



Patient case studies

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Three contrasting cases of obese patients with type 2 diabetes mellitus are presented, which illustrate the management difficulties faced by clinicians. The first raises the issue of when to commence an oral hypoglycaemic agent in a newly diagnosed but asymptomatic obese patient; the second case addresses the problem of when to commence insulin in the face of continuing weight gain and poor glycaemic control; the final case is an example of the vicious metabolic spiral which so many patients enter, with increasing body weight, poor diabetic control and associated comorbidities. The discussion that follows each case presentation recognises the considerable cardiovascular risk faced by such patients and provides guidance about possible management pathways including adjunctive anti-obesity pharmacotherapy.

Keywords: type 2 diabetes mellitus; obesity; cardiovascular risk; management programmes

Introduction

The second part of this symposium involved the presentation of three patient case studies, with accompanying audience interaction. The aim was to see how the ideas generated by the three presentations in the first part of the symposium could be incorporated into daily clinical practice. The case histories highlighted the difficulties commonly faced by diabetologists managing obese patients with type 2 diabetes.

The first case history raised the issue of when to commence oral antidiabetic therapy in the obese patient with newly diagnosed asymptomatic type 2 diabetes. The second case history addressed the problem of when to start insulin therapy in the poorly controlled obese diabetic patient receiving maximum doses of oral hypoglycaemic agents. The third patient case, which was particularly sad, illustrated the vicious metabolic spiral that can result from trying to control glycaemia in a patient with type 2 diabetes, without addressing existing obesity and the potential for 'iatrogenic' weight gain.

Patient case 1: the newly diagnosed obese type 2 diabetic patient

Presented by Luc Van Gaal, Department of Endocrinology, Universitaire Instelling Antwerpen, Antwerp, Belgium

Van Gaal: This 49-year-old man (Table 1) was recently diagnosed as having type 2 diabetes. There was a family history of diabetes, with both father and uncle suffering from the disease. The patient was asymptomatic on presentation, with no signs of recent weight loss, thirst, polyuria or infections. He was referred for a medical examination following the discovery of glycosuria. BMI was 34.2 kg/m²; above the level of 30 kg/m² which defines obesity. Similarly, waist circumference was 114 cm; above the obesity threshold of 102 cm. Fasting blood glucose was 10.2 mmol/l. HbA_{1c} was 7.6%; above the accepted level of 7%. Blood pressure and triglycerides were elevated, while HDL was moderately decreased. Thus, the patient was at risk from the metabolic syndrome. There was a trace of protein in the urine and the patient was receiving no medication.

The aims of management in such a patient should be to reduce body weight and improve glycaemic control. Reducing waist circumference, an index of central obesity, is particularly important. The aim of long-term glycaemic control in this asymptomatic patient is prevention of late complications.

There should be a realistic weight loss goal: a maintained reduction of 5–10% of initial body weight. Decreasing waist circumference is particularly important; a reduction of 10% will generally result in around a 25% reduction in visceral fat, which is most important for reducing atherogenic risk.

The patient was put on a 12-week energy deficit diet, but actually gained weight during this time. Global metabolic profile did not change to any appreciable extent, though there was a modest 0.4 mmol/l decrease in fasting glucose level. All other metabolic parameters remained unchanged. It was therefore decided to try and improve the metabolic profile by initiating metformin therapy, 500 mg tds. One of the

Table 1 Patient case 1: the newly diagnosed obese type 2 diabetic patient. The patient profile

Gender	Male, non-smoker, alcohol 2 units/d
Age	49 y
Weight	117.5 kg
Height	1.85 m
BMI	34.2 kg/m ²
Waist circumference	114 cm
Family history	Type 2 diabetes in family
Diagnosed	Asymptomatic
Fasting blood glucose	10.2 mmol/l
HbA _{1c}	7.6%
Blood pressure	150/90 mmHg
Cholesterol	6.2 mmol/l
Triglycerides	2.4 mmol/l
HDL	0.9 mmol/l
Symptoms	Trace of proteinuria
Intervention – medication	On no medication

reasons for choosing metformin was its neutral effect on body weight.

Kopelman: Okay, let's open up this case to discussion. John, how would you manage this patient?

Foreyt: I would start by assessing how ready the patient was to change. We do this using a readiness to change scale, such as that in *Weighing the Options*, published by the National Academy of Sciences. I would look at where the patient is today, establishing how he gained his weight and over what time span. I'd also see if he had stress in his job or marriage. I would then target lifestyle modifications accordingly.

Let's assume he is ready to make lifestyle changes. I would ask him to complete a food diary and assess his levels of physical activity. Gentle exercise would be the first intervention, asking him to walk for a few minutes a day and gradually building up to 30 min a day. This helps to improve the patient's feelings about themselves.

It is important to recognise that modest changes can have an important impact. We frequently use a 100/100 approach, that is, losing 100 calories a day from gentle exercise and 100 from minor dietary modification. This can be achieved, for example, by 20 min brisk walking every day and taking a little less butter on bread. By losing just 200 calories/d you lose 20 lbs in a year. Small changes are important, rather than trying to reach some 'ideal' body weight. I also work on stress management.

In this particular patient I'd be looking to achieve a 25 lb weight loss over 6 months, about 1 lb per week by losing around 500 calories a day: 250 calories/d from gentle exercise and 250/d from modest dietary changes. I'd then be looking to hold him at that 25 lb weight loss for 6 months, helping him to accept and maintain that degree of weight loss. This type of patient is a prime candidate for success.

Harmecin (Australia): I'm very impressed by the lifestyle approach. Are patients generally seen on a weekly basis and who pays for this therapy?

Foreyt: Ideally, the patient will initially be seen once a week by one of the team. In my experience a multidisciplinary approach for the management of obesity works best. We see the patient once a week for 24 weeks and then see them once every 2 weeks thereafter, eventually moving them into monthly group meetings. That's the ideal situation, but I realise that many primary care physicians can't do that. There are excellent data published by Gary Foster and colleagues showing that primary care physicians seeing patients for 10–15 min every month helps to accomplish a weight loss of around 25 lbs over 6 months. They have just published 2-year data in *Obesity Research* showing reasonably good maintenance into the second year. So if primary care physicians can help patients with a lifestyle approach, good results can be achieved, even if patients can't be seen as often as in the ideal situation that I explained earlier. As regards who pays, in the USA it's the patient who pays.

Abassy (Egypt): I would like to ask Professor Van Gaal about the trace of protein in the patient's urine. Was this investigated and if so what was the underlying cause? Was it related to hypertension, diabetes or obesity?

Van Gaal: At the time of diagnosis, many type 2 diabetics already show traces of protein, or overt microalbuminuria. I think that the trace of protein in this patient is related to his diabetic state and is probably also related to his mild hypertension. The search for other complications was negative. Obesity may also be a factor. Microalbuminuria is seen more often in obese diabetics, compared with their non-obese counterparts.

Kopelman: In concluding this case, it is interesting to note that if the patient were able to maintain a 10% reduction in his body weight, the following improvements could be anticipated: a blood pressure reduction of 10 mmHg, a 30% reduction in fasting blood glucose, a 15% reduction in HbA_{1c} and a 10% reduction in cholesterol. So, metabolic parameters would not be normalised, but they would be much closer to normal than is possible with the conventional treatment that the patient was prescribed.

Patient case 2: the long-term type 2 diabetic patient on maximum doses of oral antidiabetic agents

Presented by Hans Hauner, Diabetes-Forschungsinstitut, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

Hauner: This 60-year-old woman (Table 2) had type 2 diabetes diagnosed 3 years previously. Her BMI was 36.4 kg/m² and her waist circumference was 94 cm, so she was clearly obese. Metabolic assessment found a fasting blood glucose of 11.7 mmol/l, an HbA_{1c} of 9.1%, elevated blood pressure and dyslipidaemia. She had no apparent diabetic complications.

She was visited by a diabetes nurse, who was concerned about her weight and poor metabolic control. The patient was receiving oral antidiabetic drugs: gliclazide 160 mg bd and metformin 500 mg tds. Her physician subsequently increased her oral medication. On becoming refractory to metformin, insulin therapy was initiated. The result, unsurprisingly, was a further increase in body weight.

Kopelman: This is a situation commonly faced by clinicians. Does anyone have any immediate points about management?

Beischer (Germany): What sort of insulin therapy was initiated? I think insulin at bedtime should have been the first choice in this case.

Hauner: She had two insulin injections each day, one in the morning and one before dinner; 40 units per injection of a pre-mixed soluble and isophane preparation.

Table 2 Patient case 2: the long-term type 2 diabetic patient on maximum doses of oral antidiabetic agents. The patient profile

Gender	Female
Age	60 y
Weight	102.8 kg
Height	1.68 m
BMI	36.4 kg/m ²
Waist circumference	94 cm
Family history	No family history of diabetes
Diagnosed	First diagnosed 1995
Fasting blood glucose	11.7 mmol/l
HbA _{1c}	9.1%
Blood pressure	160/80 mmHg
Cholesterol	6.1 mmol/l
Triglycerides	3.5 mmol/l
HDL	0.9 mmol/l
Symptoms	No complications at this stage
Intervention – referral	Visited by diabetic nurse, concern about weight and glycaemic control
Intervention – medication	<ul style="list-style-type: none"> • Gliclazide 160 mg bd • Metformin 500 mg tds

Beischer (Germany): I wouldn't expect success from this regimen. I think night time insulin would have been better.

Hauner: That is certainly an alternative, but I don't think published data indicates that night time dosing is clearly superior.

Kopelman: The evidence may come from the new UKPDS results, which will be available shortly. Perhaps I could invite Luc Van Gaal to suggest another way of handling such a case.

Van Gaal: In cases like this the use of weight management drug therapy can help to postpone the need for insulin therapy. We know from studies that 5–10% weight loss can significantly improve metabolic control. We have two weight management drugs at the moment, orlistat and sibutramine.

Orlistat is a lipase inhibitor. The 1-year study of Hollander *et al*, published in *Diabetes Care* this year, found a statistically significant mean weight loss of 6.2% in patients with type 2 diabetes.¹ There was also an accompanying mean reduction in waist circumference, indicating a reduction in visceral fat. This is known to lead to a reduction in comorbid factors such as insulin resistance, lipid abnormalities, and even abnormalities of coagulation and haemostasis. Similarly, a 24-week sibutramine study involving patients with type 2 diabetes found statistically significant weight loss in the intention-to-treat and completer populations. There was a progressive downward slope, indicating that weight loss would continue after six months. So the long-term use of weight management pharmacotherapy is a consideration for physicians.

Kopelman: Any questions or comments? Gareth, have you much experience of using night time insulin in a case such as this?

Williams: This is an example of where we in the UK are behind the times compared with many other countries. We don't use night time insulin a lot in the UK. I have some colleagues who have tried night time isophane insulin together with either metformin or a sulphonylurea. They have found what Hannele Yki-Jarvinen has found over the years, that is, it's a good way for improving metabolic control without the marked weight gain that you get with full insulin dosing.² Of course, there are some patients that you cannot control using this method.

Hauner: In this particular case the key problem is increased body weight and insulin resistance due to weight gain under previous treatment. I think the first

target should be to try everything to reduce her body weight.

Beischer (Germany): Yes, but I think you need an immediate result too. I think you can combine night time insulin and weight loss therapy. Clinical studies indicate that weight gain with night time insulin is very small.

Van Gaal: Yes, it would be possible to do that, but the patient would need very close supervision. As weight decreases, you would have to progressively decrease the amount of insulin that the patient was started on.

Foreyt: I'd just like to make the point that if weight management pharmacotherapy is used it should be adjunctive to a lifestyle programme. These drugs should not be given instead of lifestyle programmes.

Van Gaal: Yes, a very important point. Weight management drugs should only be used as part of a total package of energy deficit diet, physical activity and behavioural therapy.

Kopelman: I think the concluding message is that 80% of our patients with type 2 diabetes are obese and a large number are heading toward the scenario highlighted by this patient case. Clearly, there are significant undesirable clinical and financial consequences of having to move to insulin, even night time insulin. Weight reduction is an important therapeutic strategy in such patients.

Patient case 3: the obese diabetic patient with comorbid complications

Presented by Gareth Williams, University Hospital Aintree, Liverpool, UK

Williams: This is a sad case because, in retrospect, a lot more could have been done for this patient. But we have to deal with the end result. This lady was first diagnosed as having type 2 diabetes in 1982. At this time she was obese and had a fasting blood glucose (FBG) of approximately 8 mmol/l. There was also a family history; her mother had type 2 diabetes and was also overweight.

The patient was prescribed diet and chlorpropamide and her weight fell from just above 90 kg to just below 80 kg. Her FBG also fell slightly and her doctor was generally happy. Then for some unknown reason she was switched to glibenclamide in 1983 and subsequently switched to metformin. You could argue that

this was not a logical sequence of events and that she should have been on metformin from the beginning. Anyway, in 1989 her weight increased quite markedly to more or less the original level at presentation. There was no obvious reason for this, but it was probably due to changes in lifestyle, stress and personal circumstances.

Over the next few years weight remained pretty stable at this elevated level, but blood glucose continued to rise. At the end of 1993 insulin therapy was started. Her weight rose markedly as a result, with her BMI reaching nearly 40 kg/m².

The net result is that the patient currently has numerous clinical problems (Table 3). Her FBG is now 10.1 mmol/l, so it's higher than it was at initial presentation in 1982. This is partly due to the decline in β -cell function that characterises type 2 diabetes, but medical intervention has undoubtedly contributed to the deterioration.

Her HbA_{1c} is also unacceptably high at 8.8%, her blood pressure has increased and her dyslipidaemia has also worsened. So her problems at the present time are hypercholesterolaemia, hypertension, poorly controlled type 2 diabetes and obesity. She is receiving simvastatin for her hypercholesterolaemia, losartan for her hypertension and insulin, 39 units a.m./41 units p.m., for improvement of metabolic control. This is a conventional UK insulin regimen, but just because it's conventional doesn't mean that I necessarily approve of it.

This patient puts the mythology of type 2 diabetes into true context. Her condition is not 'mild', it is serious and getting worse. There is very little statistical doubt that if her condition carries on as it is she will die prematurely from cardiovascular disease. Type 2 diabetes is not easier to treat than is type 1, but treatment targets are less rigorous. In retrospect, this may be why this patient's treatment seemed to be conducted in a rather haphazard fashion.

Table 3 Patient case 3: the obese diabetic patient with comorbid complications. The patient profile

Gender	Female
Age	57 y
Weight	100.2 kg
Height	1.66 m
BMI	37.3 kg/m ²
Waist circumference	118 cm
Family history	Mother had type 2 diabetes diagnosed in later life
Diagnosed	First diagnosed 1982
Fasting blood glucose	10.1 mmol/l
HbA _{1c}	8.8%
Blood pressure	180/90 mmHg
Cholesterol	7.9 mmol/l
Triglycerides	3.5 mmol/l
HDL	0.92 mmol/l
Symptoms	<ul style="list-style-type: none"> • Hypercholesterolaemia • Hypertension • No proteinuria
Intervention – medication	<ul style="list-style-type: none"> • Simvastatin • Losartan • Insulin (39 units a.m./41 units p.m.)

Medical intervention failed to control the patient's blood glucose. In fact, iatrogenic weight gain may have put the patient at increased risk of complications such as hypertension and dyslipidaemia. If weight loss interventions had been used early on, it may have been possible to improve her condition rather than making it worse. According to the Scottish Intercollegiate Guidelines Network, we could have expected considerable improvements if she had managed to maintain a 10% weight loss.³ Her BMI would now be 32 kg/m² rather than approaching 40 kg/m², her blood pressure would have gone down rather than up, her FBG would be 7 rather than 10 mmol/l, and her HbA_{1c} would have improved in line with that. Her lipids would also be giving us a lot less cause for concern. Ideally, we would have reduced the amount of visceral fat in the patient, as this is known to be associated with particularly adverse metabolic effects.

The point of this presentation is really to say that we need to think anew about the way that we manage our type 2 patients. Obesity is a very common problem in these patients, and it is very rare to find an obese person with type 2 diabetes who does not have other cardiovascular risk factors.

Kopelman: So the challenge is to try and intervene at an early stage. Are there any questions from the floor?

Paisey (UK): We all recognise the need for lifestyle changes and also the need to recognise the readiness of the patient to change. But what do we do with the many patients that aren't ready to change?

Foreyt: Myself and colleagues see that a lot. The Mexican Americans in our study were a good example. Many of these people didn't believe that they had any control at all over their lives, and so thought trying to reduce weight was pointless. In this case we started by personalising the risk and using psychoeducational strategies to show what small changes can do. By doing that you might start making a difference, which you then reinforce very quickly. It's not easy but it can be done.

Kopelman: In summary, I hope the message is clear that obesity is a major risk factor for cardiovascular disease, particularly in people with type 2 diabetes. We therefore need to focus our intervention strategies, looking at programmes of energy deficit diet, physical activity and behavioural therapy, possibly combined with adjunctive weight management pharmacotherapy in certain cases.

References

- 1 Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, Lucas CP, Lodewick PA, Canovatchel W, Chung J, Hauptman J. The role of orlistat in the treatment of obese patients with type 2 diabetes mellitus: a 1-year, randomized, double-blind study. *Diabetes Care* 1998; **21**: 1288–1294.
- 2 Yki-Jarvinen H, Ryysy L, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Salo S, Seppala P, Tulokas T, Viikari J, Taskinen MR. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997; **82**: 4037–4043.
- 3 Scottish Intercollegiate Guidelines Network. *The Management of Obesity in Scotland—Integrating a New Approach in Primary Healthcare*. SIGN: Edinburgh, 1996.