

Obese Diabetic Patients: Impact of Different Management Modalities

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ABSTRACT

Type 2 diabetes is one of the major public health challenges in 21st century. Both environmental changes and genetics are attributed for increased risk of type 2 diabetes. Obesity is the most critical and modifiable risk factor and should be targeted for successful management of diabetes. This review article discusses three main approaches to manage obesity. Three management modalities considered are lifestyle modifications including dietary counseling, behavior therapy and physical activity/exercise, use of pharmaceutical agents, and bariatric surgery. In most patients, lifestyle interventions produce only modest weight loss and have a diminishing effect over time. If patients are unable to respond lifestyle intervention with a weight loss of 5-10%, adjunctive pharmacological treatment may be considered. A variety of pharmacological agents have been shown to induce weight loss and preserve weight loss for longer, as well as ameliorate cardiovascular risk factors. However, the long term health benefits and safety remain unclear and thus, long term studies powered to examine mortality and cardiovascular morbidity are required. Bariatric surgery is the ultimate treatment producing massive weight loss and resolution of type 2 diabetes in nearly 100% of patients. However this is applicable only for patients with significant obesity.

Successful treatment of most overweight and obese individuals will depend upon the future development of new therapies. It also requires a paradigm shift in viewing obesity as a disease that requires treatment, rather than deferring treatment until the complications develop.

KEY WORDS: Obesity, Weight Management, Pharmacotherapy, Bariatric Surgery.

INTRODUCTION

The rapid rise in the incidence of type 2 diabetes in both adults and youth during the past several decades has been largely attributed to the unprecedented rise in obesity. Obesity is defined as a state of excessive adipose tissue mass and best viewed as a syndrome or a group of diseases rather than as a single disease entity. According to a global estimate by the WHO in 2005 there were about 1.6 billion overweight persons aged 15 years and above among which at least 400 million adults were obese (1). WHO further

projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. Figure 1 shows WHO's projected percentage of overweight population in some selected countries in 2002 and 2010.

Type 2 diabetes is a lifestyle disease that arises when genetically predisposed individuals become overweight and physically inactive. Even a minor loss of approximately 5% of body weight has a marked effect on blood glucose regulation, improves lipid profile and reduces blood pressure. In type 2 diabetes,

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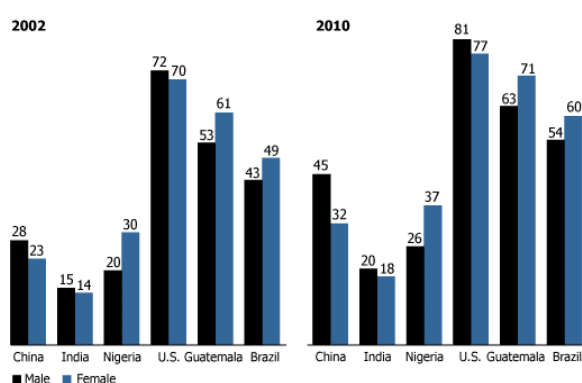


Figure 1- Percent of Population That Is Overweight, Selected Countries, 2002 and 2010 (Projected)

Note: "Overweight" is defined as having a Body Mass Index (weight in kilograms divided by height in meters squared) of between 25 and 30. "Obese" is defined as having a Body Mass Index of 30 or more.

Source: World Health Organization, "WHO Global InfoBase Online," accessed at www.who.int, on Oct. 20, 2005.

patient with intentional weight loss enjoys many potential benefits including improved metabolic control and a reduced need for anti-diabetic medication (2).

National heart, lung and blood institute has released a new practical guide to help in managing overweight patients with specific recommendations "weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes".

This review assesses the effect of different management modalities on weight loss in people with type 2 diabetes. Moreover, different studies of lifestyle modifications, pharmacological treatment and bariatric surgery to achieve weight loss in type 2 diabetes patients are discussed.

1. Impact of Lifestyle changes

Major lifestyle changes are often difficult to implement in obese type 2 diabetic patients as they have more difficulty in losing weight compared with non diabetic individuals. Although life style interventions can be effective in achieving metabolic control, patients find it very difficult to maintain lifestyle changes. Another problem in relation to weight regulation is treatment with sulfonyl ureas, insulin or glitazones which results in further weight gain.

A realistic weight loss goal for most people will be approximately 5-10 kg. For other patients, simply stabilizing their weight would be considered a success. In situations where lifestyle changes cannot be made, diabetic patient should not be followed for months without considering pharmacological treatment as this could expose the patient to unnecessary risk.

In the United Kingdom Prospective Diabetes Study, 2595 newly diagnosed patients were prescribed lifestyle changes during first three months, which produced a 1.9 % fall in HbA1c. After 3 months, the average weight loss was 5 kg. The patients were recommended a diet consisting of 50% carbohydrate, 30% fat and 20% protein including a low intake of saturated fat and with an energy restriction that was tailored to the patient's weight and level of activity by a clinical dietician. On average the patients consumed 1361 kcal/day. The patients attended an out-patient clinic once a month during the first 3 months after diagnosis. Fasting glucose was normal in 18% of the patients after 3 months. Weight loss in this group of patients averaged 11%. Approximately 50% of the patients who started with fasting blood glucose of 6.08 mmol/L had normal fasting blood glucose levels after 3 months. By comparison, only 10% of the group who had initial blood glucose of 16-22 mmol /L was able to achieve normal blood through dietary change (3). Norris et al., analyzed 72 randomized studies, who concluded no influential effect of lifestyle changes in the long term (> 6months) (4).

1.1 Dietary approach

Reduction of caloric intake is the cornerstone of any therapy for obesity. But this simple prescription is very difficult to accomplish despite a wide variety of specific dietary approaches. One common dietary approach is very low calorie diet (VLCD). It contains approximately 800 calories/day and if followed, produces a weight loss of about 10% or 10-15 kg in the course of 8-12 weeks.⁵

Although much of the weight loss is regained be reduced by combining VLCD with other lifestyle changes (5,6).

One study showed that the caloric restriction was largely responsible for correcting the hyperglycemia, since an improvement in glycemic control was observed after a few days of treatment and before any significant weight loss was obtained (7). Accordingly, discontinuation of a VLCD and resumption of a normal diet leads to a daily deterioration in glycemic control (8, 9).

1.2 Physical activity in type 2 diabetes patients

The most obvious purpose of exercise in obesity is to shift the energy balance equation towards a net negative. The effect of physical exercise has been investigated in a number of studies. In a meta-analysis of 14 trails, physical training led to a 0.66% point decrease in HbA_{1c}. Three intervention studies have demonstrated unchanged insulin resistance after physical training (10, 11). In five out of six controlled studies, physical training reduced the triglyceride concentration in the blood. (12, 13-17).

Physical activity seems to be of great importance for maintenance of weight loss over longer period. People with type 2 diabetes should be encouraged to perform resistance exercise three times per week, targeting all major muscle groups (18). General advice to people is to walk more than 10,000 steps per day.

There are several universal recommendations that should be given to patients with type 2 diabetes before they begin an exercise regimen. Individuals older than 35 should be given an exercise test to screen for potential underlying diseases like asymptomatic coronary artery disease (19). In addition, tests for proliferative retinopathy, microalbuminuria and peripheral and autonomic neuropathy should be performed. Exercise regimen should then be individualized.

1.3 Behavior therapy

1-2 years after the start of treatment, this can Behavior (i.e., self-management behavior) is one of the most fundamental sources of obesity management in diabetic patient. In a life style disease like diabetes, behavior interventions for management of obesity caused significant reduction in progression of complications (20).

Predictors of success in weight regulation

Successful treatment of obesity is defined as treatment that results in sustained attainment of normal body weight and composition without producing unacceptable treatment inducing morbidity. But, this is not an easy goal to achieve in type 2 diabetes patients.

Newly diagnosed patients seem to respond better to weight loss than those who have had diabetes for more than 5 years (21) One study analyzed the differences in weight loss in regard to number of out -patient visits. It reported that the patients with weekly out-patient visits lost an average of 6.9 kg over 16 weeks compared to 2.9 kg in the group with monthly out-patient visits. The number of visits to the out-patient clinic was highly correlated with the weight loss and improvement in HbA_{1c} (22, 4).

2. Pharmacological management

The ideal management of the obese diabetic patient involves glycemic control and weight reduction. Increased doses of insulin are required to achieve these goals in this group of patients due to progressive beta cell dysfunction and increasing insulin resistance, which in turn promotes weight gain. When insulin therapy is required in the treatment of the obese diabetic patients, combinations with oral agents can be used to minimize weight gain.

Weight increases after initiation of treatment with oral hypoglycemic agents like sulfonylureas and glitazones, while treatment with acarbose, metformin or pramlintide induces a minor weight loss of 1-2 kg (23-25). Supplementary pharmacological treatment for overweight is useful to induce greater weight loss and /or to increase the number of patients

who maintain weight loss over time (26). The obese diabetic patient who is poorly controlled with maximum oral hypoglycemic therapy may benefit from weight-reducing agents.

Although older drugs such as generic amphetamine like agents are reasonably effective in the short term, they carry risk of addiction and serious cardiovascular complications in long term use. Moreover, below listed agents have shown a positive impact on glycemic control along with their weight reducing ability. The overall summary of these agents is given in Table 1.

2.1 Orlistat (Xenical)

Orlistat is a non-systemically acting anti-

obesity agent that, in conjunction with a calorie-restricted diet, has been shown to promote weight loss and it also helps in preventing weight regain. It is approved for obese patients with a body mass index (BMI) of 30 or more kilograms/square meter or of 27 or more kilograms/square meter in the presence of other risk factors like hypertension, or hyperlipidemia. Through weight loss, orlistat improves the comorbidities associated with obesity. The effect of orlistat in type 2 diabetes has been examined in randomized trials of overweight patients treated with different types of hypoglycemic drugs and a hypo caloric low-fat diet (27-30). All studies have been limited

Table 1- Prescribing summary for orlistat, sibutramine and rimonabant

Drug	Mechanism of action	Standard dose	Potentially useful in	Major side effects	Avoid in
Orlistat	Lipase inhibitor	120mg t.i.d.	Prediabetes, diabetes, raised LDL cholesterol, HTN, preexisting cardiovascular disease	Liver failure, oxalate nephropathy	Malabsorption or chronic gastrointestinal disease
Sibutramine	Serotonin/norepinephrine reuptake inhibitor	10-15mg OD	When lack of satiety is major barrier to weight reduction, dyslipidaemia	Bleeding, seizure and serotonin syndrome	Major eating disorders, uncontrolled hypertension, tachycardia, preexisting cardiovascular disease
Rimonabant	Selective cannabinoid -1 receptor antagonist	20mg OD	Dyslipidaemia, Diabetes, metabolic syndrome	Suicidal thoughts	History of psychiatric illness, liver impairment

** t.i.d.: Thrice in a day, HTN: Hypertension, OD: Once a day, LDL: Low density lipoprotein

Table 2- Studies of orlistat effect on weight loss

Author	Study population number, duration, place	Mean age	Mean BMI	Mean weight	comparison	Outcome
Berne ²⁷	220, 1 year, Sweden	59	32.7	96	Orlistat 120mg t.i.d. vs. placebo	Three fold reduction in weight compared to placebo
Hollander ²⁸	391, 1 year, US	55	34.3	100	Orlistat 120mg t.i.d. vs. placebo	Orlistat group lost 6.2 +/- 0.45% of initial body weight vs. 4.3 +/- 0.49% in the placebo
Kelley ²⁹	550, 1 year, US	58	35.7	102	Orlistat 120mg t.i.d. vs. placebo	Orlistat group lost significantly more weight - 3.89 +/- 0.3% of baseline body weight, than the placebo group -1.27 +/- 0.3% (P < 0.001).
Lindgarde ³⁰	376, 1 year, Sweden	53	33.2	96	Orlistat 120mg t.i.d. vs. placebo	weight loss was significantly greater with orlistat compared with placebo (5.9% vs. 4.6%; P < 0.05).
Miles ³¹	156, 1 year, US and Canada	53	35.4	102	Orlistat 120mg t.i.d. vs. placebo	weight loss was greater in the orlistat than in the placebo group (-4.6 +/- 0.3% vs. -1.7 +/- 0.3% of baseline wt, P < 0.001).

to 2 years in length. Table 2 gives list of different orlistat studies in diabetic population. In all the studies a modest, but statistically significant and beneficial effect was observed on the blood glucose levels despite a reduction in the use of hypoglycemic agents. One meta-analysis also showed that HbA1c level (on average 0.45%) was lower in the orlistat group. All studies revealed a beneficial effect on blood lipids (decreased LDL cholesterol and triglycerides together with increased HDL cholesterol) (27-32).

2.2 Sibutramine

It reduces appetite and increases energy metabolism. The effect of sibutramine treatment has been investigated in several randomized trials (33-37). In all those cases, the treatment was given as a supplement to a hypo caloric diet. After 3-12 months, both in patients treated with diet alone and in patients treated with diet and sulfonylurea or metformin, there was a 2-9 kg greater weight loss with sibutramine than with placebo.

Compared with placebo, treatment with sibutramine was more frequently accompanied by an increase in diastolic blood pressure, except among patients with substantial (>10%) weight loss (35-36).

It was withdrawn from US & Canadian markets in October 2010 due to cardiovascular concerns.

2.3 Rimonabant

Rimonabant is a selective cannabinoid-1 receptor blocker. RIO-Diabetes trial evaluated rimonabant effects in 1047 type 2 diabetes patients receiving oral hypoglycemics. The study lasted for one year and study subjects

were selected from eleven countries. Weight loss was significantly greater in rimonabant group than in the placebo group (5.3kg vs. 1.4kg). Rimonabant also improved HbA1c and cardiovascular risk factors such as waist circumference, triglycerides, insulin resistance, HDL cholesterol, and blood pressure (38).

In the study evaluating rimonabant efficacy in drug-naïve diabetic patients (SERENADE) which lasted for 6 months in patients recently diagnosed with type 2 diabetes, weight loss in the rimonabant group was 6.7kg vs. 2.8kg in the placebo group. The reduction in HbA1c was -0.8% vs. -0.3 % respectively. The lipid profile improved significantly more in the rimonabant group, even after adjustment for weight loss (39).

One meta-analysis of 30 trails summarized that Orlistat, sibutramine, and rimonabant modestly reduce weight, have differing effects on cardiovascular risk profiles and have specific adverse effects. Compared with placebo, orlistat reduced weight by 2.9 kg (95% confidence interval 2.5kg to 3.2 kg), and sibutramine by 4.2 kg (3.6kg to 4.7kg). Additionally, it was also found to have reduced incidence of diabetes, improved concentrations of total cholesterol. Low density lipoprotein cholesterol improved blood pressure levels and glycaemic control in patients with diabetes, but there was an increase in rates of gastrointestinal side effects, and slightly lowered concentrations of high density lipoprotein was revealed as well (40).

2.4 Glucagon like peptides (GLP)-1 analogues

The glucagon- like peptide (GLP)- 1 analogue exenatide and liraglutide have been investigated in type 2 diabetic patients in several randomized trails lasting 12-30 weeks (41,42). Both drugs reduced HbA1c by 1-2 % and induced a weight loss of 2-4 kg on average. Currently, we do not know the potential of the GLP-1analogues in relation to magnitude of weight loss they can induce or to their efficacy in maintaining weight loss over a long period.

A 26-week, double-blind, placebo-controlled, parallel-group trial randomized 533 subjects (1:1:1) to apply once-daily liraglutide (1.2 or 1.8 mg) or liraglutide placebo in combination with metformin (1 g twice daily) and rosiglitazone (4 mg twice daily) and concluded that liraglutide combined with metformin and

a thiazolidinedione is a well-tolerated combination therapy for type 2 diabetes providing significant improvements in glycemic control (43).

To date, all antiobesity drug trials have been limited by their high attrition rates and lack of long-term morbidity and mortality data (44,45). One more drawback of pharmacological treatment is that after stopping treatment weight will increase in the first year to its level before the start of treatment.

Bariatric surgery:

Full and rapid remission of type 2 diabetes mellitus can be achieved through bariatric surgery. This management modality is mainly useful in type 2 diabetes mellitus patients who were unalterably progressive and minimally responsive to other therapies.

Common surgical procedures were used such as the roux-en-Y gastric bypass, adjustable gastric banding, biliopancreatic diversion with duodenal switch, and the sleeve gastrectomy. All these achieve their metabolic effects through a combination of intestinal bypass, hormonal changes, and volume restriction. Four out of five diabetic patients were cleared of diabetes with bariatric surgery. One study documented the long-term outcomes in a series of 608 severely obese individuals treated with the gastric bypass. Of these, 165 patients had type 2 diabetes and other 165 patients had impaired glucose tolerance (IGT). In 83% of diabetic and 99% of IGT patients, resolution of diabetes with a return to normal glycemic levels, and normalization of glycosylated hemoglobin values were observed in one study (46).

Two major series (47, 48) documented the reduction in mortality after gastric bypass.

MacDonald et al., (49) observed that in diabetics, the mortality decreased from 4.5 to 1% per year, based on a comparison group.

Consideration of both acute and long term complications of bariatric surgery is also important. The acute complications include hemorrhage, obstruction, anastomotic leaks, infection, arrhythmias, and pulmonary emboli. Long-term complications are nutritional deficiencies, internal hernias, anastomotic stenoses, and emotional disorders. Another occasional baffling complication is hypoglycemia (50) which is a condition that may appear as long as 14 yr after the surgery with plasma glucose levels as low as 30 mg%. In future, bariatric surgery may ultimately become a major tool in the long-term treatment of type 2 diabetes mellitus.

CONCLUSION

Obesity is a major—and modifiable—contributor to an alarming increase in type 2 diabetes worldwide. Lifestyle intervention with dietary counseling at best only produces a modest weight loss with diminishing effect over time. Physical activity is important for long term weight maintenance after weight loss. Pharmacological agents may be used in patients if they are unable to respond for lifestyle interventions. However, the long term safety of pharmacological treatment remain unclear, and longer term studies powered to examine mortality and cardiovascular morbidity are required. A major draw back of pharmacological agents is weight regain. Bariatric surgery is the ultimate treatment for patients with significant obesity.

Successful treatment of most overweight and obese individuals will depend upon the future development of new therapies.

Conflicts of Interest:

Authors do not have any conflicts of interest

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