Management of obesity in non-insulin-dependent diabetes mellitus

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Obesity is common in non-insulin-dependent diabetes mellitus (NIDDM) patients; in Singapore in a cohort of 314 diabetics, 44.3% were overweight. Management of obesity in diabetics differs from that in non-diabetics in that it is more urgent; weight maintenance is more difficult and hypoglycaemic medication may cause weight changes. However, like in the non-diabetic, management of obesity in the diabetic requires a pragmatic and realistic approach. A team approach is required: the help of a nurse educator, a dietitian, behaviour modification therapist, exercise therapist and others are required. A detailed history, careful physical examination and relevant investigations are required to assess the severity of the diabetic state and to exclude an occasional underlying cause of the obesity in the obese NIDDM patient. Weight loss is urgent in the obese NIDDM patient, especially for those with android obesity. There must be a reduction in energy intake. Weight loss leads to an improvement in glucose tolerance and in insulin sensitivity, as well as to a reduction in lipid levels and to a fall in blood pressure in the hypertensive. Exercise is of limited short-term value measured in terms of weight reduction, except in the younger obese NIDDM patient; but it does allow improvement in overall metabolic control and, long-term, is critical for preferred weight maintenance. The biguanide, Metformin, is the hypoglycaemic drug of choice as it leads to consistent weight reduction. The sulphonylureas may cause weight gain. Insulin should be avoided where possible as it causes further weight gain. Other hypoglycaemic agents include Glucobay (alpha-glucosidase inhibitor) and Troglitazone (insulin sensitizer) which do not alter the weight. Orlistat (lipase inhibitor) is promising as it causes reduction of weight, blood glucose and lipid levels. Anti-obesity drugs (noradrenergic and serotonergic agents) have modest effects on weight reduction in the obese NIDDM patient; a widely-used preparation, Dexfenfluramine (Adifax), has been withdrawn because of side-effects. Surgery such as gastric plication is the last resort in treating the morbidly obese NIDDM patient. Against this background, the institution of life-long food and exercise habits which favour health, body composition and fat distribution are paramount in the prevention and minimization of expression of NIDDM. The discovery of leptin in 1994 has led to intense research into energy homeostasis in obesity; hopefully this will lead to better treatment of obesity in diabetics and non-diabetics.

Key words: non-insulin-dependent diabetes mellitus, obesity, hypoglycaemic medication, Singapore.

Introduction

The term 'obesity' implies an excess of adipose tissue and excess adiposity is a health risk. As a society becomes more developed and affluent, the prevalence of obesity increases.[1] In Singapore, a 1992 national health survey of the adult population showed that 5% of Singaporeans were obese (body mass index (BMI) ≥ 30) and 21% were overweight ($25 \leq$ BMI < 30).[2] 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 prevalence of obesity (10%), followed by Malays (6%) and Chinese (3%). In women, Malays had the highest prevalence of obesity (17%), followed by Indians (13%) and Chinese (4%). In comparison, in the USA 20–30% of adult men and 30–40% of adult women are obese.[3]

Obesity is a health risk

Obesity is a health risk and even mild obesity increases the risk of premature death, diabetes mellitus, hypertension, hyperlipidaemia, atherosclerosis, coronary heart disease, gout, gall bladder disease, respiratory disease, arthritis and certain types of cancer.[3] Obesity is a chronic disease and a major health problem.[3] A further reason to treat obesity is that it is often not a desirable aesthetic, social and cultural trait.

In recent years it has been increasingly recognized that fat distribution is as important as the amount of fat carried. Fat distributed around the waist and abdomen (android type; apple-shaped) is, in terms of morbidity, more significant than fat around the hip (gynaecoid-type; pear-shaped).

Obesity and non-insulin-dependent diabetes mellitus

The association of obesity with non-insulin-dependent diabetes mellitus (NIDDM) is well established and well known. In Singapore in a cohort of 314 diabetics, 44.3% were overweight.[4] As many as 90% of NIDDM patients are overweight or obese.[5] While the mechanisms underlying the relationship between obesity and NIDDM remain to be identified, there is undoubtedly a strong association between the presence of obesity and the development of NIDDM. Cross-sectional studies showed that the largest environmental

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influence on the prevalence of diabetes in a population was its degree of obesity.[6] In the USA, the prevalence of diabetes in adults is 3.8 times higher in the overweight compared with the normal weight.[7]

The Nurses' Health Study found that the risk of developing diabetes increases from a BMI level as low as 22.[8] An increased risk of diabetes with increasing weight has been shown in prospective studies in Norway, Sweden, Israel and the USA.[5]

The development of NIDDM is also positively associated with the duration of obesity and weight gain after 18 years of age. Several studies have shown increased intra-abdominal fat in NIDDM patients; central distribution of body fat is a major risk factor of NIDDM, independent of the absolute degree of obesity.[8]

Effects of weight loss in non-insulin-dependent diabetes mellitus

The health benefits of weight loss in NIDDM have long been recognised. Weight loss in the obese NIDDM patient leads to reduction of the fasting and postprandial blood glucose and a fall in glycosylated haemoglobin. In the UK Prospective Diabetes Study of 3044 newly diagnosed NIDDM patients (1990), the reduction in fasting hyperglycaemia was greatest in patients who lost the most weight.[9]

Weight loss in the NIDDM patient leads to a reduction in insulin resistance and fasting insulin level; furthermore, it improves coexisting disorders such as hypertension and dyslipidaemia.[5] Weight loss in the obese NIDDM patient leads to a reduction of abdominal obesity and a fall in the waist/hip ratio.[10]

Almost all studies show that weight loss in NIDDM leads to reduction or elimination of the need for hypoglycaemic agents and improvement in associated disorders such as hypertension and dyslipidaemia. Further weight loss in NIDDM patients may improve morbidity and mortality; the reduction in the economic burden is also significant.[5]

Management of obesity in non-insulin-dependent diabetes mellitus

The beneficial effects of weight loss in the obese patient with NIDDM are clear-cut and unequivocal; all physicians agree that the first and most important step in managing the overweight NIDDM patient is for the patient to lose weight and maintain the loss.

Management of obesity differs from that in non-diabetics in that it is more urgent, weight maintenance is more difficult and hypoglycaemic medications may cause weight changes.

Like good glycaemic control, good weight control is hard to achieve and harder to maintain, but lasting weight reduction can improve or even 'cure' diabetes.[11]

The obese NIDDM patient may have a secondary cause of the obesity; although this is rare it has to be carefully excluded and the differential diagnosis is long. The complications of diabetes in the obese NIDDM patient have to be carefully assessed as they would influence the approach to the management of obesity in the patient.

Team approach

As in the non-diabetic, management of obesity in diabetics requires a pragmatic and realistic approach. A team approach is required to achieve satisfactory results: the physician requires the help of the dietitian, nurse educator, behavioural therapist, exercise therapist, surgeon etc. The physician usually does not have sufficient time or expertise and the help of the team is vital. Managing an obese NIDDM patient often requires the full co-operation of the family and often it involves managing the whole family as well.[12]

Diet

Energy restriction is the cornerstone of weight reduction. If energy intake is less than energy expenditure, weight loss will occur. An adult eating 1000 calories or less per day will lose weight.

Many varieties of diets have been advocated for the treatment of obesity in NIDDM; these have been reviewed in detail by Maggio and Pi-Sunyer.[5] Reports from various trials using a wide spectrum of diet have shown varying degrees of success. One of the few reports of long-term weight loss with diet is the Diabetes Treatment Study in 1986 in Northern Ireland, where 223 NIDDM patients recently diagnosed were placed on a 1450 calories per day diet for 6 months and seen monthly by physicians and a dietitian.[13] Energy intake was then increased to 2000 calories per day and the patients were seen every 3 months for up to 72 months. Average weight loss at 6 months was 9 kg and this was maintained for the 6-year study. The NIDDM could be managed by diet alone in 87% of the patients at 1 year and in 71% at 6 years. The success of the Diabetes Treatment Study has been attributed to constant and regular medical and dietary counselling and supervision.[13] In obese patients, diabetic and non-diabetic, successful weight loss with diet is often difficult to achieve and even more difficult to maintain.

For the obese NIDDM patient, the important thing is to eat less; 'it doesn't matter what you eat, so long as you don't eat it'.[11] The concept of eating less forms the basis of the very low energy diet (VLED) being advocated for the obese NIDDM patient. The energy intake varied from 400 to 1200 calories per day. A recent meta-analysis showed that obese NIDDM patients treated with VLED have generally been associated with large, significant losses of body weight and improvements in most major metabolic variables.[14] The long-term results of VLED remain to be studied.

Behavioural therapy

Behavioural therapy (BT) is based on the assumption that weight loss can be produced by changing an individual's diet and/or exercise behaviour. To change these behaviours it is necessary to change the environment 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. They also stimulate control, preplanning, cognitive restructuring and self-reinforcement techniques to help patients change their environment.[15]

In general, the rate of weight loss obtained with BT is only 0.4–0.5 kg per week. Wing in 1993 concluded that the degree of weight loss achieved and maintained in BT has increased as programmes have increased in length and have included additional components such as diet modification and exercise.[15]

In obese NIDDM patients, BT treatments have resulted in only modest weight loss, which in some cases has been associated with long-term improvement in glycaemic control. Behavioural therapy programmes have become more costly as they have increased in length.[5,15]

Exercise

In obese individuals, exercise may improve blood pressure, lipid and insulin levels and cardiopulmonary function even in the absence of weight loss. Exercise improves insulin sensitivity and acutely lowers blood glucose. Exercise may improve psychological well-being and self-esteem.

The effects of exercise on weight loss are generally modest: controlled studies of exercise have found weight loss of only 2–3 kg in those who exercise compared with the sedentary. When exercise is combined with diet, the average additional weight loss is only 1.8 kg beyond that observed with diet alone. Exercise is nevertheless considered a major determinant of long-term maintenance of weight loss.[16]

In NIDDM patients, regular exercise may have therapeutic effects on glycaemic control, cardiovascular health and psychological well-being.[5] For patients treated with oral antidiabetic drugs or insulin, exercise may require an adjustment of food intake or medication dosage. In some patients exercise may increase risk of cardiac events, injury and exacerbation of proliferative retinopathy. In general, obese NIDDM patients should be encouraged to exercise under medical supervision.

Anti-obesity drugs

The pharmacological agents available for the treatment of obese patients are shown in Table 1.

Most of the antiobesity drugs are nonadrenergic agents. Serotonergic agents (Fenfluramine and Dexfenfluramine) that were widely used were withdrawn from the market in 1997 because of possible serious side-effects.[1,12] In obese patients with depression, the antidepressant Fluoxetine (Prozac) causes short-term weight loss.

In the obese NIDDM patient, a relatively new drug available for the treatment of obesity and hyperglycaemia is Orlistat (a lipase inhibitor); it causes weight loss and improvement in the blood glucose profile.

A review by the National Task Force on the Prevention and Treatment of Obesity in the USA (1996) re-emphasised that pharmacological weight loss therapy should only be administered within a comprehensive treatment programme, that includes diet and exercise, to selected individuals for whom such therapy could improve health and reduce disease risk.[17] Weight loss of antiobesity drugs generally amount to 2–10 kg beyond the conventional weight-loss therapy alone and response is variable. Weight regain is common when drug therapy is discontinued.

In a recent review, Scheen concluded that anorectic drugs can play a useful role in the overall management of obesity provided it is recognized that the rationale of such treatment is to provide assistance to keeping to a restricted energy diet.[18]

Oral hypoglycaemic drugs and weight change

If after an adequate period (8–12 weeks) of energy restriction, exercise and in some cases use of antiobesity drug or drugs, the blood glucose and HbA1c levels in the obese NIDDM patient remain elevated, the use of an oral hypoglycaemic drug is the next step. The choice of such an oral hypoglycaemic drug is influenced by its effect on the patient's weight (Table 2).

The usual choice is the biguanide, Metformin. The efficacy of Metformin has been confirmed by the Multicentre Metformin Study Group in the USA.[19] A meta-analysis of trials between 1957 and 1994 has shown that Metformin is as effective as the Sulphonylureas with a fall of 1.2% in HbA1c for both drugs (12.5% fall from baseline). Metformin causes a net weight reduction of 5%; 4 kg weight reduction differential (–1.2 kg with Metformin vs. +2.8 kg with Sulphonylureas).[20]

Glucobay (Acarbose) is a alpha-glucosidase inhibitor. Nearly all studies have shown that it does not alter body

Table 1. Pharmacological agents available for the treatment of obese non-insulin-dependent diabetes mellitus patients

Group	Drug	Trade name	Daily dosage (mg)
A. Adrenergic agents	Benzphetamine	Didrex	25–150
	Diethylpropion	Tenuate	75
	Mazindol	Mazanor	1–3
	Phendimetrazine	Anorex	20–210
	Phentermine	Duromine/Ionamin/Panbesy	15–37.5
B. Serotonergic agents	Fenfluramine*	Ponderax	60
	Dexfenfluramine*	Adifax	30
	Fluoxetine	Prozac	60
C. Lipase inhibitor	Tetrahydrolipstatin	Orlistat	360

*Withdrawn in 1997 because of side-effects (i.e. pulmonary hypertension and valvular heart disease).

Table 2. Oral hypoglycaemic drugs and weight change

Group	Drug	Weight Change
A. Sulphonylurea	Tolbutamide, Glibenclamide etc.	Weight gain (common)
B. Biguanide	Metformin	Weight loss (usual)
C. Alpha-glucosidase inhibitor	Glucobay, Diastabol	Weight loss (initial) or no change
D. Lipase inhibitor	Orlistat	Weight loss (usual)
E. Thiazolidinedione (insulin sensitiser)	Troglitazone	Neutral

weight and may be beneficial on weight maintenance. It does not cause weight gain such as is often seen when NIDDM is treated with sulphonylurea or insulin. Acarbose has been advocated for the treatment of the elderly NIDDM patient.[21] Diastabol is another drug in the same class as Acarbose (Glucobay) (Table 2).

Orlistat, a lipase inhibitor, is a promising agent to treat the obese NIDDM patient; it promotes weight loss and improves the diabetic's control. In 230 obese NIDDM patients, Orlistat achieved consistently greater weight loss compared to placebo; at 12 months weight loss with Orlistat weight loss averaged 8.5 kg compared with 5.4 kg for placebo; further total and low-density lipoprotein (LDL) cholesterol fell significantly.[22]

Troglitazone is effective both as a monotherapy and in combination with sulphonylurea.[21] It is weight neutral and its potential remains to be proven. Troglitazone reduces insulin resistance in NIDDM; improves glycaemic control, reduces triglycerides and increases HDL cholesterol levels.[23]

In the obese NIDDM patient insulin should be avoided where possible as insulin promotes weight gain.

Bariatric surgery

In the morbidly obese (BMI ≥ 40) NIDDM patient where life is threatened by the obesity, surgery may be the last option.[3,12] Gastric bypass and gastric plication are the usual surgical procedures.

The available data, derived largely from non-controlled studies, indicate that gastric surgery may result in long-term weight loss and major improvements of glycaemic control.[3] There is a need for long-term clinical trials; one such ongoing trial is the Swedish Obese Subjects (SOS) Study.[5] This prospective controlled trial is designed to compare 10-year mortality and morbidity in 1000–4500 obese subjects treated by gastric surgery or conventional treatment.

The role of surgery in treating obesity in diabetics and non-diabetics remains unclear.[5,12]

Discussion

'Fatty bashing' is the licensed sport of the diabetic clinic. It is a simple way of shifting blame to our patients, while releasing the frustration behind that sympathetic smile and the thwarted urge to be good. Our moral censure will be all the more sincere if we have managed to avoid the personal stigma of obesity; thus, perhaps we should look a bit harder at ourselves before we sit in judgement on our patients.[11]

Perhaps the main reason why weight control in the obese (diabetic and non-diabetic) is hard to achieve and even harder to maintain is that the precise cause or causes of obesity are completely unknown. Against this background, tremendous hopes were aroused by the discovery in 1994 of the *ob* gene and its product by Zhang, Proenca, Maffei *et al.*[24] 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. In *ob/ob* mice, which are markedly hyperphagic and obese, the *ob* gene is mutated and no leptin is produced; when given leptin the mice stop eating and lose weight.

Suddenly leptin has become a new fat actor, spawning 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.* reported that serum leptin concentrations in adipocytes in obese humans were elevated and that there was a strong positive correlation between serum leptin and percentage of body fat, BMI and basal serum insulin concentrations.[25] These results suggest that the adipocytes of humans produce leptin when the adipose mass increases and there is resistance to the action of leptin, so that the increase in adipose tissue mass is maintained. The problem in obese humans is decreased sensitivity to leptin but the nature and actions of the effector system for leptin are not known.

In Singapore we found that the serum leptin in normal subjects is correlated to BMI; leptin in females tended to be higher than in males and there was little difference in leptin levels between the Chinese, Malays and Indians.[26] Serum leptin levels in diabetics were associated with BMI in males and females; female diabetics had a higher leptin level compared to males. Leptin concentration is related to insulin resistance in obese diabetics.[27] In Malaysia, leptin levels in insulin-dependent diabetes mellitus (IDDM) and NIDDM patients showed significant positive correlation with BMI; besides gender, circulatory insulin level is also an important factor in influencing leptin secretion.[28]

To date, research into leptin has not produced a breakthrough for the treatment of human obesity; however, 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.

At present the management of obesity in NIDDM patients requires great patience on the part of the physician and patient. A team approach is required to achieve satisfactory results: the diabetologist requires the help of the dietitian, nurse educator, behavioural therapist, exercise therapist, surgeon etc. Anti-obesity drugs should be considered as only one component of a weight reduction programme.

When an oral hypoglycaemic drug is required for the overweight NIDDM patient, Metformin is the drug of choice as it induces weight loss compared to the sulphonylureas.[19,20] Lipase inhibitor (such as Orlistat) improves glycaemic control with weight reduction. Alpha-glucosidase inhibitors (such as Acarbose or Diastabol) and Troglitazone improve glycaemic profiles without causing weight gain.[21]

New drugs for the treatment of obesity continue to be discovered. A third beta-adrenergic receptor has been reported and in rodents drugs targeted to this receptor prevent or correct obesity. In humans, treatment with a number of different selective beta-3-adrenoceptor agonists has yielded conflicting results.[29]

Until a breakthrough in obesity research is found, the treatment of obesity in the obese NIDDM patient remains slow and frustrating. It is important not to discourage our patients. Some weight loss is better than none and even modest weight loss is useful and desirable.

Conclusion

The management of obesity in diabetics differs from that in non-diabetics in that it is more urgent; weight maintenance is

more difficult and hypoglycaemic medication may cause weight changes. As in the non-diabetic, management of obesity in diabetics requires a pragmatic and realistic approach. A team approach is required: the help of the nurse educator, the dietitian, behaviour modification therapist, exercise therapist and others are required. Weight loss is an urgent need in the obese NIDDM patient, especially for those with android obesity. There must be a reduction in energy intake. Weight loss leads to an improvement in glucose tolerance and in insulin sensitivity, as well as to a reduction in lipid levels and to a fall in blood pressure in the hypertensive. Exercise is of limited short-term value, measured in terms of weight redution, except in the younger obese NIDDM patient; but it does allow improvement in overall metabolic control and, long-term, is critical for preferred weight maintenance. Metformin is the hypoglycaemic drug of choice as it leads to consistent weight reduction. The sulphonylureas may cause weight gain. Insulin should be avoided where possible as it causes further weight gain. Other hypoglycaemic agents include Glucobay (alpha-glucosidase inhibitor) and Troglitazone (insulin sensitizer), which do not alter the weight. Orlistat (lipase inhibitor) is promising as it causes reduction of weight, blood glucose and lipid levels. Anti-obesity drugs (noradrenergic and serotonergic agents) have modest effects on weight reduction in the obese NIDDM patient. Surgery such as gastric plication is the last resort in treating the morbidly obese NIDDM patient. The discovery of leptin in 1994 has led to intense research into energy homeostasis in obesity; hopefully this will lead to better treatment of the obese NIDDM patient. Against this background, the institution of life-long food and exercise habits which favour health, body composition and fat distribution are paramount in the prevention and minimization of expression of NIDDM.

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