. Each proponent claims that the presence or absence of certain foodstuffs is desirable for more effective weight loss!

Very low calorie diet requires close medical supervision to ensure adequate electrolytes, protein, vitamins and fluid intake. Such diet can rarely be maintained and a more realistic caloric deprivation is often better.

The major problem in the treatment of obesity is not weight reduction but maintenance of the reduced weight. Provided the dietician/therapist works hard and long enough, most motivated patients can eventually lose weight. Unfortunately, only the rare patient maintains the weight loss on a long-term basis. Obesity is an eating disorder and the underlying aetiology is not reversed by limited food intake[1,2].

Behavioural therapy

Behavioural therapy is based on the assumption that weight loss can be produced by changing an individual's diet and/or exercise behaviours. To change these behaviours, it is necessary to change the environmental antecedents and consequences that control them. Behavioural therapy programmes include strategies such as self-monitoring to help patients learn about their eating habits and exercise behaviours and stimulus control, preplanning, cognitive restructuring and self-reinforcement techniques to help patients change their environment[9].

Brownell and Jeffrey (1989)[10] reviewed the results of behavioural weight-control studies published from 1974 to 1986; they reported weight losses achieved in behavioural interventions had improved markedly over time, increasing from a mean weight loss of 3.86 kg in 1974 to a mean weight loss of 10.0 kg in 1986.

Behavioural therapist may be either a psychiatrist or a psychologist.

Exercise

Exercise has a place in any weight reduction programme. In theory the utilisation of calories should be as valuable as the restriction of caloric intake. Exercise has to be fairly strenuous and regular to produce significant caloric expenditure. For example if one expends 5 calories per minute on a brisk walk it would require a full hour to lose 300 calories; over a 4-month period a weight loss of 4.5 kg would be achieved[1,2].

Incorporation of regular exercise into overall weight reduction programme improves the chances that weight loss will be maintained.

For each obese patient, the exercise programme should be pragmatic and realistic.

Antiobesity drugs

The results of longer-term studies of weight reduction emphasize the difficutly of using nutrition and behaviour therapy (even when combined with an exercise programme) to maintain weight loss over an extended period for many patients and provide a rationale for the use of pharmacological agents to help patients achieve and maintain desirable weight[11]. Pharmacological agents commonly available for the treatment of obese patients are listed in Table I.

Table I – Pharmacological agents available for the treatment of obese patients

Group	Drug	Trade Name	Daily Dosage in mg
Adrenergic agents	Benzphetamine	Didrex	25 - 150
	Diethylpropion	Tenuate	75
	Mazindol	Mazanor	1 - 3
	Phendimetrazine	Anorex	20 - 210
	Phentermine	Duromine/Ionamin/Panbesy	15 - 37.5
	Phenylpropanolamine	Dexatrim	25 - 75
Serotonergic agents	Fenfluramine	Ponderax	60
	Dexfenfluramine	Adifax	30
	Fluoxetine	Prozac	60
Digestion/ absorption inhibitor	Acarbose	Glucobay	300

Adrenergic agents

The first adrenergic (noradrenergic) agent used to treat obesity was amphetamine; its use was abandoned due to its addictive tendency. The use of adrenergic drugs to treat obesity has been reviewed recently by Bray (1993)[12] and Silverstone (1993)[13]. In Singapore, phentermine is available under the trade names of Duromine, Ionamin and Panbesy.

The Food and Drug Administration in the USA analysed the effectiveness of amphetamine-like drugs in over 200 studies involving 4,543 subjects treated from 4 to 20 weeks (Scoville, 1975)[14]. After 4 weeks of therapy, the dropout rate for patients receiving the active drug was 24.3% compared with 18.5% for those receiving placebo; 44% of patients receiving the active drug lost 0.45 kg or more per week compared with 26% of patients receiving placebo. After combining data for all patients at their final weight, Scoville (1975) found that patients taking the active drug lost about 0.23 kg per week, more than did those taking placebo. He noted that "because drugs do not provide complete cures, however, is no reason to reject them out of hand; partial success is clearly better than failure"[14].

In contrast to the amphetamine-like group of drugs that act centrally, there are many peripheral acting beta-adrenergic agents that also have antiobesity properties. The results of several studies on these experimental agents were reported in a recent symposium (Bray, York and DeLany, 1992)[15].

Serotonergic agents

In this group, fenfluramine (Ponderax) and dexfenfluramine

(Adifax) are widely used. The actions of these serotonergic drugs have been reviewed by Silverstone (1993)[13] and Bray (1993)[12]. Several long-term studies with fenfluramine and dexfenfluramine have been reported[16-18]. Among patients who remain in the trials, fenfluramine is more effective than placebo in producing and maintaining weight loss for periods up to one year.

Further, dexfenfluramine improves glucose control independently of weight loss in obese diabetic patients[19,20]. Arterial blood pressure is also reduced, possibly mediated by a decrease in noradrenergic activity[21].

Fluoxetine (Prozac) is an inhibitor of serotonin uptake and is marketed as an antidepressant; it also produces weight loss. Over a short period fluoxetine causes weight loss but for more than 16 to 20 weeks, most began to gain weight[22].

Digestion and absorption inhibitors

Acarbose (Glucobay) is a disaccharidase inhibitor and is marketed as a hypoglycaemic drug for the treatment of obese non-insulin-dependent diabetics. Its use as an antiobesity drug is limited as it may cause malabsorption[19]. Initial studies in man with the novel gastrointestinal lipase inhibitor, tetrahydrolipstatin, have also been reported[23].

PEPTIDES AND OTHER AGENTS

Ephedrine, a thermogenic agent, in combination with caffeine and/or xanthine and/or aspirin promotes short and long-term weight loss and deserves further studies[24].

Many peptides (cholecystokinin and its analogues, anorectin, enterostatin, neurotensin, bombesin, etc) have been reported to inhibit food intake and hence have potential as an antiobesity agent. These studies are experimental and have as yet no established clinical value[25,26].

Other new preparations being developed as antiobesity drug include agents that inhibit gastric emptying, stimulate lipid oxidation, nonabsorbable fat and agents that increase thermogenesis[12].

Surgery

In severe obesity or morbid obesity (BMI greater than 40) when all attempts at weight reduction have failed, surgery is the only option left. Surgery is justified when the morbid obesity endangers the patient's life (such as when respiratory and/or cardiac failure are present). Earlier surgical procedures involve some form of jejunoileal bypass; weight loss was very successful and sustained; unfortunately complications were common and even fatal. Such procedures have since been abandoned.

Gastric bypass and gastric plication are the usual surgical procedures to treat severe obesity. Such procedures are successful but patients often regain some weight over time. Operative mortality is under 1% but iron, Vitamin B_{12} and thiamine deficiencies may be late complications[27].

Other procedures include jaw wiring and placement of gastric balloons. Liposuction is useful for only cosmetic purposes[2].

Plastic surgery to correct folds of loose skin is usually required after weight loss has been achieved through gastric bypass or plication.

DISCUSSION

Obesity refers to an excess of body fat. In most cases, it develops in the absence of any underlying disease process; it is rarely due to another primary disorder (such as hypothyroidism, Cushing's syndrome, hypogonadism etc). It is always due to greater energy intake than is expended. The mystery lies in the cause of energy imbalance[2].

Recently, there has been a tremendous surge of interest in understanding the mechanisms controlling energy homeostasis catalysed by the discovery of the ob gene and its product in 1994 by Zhang et al[3]. The ob protein, termed "leptin" from the Greek word "leptos" (meaning thin), is produced in adipose tissue and is thought to act as an afferent satiety signal in a feedback loop that putatively affects the appetite and satiety centres of the brain. The ultimate effect of this loop is to regulate body fat mass[3,28]. In ob/ob mice, which are markedly hyperphagic and obese, the ob gene is mutated and no leptin is produced; when given leptin, they stop eating and lose weight.

Suddenly leptin has become a new "fat actor" (Hamilton, 1996)[29] and spawn hope that it may become the ideal pharmacologic agent to treat obese patients. Unfortunately the obese patient does not resemble the obese ob/ob mouse. Considine et al (1996)[30] found that serum leptin concentrations and the levels of ob messenger RNA (mRNA) in adipocytes in obese humans are elevated and there is a strong positive correlation between serum leptin and the percentage of body fat, the body mass index, and basal serum insulin concentrations. These results suggest that the adipocytes of humans produce leptin when the adipose mass increases and that there is resistance to the action of leptin, so that the increase in adipose-tissue mass is maintained. The problem in the obese human subjects, therefore, is decreased sensitivity to leptin, but the nature and actions of the effector system for leptin are not known.

Leptin could be a satiety hormone. A loop system may be envisioned in which food intake could trigger insulin and glucocorticoid output, thereby causing fat deposition and then secretion of leptin, leading to satiety (Rohner-Jeanrenaud, Jeanrenaud, 1996)[31]. As food intake is controlled by the brain (hypothalamus), the afferent loop for food intake could be the appetite-stimulating (orexigenic) hypothalamic peptide neuropeptide Y. In animal models of obesity, hypothalamic concentrations of neuropeptide Y are high and intracerebroventricular infusions of neuropeptide Y cause obesity in normal rats[31]. Intracerebroventricular infusions of neuropeptide Y also cause an increase in adipose tissue leptin mRNA levels. Thus, high neuropeptide Y concentrations in the brain cause many features of obesity syndromes.

The results of Considine et al (1996)[30] suggest that in obese patients, a fundamental mechanism of obesity is insensitivity to the action of leptin, presumably in the hypothalamus. Whether the insensitivity to leptin is due to mutations of the gene for leptin receptors in the brain, post-receptor abnormalities in leptin signal transduction or other abnormalities in hypothalamic functions is unknown. Despite these uncertainties, the discovery of leptin by Zhang et al (1994)[3] represents a remarkable breakthrough in the understanding of the pathophysiology of obesity. Normal body-fat mass may be maintained by means of a central-peripheral loop system which is dysregulated in obese humans (Rohner-Jeanrenaud, Jeanrenaud, 1996)[28].

It is interesting to note that supplementing the diet of ob/ob female rats with leptin not only reduces fat mass, but also restores fertility[29].

Todate, research into leptin has not produced any practical application for the treatment of obesity in man; but it is not impossible that the frantic pace of research of leptin and related substances may in the near future produce an analogue of leptin or neuropeptide Y that can be used to treat obesity in man.

At present, the management of obesity (idiopathic) requires great patience on the part of the physician and patient. A team approach is required to achieve good results: the physician requires the help of the dietician, behaviour therapist/psychiatrist, exercise therapist, surgeon, plastic surgeon, etc.

Drugs should be considered as only one component of a weight reduction programme. At present, the clinician has the choice of one of the adrenergic drugs (such as diethylpropion,

mazinol, phentermine, etc) or one of the serotoninergic agents (fenfluramine, dexfenfluramine or fluoxetine). For the patient with a history of depression, one of the adrenergic drugs is the first choice, while for the anxious patient, a serotoninergic drug is preferable[13]. For the obese patient who is also diabetic and/or hypertensive, dexfenfluramine is preferable as it also improves glucose tolerance and lowers the blood pressure. The obese patient with non insulin-dependent diabetes may also benefit from a trial of Acarbose (Glucobay), a disaccharidase inhibitor. The obese non-insulin-dependent diabetic may also benefit from treatment with metformin; in 7 of 9 studies, metformin caused a significant weight loss; overall there was a 4kg weight loss[32]. Over indulgences leading to weight gain is not uncommon in depression. Treatment of the obese depressed patient with fluoxetine (an antidepressant) may lead to weight loss as well.

The incidence of the side effects of antiobesity drugs is modest and there is little evidence that such drugs are being abused by the target population, ie patients who are obese. There is no evidence of addiction potential. Intermittent drug treatment of obesity is not recommended because the incidence of side effects appears to be greatest when drugs are either started or stopped. Thus the overall incidence of side effects may increase with intermittent therapy[8]. Anecdotal reports of pulmonary disease in humans and in neurotoxicity in squirrel monkeys during fenfluramine treatment mandate caution in its long-term use[8].

Goldstein and Potvin (1994)[11] reviewed 20 weight reduction studies of the effect of greater than 6 months of antiobesity drugs on weight loss and its maintenance to determine the benefits of long-term treatment. The agents alone or in combination with adjunctive therapy were significantly more effective than placebo or diet therapy alone in producing weight loss. Across the studies, the greatest amount of weight loss generally occurred at about 6 months of treatment. In general, the adverse effects of the antiobesity drugs were described as mild or tolerable.

As obesity prevalence is rising and antiobesity drugs cause modest weight loss and slowly, many slimming centres, weight loss nutrients/diets and across-the-counter preparation have their ardent advocates. It is estimated that the slimming industry in the USA is worth about US$33 billion dollars per year[29]. Many commercial preparations (such as Carnitine fat burner, Burn 2 Trim, MinusFat, Success Herbal teas and pills, etc) are available: their efficacy remains unproven but they do sell. Many slimming centres (such as Weight Watchers International) are also popular.

In morbid obesity, when the life of the patient is endangered surgery by gastroplasty or gastric plication may be life-saving.

SUMMARY

Obesity is common and its prevalence is rising. In Singapore, a national health survey in 1992 showed that 5% of the adult population were obese and 21% were overweight. Obesity causes much morbidity and mortality and treatment is desirable. The majority of obese patients have no known cause but it is essential to exclude any underlying cause before treatment. Antiobesity drugs should only be used as an adjunct to an adequate programme of dietary restriction, exercise and behavioral modification. Serotonergic drugs and adrenergic agents are available in the treatment of obesity. The short-term efficacy and safety of antiobesity drugs such as fenfluramine and d-fenfluramine are proven. The long-term use of antiobesity drugs used singly or in combination remains to be established. Digestion and absorption inhibitors such as saacharidase and lipase inhibitors may prove to be useful antiobesity agents. Many peptides with weight reduction properties are undergoing extensive studies: their clinical applications are experimental. The treatment of obesity is difficult and frustrating and antiobesity drugs have an established short-term role. In morbid obesity, where the life of the obese patient is in danger, surgery (such as gastric plication) may be life-saving.

The recent discovery of leptin (1994) and neuropeptide Y (1995) are important breakthrough in the study of energy homeostasis in obesity. Hopefully, further research may lead to the availability of more effective preparations for the treatment of obesity in man.

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