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Current Management Strategies for Coexisting Diabetes Mellitus and Obesity

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Contents

Abstract

Besides genetic predisposition, obesity is the most important risk factor for the development of diabetes mellitus. Weight reduction has been shown to markedly improve blood glucose control and vascular risk factors associated with insulin resistance in obese individuals with type 2 diabetes. Therapeutic strategies for the obese diabetic patient include: (i) promoting weight loss, through lifestyle modifications (low-calorie diet and exercise) and antiobesity drugs (orlistat, sibutramine, etc.); (ii) improving blood glucose control, through agents decreasing insulin resistance (metformin or thiazolidinediones, e.g. pioglitazone and rosiglitazone) or insulin needs (α-glucosidase inhibitors, e.g. acarbose) in preference to agents stimulating defective insulin secretion (sulphonylureas, meglitinide analogues);

and (iii) treating common associated risk factors, such as arterial hypertension and dyslipidaemias, to improve cardiovascular prognosis. Whenever insulin is required by the obese diabetic patient after failure to respond to oral drugs, it should be preferably prescribed in combination with an oral agent, more particularly metformin or acarbose, or possibly a thiazolidinedione. When morbid obesity is present, both restoring a good glycaemic control and correcting associated risk factors can only be obtained through a marked and sustained weight loss. This objective justifies more aggressive weight reduction programmes, including very-low-calorie diets and bariatric surgery, but only within a multidisciplinary approach and long-term strategy.

Type 2 diabetes mellitus is strongly associated with obesity.[1] Over 80% of patients with type 2 diabetes are overweight or obese, and the risk of developing type 2 diabetes increases in an exponential manner according to body mass index (BMI).[2] Even moderate weight excess should be considered as a significant risk factor provided that the adipose mass is predominantly located as visceral or mesenteric fat, a morphotype that is more prevalent in men than in women.[3,4] The deleterious effect of such weight excess on blood glucose control is classically attributed to insulin resistance.[5,6] However, only obese individuals prone to develop defective insulin secretion, due to genetic predisposition and/or environmental factors, will develop overt type 2 diabetes.[7] Furthermore, insulin-resistant obese patients with diabetes have a higher prevalence of other vascular risk factors, such as arterial hypertension and dyslipidaemias. This segregation of risk factors, known as metabolic syndrome, insulin resistance syndrome or syndrome X, explains the very high cardiovascular morbidity and mortality rates in such a population.[8,9] Conversely, numerous studies have demonstrated, for some time,[10] that weight loss markedly and rapidly improves the glycaemic control of obese diabetic patients,[11-15] and also reduces the severity of comorbidities[16] and improves overall prognosis.[17] Thus, one key issue in the management of obese patients with type 2 diabetes is to succeed in obtaining a significant and sustained weight loss through lifestyle modifications.[18] However, when necessary, the management of the obese diabetic patient should also include pharmacological treatments targeted to specifically reduce bodyweight (e.g. antiobesity agents), improve blood glucose profile (e.g. antidiabetic drugs) and/or correct frequently associated vascular risk factors (e.g. antihypertensive and hypolipidaemic agents)[18] [figure 1].

1. Non-Pharmacological Approaches

1.1 Lifestyle Modifications

Lifestyle modification is the cornerstone of both the prevention of type 2 diabetes in at risk overweight individuals and the treatment of obese patients with type 2 diabetes.[19-21] However, recent US findings of the Third National Health and Nutrition Examination Survey (NHANES III) showed that the majority of overweight individuals with type 2 diabetes did not engage in recommended levels of physical activity and did not follow dietary guidelines.[22]

In a large epidemiological study on >80 000 American nurses, adequate diet and lifestyle were associated with a lower risk of type 2 diabetes, and changes in bodyweight were the strongest predictor for developing the disease or not.[23] Two recent prospective studies, the Finnish Diabetes Prevention Study[24] and the Diabetes Prevention Program in the US,[25] demonstrated after a mean follow-up of about 3 years that life-style modifications, including diet and physical exercise, can reduce by 58% the relative risk of developing overt type 2 diabetes in obese patients with impaired glucose tolerance. Interestingly, these remarkable results were obtained

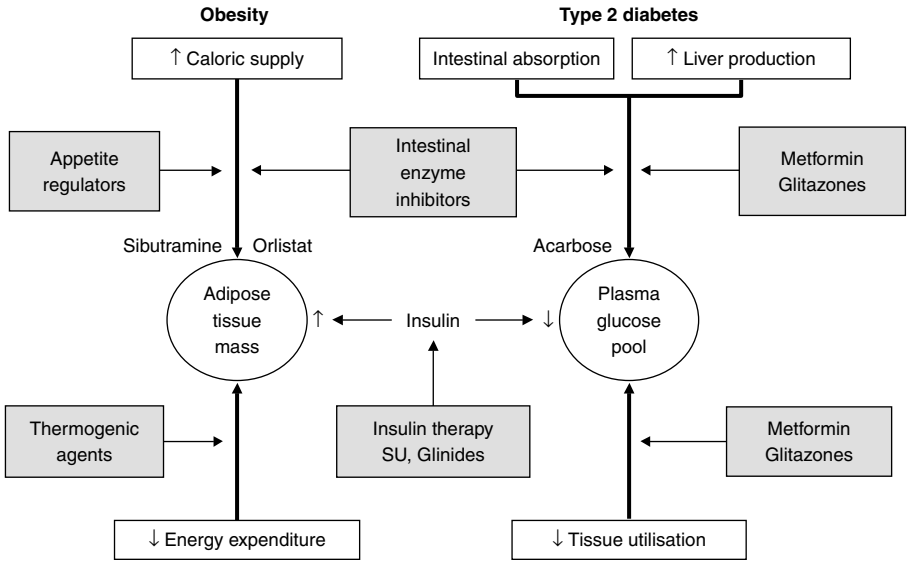

Fig. 1. Integrated scheme illustrating the sites of action of the main drugs used in the treatment of the obese diabetic patient. **SU** = sulphonylurea.

while a moderate weight reduction of only 3–4 kg was attained.

Initial recommendations to any obese diabetic patient should include optimisation of the meal plan and enhancement of physical activity. The three main goals in the dietary management of obese diabetic patients are: (i) to achieve and maintain a reasonable bodyweight; (ii) to keep blood glucose levels in an as near-normal range as possible; and (iii) to achieve optimal serum lipid and blood pressure levels. However, controversies still persist as far as calorie content and diet composition for treating obesity in type 2 diabetes.[26] A daily energy deficit of 500–1000 kcal (2093–4186kJ) mobilises fat preferentially and causes 0.5–1.0kg weight loss per week. In particular, dietary fat should be restricted as it is the most energy-rich macronutrient, its metabolism favours triacylglycerol deposition and adiposity, and it may increase insulin resistance.[19] The emphasis for medical nutrition therapy in type 2 diabetes should be placed on achieving glucose (55% of energy intake as carbohydrates, with limitation of sucrose and advice on consuming fibres), lipid (reduction in saturated fat and cholesterol consumption), and blood pressure (limitation of sodium intake) goals.[27]

Unfortunately, dietary counselling, especially calorie restriction, has a poor long-term success rate, in obese people in general, and in obese diabetic individuals in particular.[13,28,29] An interesting comparative study demonstrated that obese individuals with type 2 diabetes are less successful in losing bodyweight than obese individuals without type 2 diabetes.[30] In a study comparing the results of four weight reduction classical strategies (regular clinic visits, behavioural group therapy, the serotoninergic anorectic agent dexfenfluramine, or combined home and clinic visits) in overweight diabetic patients, the mean weight loss was rather modest (between 1–3kg) after 12 months of follow up, whatever the strategy considered, and indeed not sufficient to significantly improve glycosylated haemoglobin (HbA_{1c}) levels.[31] Even if several studies have demonstrated that a modest weight loss can improve the metabolic control of obese diabetic patients in the short-term (reviewed in Goldstein[32] and Bosello et al.[33]), only a major weight reduction can drastically reverse severe hyperglycaemia in the long-term. This has been shown in a study performed in 114

obese patients with type 2 diabetes who underwent a 12-month follow-up after a 10- to 16-week behavioural weight-control programme:[34] only the very small subgroup of six patients who showed a marked and prolonged weight reduction >13.6kg exhibited a substantial reduction in both fasting blood glucose and HbA_{1c} levels after 1 year.

Exercise combined with calorie restriction has been shown to result in greater loss of adipose tissue mass and relative preservation of lean body mass than calorie restriction alone.[21] The commonly held view that exercise alone is not a useful strategy for obesity reduction is drawn from studies with limitations that confound interpretation. Recent evidence counters the dogma that daily exercise produces only modest weight loss, and suggests that exercise without diet restriction is an effective strategy for reducing obesity and related comorbidities.[21,35] An appropriate exercise programme should be an adjunct to diet and/or drug therapy to improve glycaemic control, reduce certain cardiovascular risk factors, and increase psychological well-being in individuals with obesity and type 2 diabetes.[36,37] As reviewed in detail elsewhere,[21,36-39] several studies have suggested that regular physical exercise may significantly improve insulin sensitivity and glucose tolerance. However, such metabolic improvements have usually been reported under training programmes that many obese diabetic patients may find difficult to comply with,[22] and only a transient beneficial effect on the glycaemic control may be observed with little long-term benefit.[40]

In general, an exercise programme should consist of moderately intense aerobic exercises that can be sustained for 30 minutes or longer, and do not result in a sustained heart rate higher than 60–70% of the person's predetermined maximum heart rate. If the obese diabetic patient does not have proliferative retinopathy or hypertension, some resistance training or high-intensity exercises may also be well tolerated. To produce a significant increase in cardiovascular fitness, to achieve improved insulin sensitivity and glycaemic control, and to use exercise as an adjunct to diet to lose or maintain reduced bodyweight, patients should exercise at least 3 days a week, although 5–7 days a week is preferable.[21]

1.2 Very-Low Calorie Diets

Very low calorie diets (VLCDs) provide 400–800 kcal/day of high-quality protein and carbohydrate fortified with vitamins, minerals and trace elements. Current diets should not be confused with the VLCDs and liquid-protein diets of the late 1970s that were linked to more than 60 fatalities, mainly due to cardiac arrhythmias.[41-43] Such complications appeared to arise from vitamin and mineral deficiencies, the prolonged period of dieting, and the poor quality and/or inadequate amount of protein consumed.[41-43] Several studies indicated that VLCDs can be safely used by obese diabetic patients in a medical setting closely supervised by an experienced physician and that the numerous metabolic benefits derived from VLCD therapy outweigh the risks, at least in short-term studies.[44-46] Improvement in glycaemic control occurs quickly, resulting from increased insulin action in the liver and peripheral tissues, and enhanced insulin secretion.[45] It occurs with only modest weight reduction, suggesting that caloric restriction plays a more critical role, at least initially.[47,48] Such an improvement may be so impressive after VLCD that insulin therapy may be delayed in most obese diabetic patients not adequately controlled with oral drugs anymore.[49] Even if recidivism is frequent, some data suggested that VLCD therapy might provide long-term benefits to the obese diabetic patient, despite some weight regain.[45,46] The conclusions of a meta-analysis of 89 studies involving 1800 subjects were that dietary strategies are most effective for promoting short-term weight loss in type 2 diabetes.[12] Diet, especially VLCDs, are very effective for obtaining weight losses between 5–10kg, and consequently to improve HbA_{1c} levels. However, the authors of this systematic review pointed out a number of inaccuracies or missing information concerning the description of subjects, interventions or longitudinal outcomes beyond 12 months after intervention.

Finally, both the efficacy and the safety of VLCDs remain questionable on a long-term basis. While VLCD is an effective approach to induce rapid weight loss and correction of hyperglycaemia in the short-term, body homeostasis tends to counteract the effects of such severe energy restriction, and the risk of weight regain, with secondary rise in blood glucose, is rather high in the long-term. In addition, when VLCDs are maintained for a too long period of time, deficits may occur which could lead to serious hazards.[42,43] Therefore, VLCDs appear to play only a minor role in the overall management of obese patients with type 2 diabetes.[46]

1.3 Anti-Obesity Surgery

The crucial contribution of weight excess to hyperglycaemia in the obese diabetic patient justifies that aggressive weight reduction strategies may be considered in well-selected individuals with severe obesity (BMI >35 kg/m^2), refractory to medical approaches, and associated with persistent hyperglycaemia despite appropriate glucose-lowering treatments.[18,50] When dealing with morbid obesity (BMI >40 kg/m^2), the physician should realistically consider the chances of weight loss with the medical approach, i.e. restricted diet possibly associated with anti-obesity agents, as compared to surgery.[51] In addition, considering the complexity of such integrated pathologies, the decision to manage the morbidly obese diabetic patient with bariatric surgery should only be taken by a multidisciplinary team, including a dietician/nutritionist, an internist/diabetologist, a surgeon, a general practitioner and a psychologist.

Several studies have reported that bariatric surgery is able to induce large and sustained weight loss, and to normalise blood glucose control in most obese diabetic patients. Remarkable results have been demonstrated after gastroplasty,[18,50,52,53] gastric bypass[54,55] or biliopancreatic diversion[56] in patients with mild or severe diabetes. In morbidly obese diabetic patients, pure restrictive gastric procedures such as vertical gastroplasty or adjustable silicone gastric banding may be less effective than more aggressive procedures, superimposing malabsorption to food restriction, such as gastric bypass and biliopancreatic diversion. However, the latter procedures may be associated with a higher rate of complications, and favourable results have been reported with less aggressive laparoscopic adjustable gastric banding in diabetic patients, even with morbid (BMI >40 kg/m^2) obesity.[50,52,53] The metabolic improvement following weight loss allows the suppression or at least drastic reduction of antidiabetic drugs, especially insulin and sulphonylureas, in most patients. In addition to the improvement of glycaemic control, weight loss following anti-obesity surgery resulted in a clear-cut reduction of other risk factors such as arterial hypertension and dyslipidaemias.[18,50,52,53]

Preliminary results of the large prospective Swedish Obese Subjects (SOS) study[57] showed a dramatic reduction in the incidence of type 2 diabetes (diagnosis based on questionnaires) 8 years after a drastic weight loss resulting from bariatric surgery, confirming previous pilot results.[58] These remarkable results regarding type 2 diabetes contrast with the far less impressive impact on arterial hypertension, as the latter effect tended to vanish from year 2 to 8 of follow-up.[57] Interestingly, the SOS study compared long-term results in obese patients submitted to either gastroplasty or gastric bypass. The latter exhibited a greater weight loss during the first 2 years after bariatric surgery, but a trend to weight regain was observed with both surgical procedures up to 8 years of follow up.[57]

The ultimate objective of anti-obesity surgery is not to reduce risk factors but to improve the prognosis and the quality of life of the obese patient. No prospective study has demonstrated yet that bariatric surgery prolongs life expectancy when compared to medical supervision, especially in a population with type 2 diabetes. Nevertheless, a retrospective study reported that for every year of a 6–9 year follow-up, obese diabetic patients in the control group (medical treatment) had a 4.5% chance of dying versus a 1.0% chance for those in the group treated by gastric bypass ($p < 0.0001$).[59] This improvement in the mortality rate of the surgical group was primarily due to a decrease in the number of cardiovascular

deaths. Such favourable results, which are in agreement with the remarkable reduction of risk factors, should be verified in a large prospective study such as the ongoing SOS study.[57] It is indeed crucial to demonstrate in long-term prospective studies that morbidity and mortality of ex-obese people are reduced years after undergoing bariatric surgery. While there is some concern over the failure of most procedures used to decrease bodyweight to improve the life expectancy of non-diabetic obese patients, the positive impact of surgery might be easier to demonstrate in obese individuals with type 2 diabetes mellitus, a subpopulation at very high risk in absence of adequate weight loss.[17]

2. Pharmacological Approaches

2.1 Anti-Obesity Drugs

A variety of pharmacological compounds have been used to promote weight loss in obese patients, without and with type 2 diabetes,[18,60-64] and new antiobesity agents are still in development.[65]

2.1.1 Classical Drugs Affecting Food Intake

Numerous studies have been published with anorectic agents in obese non-diabetic patients,[60,61,66,67] but only a few in obese individuals with type 2 diabetes.[18,62-64] A majority evaluated the serotoninergic compounds (dex)fenfluramine and fluoxetine. Most placebo-controlled, double-blind clinical trials lasted 12 weeks, and only very few studies were extended up to 1 year or more.[68] In obese diabetic individuals, the drug-associated additional weight reduction (rather modest in most patients) was associated with a moderate decrease (significant in about half of the studies) in fasting plasma glucose and HbA_{1c} levels (reviewed in Scheen and Lefèbvre[18]). Interestingly, several studies showed that serotoninergic agents could improve insulin sensitivity independently of weight reduction. This has been demonstrated with fenfluramine, dexfenfluramine and fluoxetine, in short-term studies using various methods, especially the euglycaemic hyperinsulinaemic clamp technique (reviewed in Scheen and Lefèbvre[18,62] and Kosmiski and Eckel[63]). The improvement of insulin action was associated with a significant reduction of fasting plasma glucose levels in half of the studies, as well as with an improvement of various cardiovascular risk factors. Unfortunately, fenfluramine and dexfenfluramine, the two compounds that have been best evaluated and provided the most impressive metabolic improvement, were withdrawn from the market after the description of fatal pulmonary hypertension and valvular heart disease.[61]

Benfluorex, which is structurally related to fenfluramine, is a known hypolipidaemic agent with possible glucose-lowering effects, especially in the obese diabetic patient (reviewed in Arnaud and Nathan,[69] Reaven[70] and Ravel[71]). It has been shown to improve glucose tolerance in obese individuals with type 2 diabetes by increasing sensitivity to insulin without directly stimulating insulin secretion.[72] Several double-blind, placebo-controlled trials showed that benfluorex improves the metabolic control of obese patients with type 2 diabetes treated with diet alone,[73] sulphonylurea,[74] metformin[75] or insulin.[76,77] However, this compound is only available in some countries.

Two medications, sibutramine and orlistat, have been approved for long-term treatment of obesity, provided that they are given in combination with appropriate dietary restriction. Interestingly, several randomised placebo-controlled clinical trials have been specifically performed with these two drugs in obese patients with type 2 diabetes mellitus.[78]

2.1.2 Sibutramine

Sibutramine, a noradrenaline and serotonin reuptake inhibitor, has been shown to produce a dose-related weight loss in obese individuals, with optimal doses of 10–15 mg/day.[79] The multicentre, prospective Sibutramine Trial of Obesity Reduction and Maintenance (STORM) clinical study showed that almost all patients who persisted with the management scheme combining restricted diet and sibutramine can achieve at least a 5% weight loss, and over half can lose more than 10% weight within 6 months.[80] Furthermore, sustained weight loss was maintained in most patients continuing therapy with sibutramine for 2 years, whereas weight regain was

Table I. Results of randomised, placebo-controlled trials with sibutramine in obese patients with type 2 diabetes. Results are expressed as differences between changes with sibutramine (S) versus placebo (P). Only studies randomising at least 30 patients in each group are included

Study	No. P/S (mg/day)	Duration (weeks)	Antidiabetic treatment	BW (kg)	FPG (mmol/L)	HbA_{1c} (%)
Heath et al.[82] and Rissanen et al.[88]	122/114 (15)	52	Diet	−4.5	−0.2	−0.10
Finer et al.[84]	44/47 (15)	12	Diet/SU/MET/INS	−2.5	−1.7	−0.40
Fujioka et al.[85]	86/89 (20)	24	Diet/SU/MET	−3.9	−0.4	−0.10
Gokcel et al.[86]	30/30 (20)	24	SU + MET	−10.1	−6.1	−2.20
Serrano-Rios et al.[87]	65/69 (15)	24	SU	−2.8	−0.2	−0.05
McNulty et al.[89]	64/68 (15)	52	MET	−5.3	−0.1	−0.53
	64/62 (20)	52	MET	−7.8	+0.1	+0.09

BW = bodyweight; **FPG** = fasting plasma glucose; **HbA_{1c}** = glycosylated haemoglobin; **INS** = insulin; **MET** = metformin; **SU** = sulphonylurea.

noticed in most patients randomised to placebo, thus demonstrating that sibutramine favours weight maintenance in the long-term. Owing the close relationship between obesity and type 2 diabetes, sibutramine may be useful in the treatment of obese diabetic patients.[81] In patients with type 2 diabetes, sibutramine-induced weight loss was accompanied by a shift towards improved metabolic control, and the reduction in fasting plasma glucose was proportional to the degree of weight loss[82] (reviewed in Scheen and Lefèbvre[18]).

A meta-analysis of placebo-controlled studies performed in modestly hyperglycaemic obese patients showed that greater improvements in fasting plasma glucose levels were observed in the group receiving the active drug.[83] This difference is probably explained by the fact that more patients receiving sibutramine than placebo achieved significant weight loss; the observation that changes in plasma glucose levels observed with sibutramine and placebo were similar for the same degree of weight loss indeed suggests an indirect rather a direct action of the drug on glucose metabolism. Favourable results were reported with sibutramine in four 6-month[84-87] and two 1-year[88,89] randomised clinical trials (table I).

All studies demonstrated that, when compared to placebo, an average 3–5kg further weight loss resulting from the prescription of sibutramine is sufficient to slightly improve fasting blood glucose and glycated HbA_{1c} levels, the effect being significant in patients losing ≥10% of their baseline bodyweight. Interestingly, these changes were associated with improvement of other metabolic vascular risk factors, such as lipid parameters, but not arterial hypertension. A recent study comparing sibutramine (10mg twice daily) with orlistat or metformin in obese females reported that sibutramine was the most effective agent in terms of weight reduction, and was as effective as the two other compounds in reducing cardiovascular risk and decrease the risk of type 2 diabetes.[90]

It should be pointed out that sibutramine is not effective in all individuals (explaining why average weight reduction is rather moderate in a large group of obese subjects), and so-called good responders should be detected during the first 3 months of therapy by a weight loss greater than 5% of initial bodyweight. In addition, because of its mechanism of action, sibutramine slightly increases heart rate and arterial blood pressure, adverse effects that may be harmful in some patients. Because of these contrasted effects of sibutramine on cardiovascular risk profile, a large (>9000 patients), prospective, randomised, placebo-controlled, long-term (>4 years) trial (Sibutramine Cardiovascular Morbidity and Mortality Outcomes study or SCOUT) is ongoing to demonstrate both the efficacy and the safety of the drug in high-risk obese individuals, half of who have diabetes.

2.1.3 Orlistat

Orlistat, a semisynthetic derivative of lipstatin, is a potent and selective inhibitor of gastric and pancreatic lipases.[91] When administered with fat-containing foods, it partially inhibits the hydrolysis of

Table II. Results of randomised, placebo-controlled trials with orlistat (120mg three times daily) in obese patients with type 2 diabetes. Results are expressed as differences between changes with orlistat (O) versus placebo (P). Only studies randomising at least 30 patients in each group are included

Study	No. P/O	Duration (weeks)	Antidiabetic treatment	BW (% initial)	FPG (mmol/L)	HbA_{1c} (%)
Hollander et al.[102]	159/162	52	SU	−1.9	−0.56	−0.46
Miles et al.[103]	254/249	52	MET	−2.9	−1.30	−0.29
Hanefeld & Sachse[107]	180/189	52	SU	−1.8	−0.90	−0.50
Halpern et al.[104]	174/164	24	SU/MET/SU + MET	−1.7	−0.99	−0.40
Deerochanawong[105]	126/126	24	SU/MET/SU + MET	−1.6	−0.79	−0.29
Bonnici[106]	142/142	24	SU/MET/SU + MET	−2.6	−0.96	−0.50
Kelley et al.[108]	269/266	52	Insulin	−2.6	−0.55	−0.35
Jacob et al.[109]	749/741	52	SU	−	−1.09	−0.42
Jacob et al.[109]	538/550	52	MET	−	−1.18	−0.34

BW = bodyweight; **FPG** = fasting plasma glucose; **HbA_{1c}** = glycosylated haemoglobin; **MET** = metformin; **SU** = sulphonylurea.

triacylglycerols, thus reducing the subsequent absorption of monoacylglycerols and free fatty acids. Orlistat treatment results in a dose-dependent reduction in bodyweight in obese individuals, with an optimal dosage regimen of 120mg three times daily, and is generally well tolerated apart from some intestinal adverse effects during the first few days or weeks of administration.[92]

Several 1-year and 2-year trials showed that orlistat, when used with a health-promoting, low-fat and moderately energy-restricted diet, confers some advantages in the long-term management of obesity.[92-94] Weight loss was significantly greater in the orlistat than in the placebo group, with a specific reduction in total and low-density lipoprotein (LDL) cholesterol serum levels of greater magnitude than that expected from weight loss (Obelhyx study[95]). Interestingly enough, orlistat-associated moderate weight loss was shown to have beneficial effects on insulin sensitivity and β-cell function, and to significantly reduce the relative risk of developing overt type 2 diabetes in obese patients with impaired glucose tolerance.[96,97] In addition, orlistat favourably influences coronary heart disease risk profile in obese individuals.[98]

The results of a large (n = 3277), prospective, randomised, placebo-controlled, 4-year clinical trial with orlistat (120mg three times daily) have been presented recently.[99] XENDOS (XENical in the prevention of Diabetes in Obese Subjects) demonstrated that orlistat resulted in a weight reduction of 2.8kg in obese subjects (BMI >30 kg/m^2), a difference that was sufficient to significantly reduce the cumulative incidence of type 2 diabetes (−37%; p = 0.0032), especially in those with impaired glucose tolerance. XENDOS demonstrates that an antiobesity agent, like orlistat, is able to reduce the progression to diabetes in obese subjects compared with lifestyle changes alone, thus providing further argument to use this drug in obese diabetic patients.[99]

Orlistat may also be used in the treatment of obese patients with type 2 diabetes[100,101] (table II). A large multicentre, randomised, double-blind, placebo-controlled group study was undertaken to determine the effects of orlistat (120mg three times daily) in obese patients with type 2 diabetes receiving sulphonylurea hypoglycaemic agents.[102] After 1-year of treatment, a mean difference of 2.4kg weight loss was observed in the orlistat group versus the placebo group, an effect that was associated with significant reductions in fasting blood glucose and HbA_{1c} levels. Furthermore, a significant reduction in the dose of oral glucose-lowering agents was seen in the orlistat group as well as an improvement of lipid parameters.

Such positive results were confirmed in further studies in obese diabetic patients treated with diet alone,[100,101] metformin,[103] metformin and/or sulphonylurea,[104-107] or even insulin[108] (table II). In overweight or obese patients with type 2 diabetes who had suboptimal metabolic control with insulin therapy, orlistat treatment for 1 year produced sig-

nificantly greater decreases, compared with placebo, in bodyweight, HbA_{1c} levels, fasting serum glucose, and the required doses of insulin and other diabetic medications as well as greater improvements in total cholesterol, LDL cholesterol and the ratio of LDL to high-density lipoprotein (HDL) cholesterol.[108]

A recent retrospective analysis of pooled data from seven multicentre, double-blind trials assessed the effect of orlistat in overweight or obese patients with type 2 diabetes. It demonstrated that orlistat has a beneficial effect on HbA_{1c} that: (i) is, as with all other oral hypoglycaemic agents, proportional to the starting HbA_{1c} level (and best evidenced in patients with HbA_{1c} levels ≥8%);[110] (ii) is similar in patients receiving maximal or near maximal doses of metformin or sulphonylureas as in the overall treatment group;[109] and (iii) can be attributed to a significant reduction of insulin resistance as assessed with the HOMA (homeostasis model assessment) method.[111]

Although no direct comparative studies are available, comparison of results of sibutramine trials (table I) and orlistat trials (table II) suggests that orlistat is slightly less effective than sibutramine in reducing bodyweight, but that it exerts a more consistent and greater improvement of blood glucose control in obese patients with type 2 diabetes. Finally, a Markov health economic model suggested that orlistat is cost-effective in the management of high risk obese patients with type 2 diabetes.[112]

2.2 Antidiabetic Drugs

Five pharmacological classes of oral agents are currently used for treating type 2 diabetes: sulphonylureas, meglitinide analogues, biguanides, α-glucosidase inhibitors and thiazolidinediones (table III).[113-115] In patients who fail to respond to oral treatment, insulin therapy may be prescribed, alone or in combination with oral agents. The selection of an oral antidiabetic agent depends on several factors, which include the severity of hyperglycaemia and some characteristics of the patient, especially the presence of obesity.[116-118]

Table III. Pharmacological management of obese patients with type 2 diabetes

Anti-obesity drugs
Sibutramine
Orlistat
Antidiabetic drugs
Sulphonylureas: glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, etc.
Meglitinide analogues: repaglinide, nateglinide
Biguanides: metformin
α-Glucosidase inhibitors: acarbose, miglitol, voglibose
Thiazolidinediones: rosiglitazone, pioglitazone
Insulin and combined therapy with oral agents
Drugs treating associated risk factors
Hypertension
ACE inhibitors, AT_1-receptor antagonists
Selective β-blockers, diuretics
Calcium channel antagonists
Dyslipidaemias
HMG-CoA reductase inhibitors (statins)
Fibric acid derivatives

2.2.1 Sulphonylureas

When insulin secretion becomes insufficient to compensate for insulin resistance, administration of sulphonylureas, which stimulate insulin release from pancreatic islet β cells, may be the only solution to protect against severe hyperglycaemia.[119,120] However, sulphonylurea therapy may favour further weight gain and, thus, should be accompanied by appropriate dietary counselling.[121] Classically, sulphonylureas are not considered as first choice pharmacological treatment in obese diabetic patients.[116-118]

2.2.2 Meglitinide Analogues

New insulin secretagogues (repaglinide, nateglinide) are now available for the treatment of type 2 diabetes, as monotherapy and/or in association with either metformin or a glitazone.[122] Compared with sulphonylureas, they are characterised by an earlier onset and shorter duration of action, resulting in a better control of postprandial hyperglycaemia and a lower risk of late hypoglycaemia.[123,124] Such a insulin kinetics profile results in a lower overall postmeal insulin secretion with meglitinide analogues than with sulphonylureas, a profile that should be favourable as far as bodyweight control is con-

cerned. However, no long-term, direct comparative studies are available as yet, so that the precise place of such compounds in the treatment of obese patients with type 2 diabetic is not known.

2.2.3 Metformin

Metformin is the only biguanide compound still available in most countries. Since its early use in Europe, it has been more particularly recommended in obese rather than non-obese patients with type 2 diabetes. Indeed, the drug lowers plasma glucose levels without increasing (and even by concomitantly decreasing) circulating insulin concentrations, suggesting that it may improve insulin sensitivity. Furthermore, in contrast to sulphonylureas, metformin neither increases bodyweight nor causes hypoglycaemia.[125-130] It may also favourably influence some markers of the metabolic insulin resistance syndrome,[131,132] and exert some protective vascular effects.[133] Thus, metformin is now considered as first-line antidiabetic drug in obese diabetic patients, provided that classical contra-indications (essentially renal insufficiency because of a higher risk of lactic acidosis) have been excluded.[116-118]

The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that metformin monotherapy was associated with a significant reduction in diabetes-related complications and cardiovascular morbidity compared with diet alone or even with intensive therapy using sulphonylureas or insulin in obese subjects with newly diagnosed type 2 diabetes.[130,134] In addition, this study clearly showed that, despite a similar improvement in blood glucose control, weight gain was significantly less pronounced with metformin than with sulphonylureas or insulin. The mechanisms for such a difference remain unclear. However, two recent studies demonstrated that metformin therapy was associated with a significant reduction in food intake in obese non-diabetic individuals[135] and in insulin-treated obese patients with diabetes.[136] The latter study also showed that metformin prevents weight gain in patients with type 2 diabetes receiving exogenous insulin. Thus, such an anorectic effect of metformin represents a further argument to consider the biguanide compound as a first choice antidiabetic agent in obese patients with type 2 diabetes.[116-118] Metformin should also be considered as a valuable adjunct to insulin therapy in patients with type 2 diabetes who have initial overweight or progressive weight gain with insulin.[136-138]

2.2.4 α-Glucosidase Inhibitors

α-Glucosidase inhibitors (acarbose, miglitol, voglibose) retard the intestinal absorption of complex carbohydrates. They also reduce postprandial hyperinsulinaemia and do not promote weight gain; they may represent a useful adjunct therapy for the obese patient with diabetes insufficiently controlled by diet alone or in combination with other classical antidiabetic drugs.[139-141]

In the UKPDS, acarbose significantly improved glycaemic control over 3 years in patients with established type 2 diabetes, irrespective of concomitant therapy for diabetes. Mean bodyweight was significantly less at 1 year in patients allocated to acarbose compared with those receiving placebo, but no significant differences were seen at 2 or 3 years.[141] Two double-blind, placebo-controlled studies showed that acarbose has potential clinical utility for improving glycaemic control in overweight patients with type 2 diabetes inadequately controlled with metformin.[142,143] A recent study demonstrated that acarbose, by decreasing postprandial blood glucose levels, indirectly improves both insulin resistance and secretion in obese patients with type 2 diabetes.[144] Finally, the recently published STOP-NIDDM trial demonstrated that acarbose is able to significantly reduce the progression from impaired glucose tolerance to overt type 2 diabetes in obese patients,[145] a preventive effect attributed to similar mechanisms on insulin sensitivity and/or secretion.[146]

2.2.5 Thiazolidinediones

Thiazolidinediones – troglitazone, withdrawn from the market because of liver toxicity, rosiglitazone, pioglitazone, etc. – are a new class of pharmacological compounds, which work by enhancing insulin action ('insulin sensitisers') and, thus, promoting glucose utilisation in peripheral tissues and suppressing gluconeogenesis in the liver.[147] Thus, they are potentially interesting in obese

diabetic patients with insulin resistance. Thiazolidinediones act through a member of the nuclear hormone receptor superfamily peroxisome proliferator activated receptor (PPAR)-γ, and enhance the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.[148] Thiazolidinediones stimulate adipogenesis and reduce plasma free fatty acid (FFA) levels. Stimulation of PPAR-γ may decrease the release by the adipocytes of various signalling molecules, such as FFA, leptin and tumour necrosis factor (TNF)-α, which are all able to counteract the hypoglycaemic action of insulin.[147,148]

Numerous studies have demonstrated that thiazolidinediones, including troglitazone,[149] rosiglitazone[150] and pioglitazone,[151] improve blood glucose control in (obese) patients with type 2 diabetes, either treated with diet alone, sulphonylureas, metformin or insulin. Whereas about 25–50% of the patients with type 2 diabetes are considered as poor responders to such a pharmacological approach, it has been reported that obese diabetic patients may show a greater blood glucose reduction than those who are not overweight. A positive synergism between metformin and troglitazone has been reported, the former exerting its action predominantly in the liver, while the latter increases insulin sensitivity predominantly in the skeletal muscle.[152] Such a complementary effect was confirmed with the combination of metformin and rosiglitazone,[153] and with the combination of metformin and pioglitazone.[154] Interestingly, glitazones may also favour pancreatic rest and, thus, retard or prevent the progressive β-cell failure seen in obese individuals at risk of developing type 2 diabetes,[155] or possibly in patients newly-diagnosed with type 2 diabetes. Thus, whereas the glucose-lowering effect of glitazone occurs only progressively within a few weeks to months, a sustained favourable effect on blood glucose control might be expected. Whether this effect will result in postponing secondary failure to oral agents and switch to insulin remains an open question.

The effects of glitazones on lipid profiles are less clear, as treatment was associated with mild increase in both LDL and HDL cholesterol levels, with no consistent effects on serum triglyceride levels (moderate reduction with pioglitazone but no change with rosiglitazone).[149-151]

Several clinical trials have reported a mild, although significant, weight gain in patients with type 2 diabetes treated with glitazones for several months.[156] The mechanisms responsible for such a weight gain remain poorly understood, although both subcutaneous fat accumulation and some fluid retention have been described. Such compounds acting on the nuclear receptor PPAR-γ may promote adipogenesis,[147,148] and troglitazone has been shown to reduce plasma leptin levels and increase hunger in patients with poorly controlled type 2 diabetes.[157] Several studies, with troglitazone,[158-160] rosiglitazone[161] or pioglitazone,[162] demonstrated that thiazolidinedione compounds may increase subcutaneous fat deposition, but in contrast decrease visceral fat, thus contributing to a redistribution of adipose tissue. As visceral fat exerts much more deleterious effects than subcutaneous fat, this may result in a favourable metabolic profile despite moderate weight gain. However, no long-term prospective data are available investigating the final effects of glitazones on bodyweight and on its two main components, subcutaneous fat and visceral fat, in patients with type 2 diabetes. Indeed, although such a pharmacological approach may be interesting in obese diabetic individuals because of its positive action on insulin sensitivity, glucose control and other vascular risk factors,[163] its clinical interest might vanish with time if such a promoting effect on weight gain is confirmed in long-term studies.

2.2.6 Insulin and Combined Therapy

While exogenous insulin is effective in normalweight or overweight patients with type 2 diabetes who have failed to respond to oral hypoglycaemic agents,[164] insulin therapy is rarely a good option in the obese or very obese diabetic patient because of massive insulin resistance and high risk of further weight gain.[165] Furthermore, it has been reported that insulin treatment in the obese individual may result in a significant increase in arterial blood pres-

sure, probably because of some fluid retention and weight gain. Thus, insulin therapy should be accompanied by a reinforcement of dietary habits, with further reduction in salt and calorie intake.[166]

As type 2 diabetes is an heterogeneous disease with multiple metabolic and hormonal abnormalities,[1] it appears logical to combine drug therapies in order to have a positive impact on various sites.[113-118] Even when insulin is necessary, it is generally prescribed in combination with oral drugs to promote its action and/or to avoid excessive weight gain, especially in obese individuals (reviewed in Scheen and Lefèbvre,[18] Yki-Järvinen,[167] Buse[168] and Herman[169]).

As already mentioned in section 2.2.3, metformin appears to play a favourable role to this respect.[136-138] Bedtime insulin plus metformin conferred the most benefits among several options investigated in a randomised 1-year study: after a progressive decrease over time, HbA_{1c} levels reached lower values and there were fewer hypoglycaemic episodes and less weight gain in the insulin-metformin group compared with the other treatment groups.[170] Besides an insulin-sparing effect, the addition of metformin to insulin in obese diabetic patients resulted in a significant reduction of various metabolic cardiovascular risk factors.[171]

The combination of insulin with acarbose is a further option when there is a significant postprandial hyperglycaemia.[172,173] Because of the presence of severe insulin resistance in obese diabetic patients, the addition of a thiazolidinedione, as an insulin sensitiser, to exogenous insulin appears to be a rational therapeutic option and favourable results were reported with either rosiglitazone[150,174] or pioglitazone.[151,175] However, the combination of insulin and a thiazolidinedione may lead to some fluid retention and, rarely, to worsening of heart failure, so that this combined treatment that is recognised in the US is not accepted in Europe yet.

Finally, clinical studies in insulin-treated obese patients with type 2 diabetes showed that mealtime subcutaneous injection of pramlintide, a synthetic, equipotent and soluble peptide analogue of human amylin, which slows the rate of gastric emptying and reduces postprandial hyperglucagonaemia, leads to a combined improvement in glucose and weight control.[176,177] In a 52-week, double-blind, placebo-controlled, multicentre, large-scale phase III study, mealtime amylin replacement with pramlintide 120μg twice daily, as an adjunct to insulin, resulted in a sustained lowering of HbA_{1c} (−0.62%; $p < 0.05$) that was accompanied by a mean reduction in bodyweight (−2.1kg; $p < 0.05$ vs placebo) in obese patients with poorly controlled type 2 diabetes.[177] Because of these clinical benefits, pramlintide may become a valuable addition to the arsenal of therapies available to insulin-requiring obese patients with type 2 diabetes.[178]

2.3 Drugs Treating Associated Risk Factors

Atherosclerosis, especially coronary artery disease, causes much of the serious morbidity and mortality in (obese) patients with type 2 diabetes.[179] Diabetes mellitus magnifies the cardiovascular risk, not only because of chronic hyperglycaemia, but also because of numerous associated vascular risk factors.[180] Indeed, most obese diabetic patients have arterial hypertension and dyslipidaemias (classically increased plasma FFA levels, hypertriglyceridaemia, low HDL cholesterol levels, excess in small dense LDL and postprandial hyperlipaemia).

As already discussed in section 1.1, lifestyle changes, especially weight-reducing diet and exercise, are able to improve such cardiovascular risk factors, in addition to lowering blood glucose levels. Furthermore, drugs specifically targeted at lowering arterial blood pressure (reviewed in Beckman et al.,[179] Kjeldsen et al.[181] and Kaplan[182]) and improving lipid profile (reviewed in Beckman et al.,[179] Garg and Grundy[183] and Gotto[184]), have been evaluated in numerous recent randomised controlled trials.[180] These pharmacological agents provided evidence of not only being able to reduce cardiovascular morbidity and mortality in non-diabetic patients, but also to improve the well-known poor cardiovascular prognosis in various subgroups of obese diabetic patients who participated in these trials.

Nevertheless, a recent US study reported that hypercholesterolaemia and hypertension were managed less aggressively than hyperglycaemia in a randomly selected cohort of patients with type 2 diabetes.[185] In the Optimise Cardiovascular Prevention in Diabetics (OCAPI) Belgian survey, only a minority of patients with type 2 diabetes reached the targets of blood pressure and lipid profile control, despite the fact that half of them received antihypertensive treatment and one third received hypolipidaemic agents.[186]

2.3.1 Antihypertensive Agents

Arterial hypertension and type 2 diabetes are two bad companions.[187,188] Vigourous control of blood pressure decreases the rate of cardiovascular events more in patients with type 2 diabetes than in those without diabetes.[189] In the UKPDS, control of high blood pressure represented the most important intervention, limiting cardiovascular events more effectively than tight glycaemic control.[190] In this study, captopril and atenolol as initial therapy had similar efficacy.[191] However, achieving new target blood pressure levels (130/85mm Hg) usually requires more than one agent in obese individuals, whether they are diabetic or not.

Diuretics, β-blockers, ACE inhibitors, angiotensin AT_1-receptor antagonists, and calcium channel antagonists all effectively decrease blood pressure in patients with type 2 diabetes.[181,182] As β-blockers moderately increase bodyweight and as some fluid expansion exists in almost all obese individuals, low-dose diuretics rather than agents blocking β-adrenoreceptors should be first considered in obese diabetic patients. ACE inhibitors may represent a valuable option as they were shown to improve insulin sensitivity and to reduce the risk of type 2 diabetes in obese hypertensive patients,[192] as well as to improve both cardiovascular morbidity and mortality in high-risk patients.[193] Finally, a recent prospective study (Losartan Intervention For Endpoint reduction in hypertension [LIFE]) demonstrated that losartan, a selective antagonist of angiotensin II AT_1 receptors, significantly improves the cardiovascular prognosis of hypertensive patients with type 2 diabetes compared with atenolol, a selective blocker of β_1 adrenoceptors.[194]

2.3.2 Hypolipidaemic Agents

The lipid abnormalities that develop in type 2 diabetes and their role in atherogenesis have important therapeutic implications.[183] Pharmacological interventions decrease cardiovascular events in patients with diabetes, as borne out by several large-scale clinical trials with HMG-CoA reductase inhibitors (statins).[184] Coronary events were significantly reduced (by about 50%) with simvastatin in patients with diabetes and hypercholesterolaemia in the Scandinavian Simvastatin Survival (4S) study.[195] In several clinical trials with pravastatin (Cholesterol in Recurrent Events [CARE], Long-term Intervention with Pravastatin in Ischemic Disease [LIPID], West of Scotland Primary Prevention [WOSCOP]), the reduction of cardiovascular major endpoints was almost similar (almost 30–35%) in diabetic versus non-diabetic subjects.[184] In the recent Heart Protection Study (HPS), which included more than 4000 subjects with diabetes, simvastatin decreased the risk of acute coronary syndrome, stroke and revascularisation by 25% in the subgroup of diabetic patients.[196]

Fibric acid derivatives represent another drug class potentially of benefit in diabetic patients with dyslipidaemia because they raise HDL cholesterol and lower triglyceride levels. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT), patients with diabetes represented 25% of the 2531 male participants. Treatment with gemfibrozil reduced risk of myocardial infarction by 24%, an effect comparable with that observed in nondiabetic patients.[197] Another placebo-controlled, prospective trial, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study is still ongoing to demonstrate the protective effect of fenofibrate in patients with type 2 diabetes and dyslipidaemia. Finally, although of potential interest in combination therapy of statins and fibric acid derivatives in numerous diabetic patients with combined dyslipidaemia, this approach warrants careful monitoring for muscle injury.

3. Obesity, Type 2 Diabetes and Metabolic Syndrome: a Holistic Approach

Approximately one in five US adults has metabolic syndrome (or syndrome X), a cluster of metabolic abnormalities identified by three or more of the following indications: abdominal obesity, hypertriglyceridaemia, low HDL cholesterol, high blood pressure and high fasting glucose.[198] By definition, most obese people with type 2 diabetes have dysmetabolic syndrome, a condition that is responsible for the high cardiovascular morbidity and mortality in this population. Therefore, targeting metabolic syndrome as a whole rather than specifically treating one of its components should be considered as a key objective in the management of such individuals.

In its early stages, dysmetabolic syndrome can often be effectively managed through diet and exercise, and weight loss is a key-component of the treatment. A recent review quantitates the effects of weight loss on coronary risk factors.[199] For every kilogram of weight loss the following favourable changes occur: fasting serum cholesterol, –1.0%; LDL cholesterol, –0.7%; triglycerides, –1.9%; HDL cholesterol, +0.2%; systolic blood pressure, –0.5%; diastolic blood pressure, –0.4%; and fasting blood glucose, –0.2 mmol/L.[167] In obese diabetic patients, weight losses of as little as 5% of initial bodyweight, achieved through diet and exercise, are already associated with significant improvements in HbA_{1c}.[32]

Although, for the purpose of clarity, each of the components of syndrome X has been discussed separately in this review, the management of the patient should consider the integrated disease that constitutes the metabolic syndrome entity. Thus, in patients failing to respond to lifestyle modifications, drugs targeting insulin resistance should first be considered. It is no wonder that some drugs used for the management of these metabolic abnormalities show a remarkable degree of interchangeability for the treatment of the separate pathologies: for instance thiazolidinediones may somewhat reduce arterial blood pressure,[149-151] while ACE inhibitors may enhance insulin sensitivity.[192]

In dealing with obesity and type 2 diabetes, two chronic diseases, the time limitations of the current therapeutic approaches should be adequately stated. For instance, considering anti-obesity agents, such as sibutramine and orlistat, weight maintenance is at least as important as initial weight loss. In this respect, VLCDs appear to have the least favourable long-term outcomes, whereas bariatric surgery provides the more sustained weight reduction, even if some weight regain may also be observed in the long-term. As far as glucose-lowering agents are concerned, protection of β cells should be considered as a key objective as the UKPDS has nicely demonstrated that β-cell exhaustion is mainly responsible for the progressive deterioration of blood glucose control following diagnosis of type 2 diabetes, in both non-obese and obese individuals.[200] Reduction of insulin resistance should be considered as a major objective in the obese diabetic patient, and the preference should be given to drugs that do not promote weight gain and favourably influence metabolic abnormalities associated to syndrome X. Consequently, at present time, metformin is considered as the first-choice drug, with as alternative or combined therapy, acarbose or possibly thiazolidinediones.

Finally, besides the presence of other components of metabolic syndrome, the severity of obesity[4] and the degree of hyperglycaemia[118] are two important factors that may influence the strategies of overall management in clinical practice. The more severe the risk factor is, the more aggressive the treatment procedure may be. For instance, as currently available anti-obesity agents are not able to help most morbidly obese diabetic patients, those individuals should be preferably oriented towards bariatric surgery, but only after failure of medical interventions and within a multidisciplinary approach.

4. Conclusions

The control of bodyweight appears to be crucial for both the prevention and the treatment of type 2 diabetes in obese patients. The management of the obese diabetic patient should combine strategies that

aim at reducing weight excess, lowering chronic hyperglycaemia and correcting other risk factors.

Weight loss is a major target in treating obese patients with type 2 diabetes as it allows simultaneous improvement in both glycaemic control and associated risk factors. Lifestyle modifications should be used first in all patients, and VLCDs should be reserved for selected patients refractory to classical approaches. Recently available anti-obesity drugs, such as sibutramine and orlistat, can be used in adjunct therapy to diet as the additional weight loss, even though modest on average, was able to improve blood glucose control and other risk factors, such as arterial hypertension and dyslipidaemias.

When antihyperglycaemic agents are required, agents acting on insulin sensitivity (metformin, maybe thiazolidinediones) or on carbohydrate intestinal absorption (α-glucosidase inhibitors) should be preferred to the agents stimulating insulin secretion (sulphonylureas) that usually favour weight gain.

Aggressive weight reduction programmes may be used in severely obese individuals with type 2 diabetes, refractory to conventional diet and drug treatment, instead of prescribing high doses of insulin. In particular, bariatric surgery, mainly gastroplasty and gastric bypass, may be helpful in diabetic patients with morbid obesity, provided that it is performed by a well trained multidisciplinary team in well selected and carefully supervised patients.

Even if targeting weight excess rather than hyperglycaemia *per se* may be a valuable alternative in selected obese patients, long-term prospective studies are required to more precisely determine the place of each strategy in the overall management of patients with both obesity and type 2 diabetes.

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