Brief Report

Failure of Insulin Treatment in Obese Patients with Non–insulin-dependent Diabetes Mellitus

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A number of experts recommend the use of insulin for patients with non–insulin-dependent diabetes mellitus (NIDDM) who fail to respond to diet, exercise, and oral hypoglycemics, even when the patient is morbidly obese. This article describes the use of insulin in two obese patients with NIDDM whose obesity worsened following the institution of insulin therapy.

In some cases the risk for increased obesity and its complications following the institution of insulin may offset the potential benefits of insulin therapy itself. There are two main drawbacks associated with insulin therapy in these patients. First, from a medical point of view, insulin has a lipogenic effect and may actually contribute to weight gain, hyperinsulinemia, and increased insulin resistance in obese patients with NIDDM. Second, from a behavioral point of view, the institution of insulin therapy may shift the patient's and physician's focus from the preferred lifestyle adjustments to the numerous details associated with insulin use and monitoring. Since weight gain and sedentary activity are themselves risk factors for coronary artery disease, the benefits of decreased blood glucose levels should be balanced against the risk of increased weight gain in these patients.

Key words. Diabetes mellitus, non–insulin-dependent; insulin; obesity; blood glucose. (*J Fam Pract 1993; 37:76-81*)

Ensuring the optimal management of patients with non–insulin-dependent diabetes mellitus (NIDDM) is a challenge for virtually all primary care physicians. Low-calorie diets and increased exercise, with or without the addition of oral hypoglycemics, are routinely recommended as a fundamental part of the treatment of obese patients. Nonobese (lean) patients with NIDDM sometimes require additional insulin therapy. Insulin treatment is also started in many obese patients who fail to respond to diet, exercise, and oral hypoglycemics, in an attempt to achieve better glycemic control. In fact, 29% of all diabetic patients in the United States have NIDDM that is being treated with insulin, and more than 75% of the patients who are receiving insulin therapy have NIDDM.[1]

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A number of groups of experts, including the American Diabetes Association, recommend the use of insulin in this manner and suggest that glycemic control will eventually be achieved in almost all diabetic patients, thus reducing the risk of microvascular complications.[2–5] A variety of possible treatment protocols for insulin, either alone or in combination with oral hypoglycemics,[6] are recommended by these authorities, yet there are no clear outcome-based studies showing benefit with respect to long-term morbidity and mortality.[7] Although the initiation of insulin in patients with ketoacidosis is an accepted medical practice, this complication is a relatively unusual occurrence in obese patients with diabetes.

Obesity is considered a risk factor for NIDDM, and the vast majority of patients with NIDDM (80% to 90%) are obese. Obese patients with NIDDM who lose weight lower their blood glucose and endogenous insulin levels[3,8–11] and presumably reduce the risk for complications. On the other hand, treating obese patients who have NIDDM with insulin may increase obesity, regardless of improvement in glycemic control.[12,13] Although a recent study of NIDDM patients treated with insulin

documented increased subjective well-being and a decrease in glycosylated hemoglobin relative to a control group treated with oral hypoglycemics, all four subgroups treated with insulin gained weight whereas the control group actually lost weight.[13] Obesity adds to the morbidity and mortality of these patients, and serves as an independent risk factor for macrovascular and microvascular disease.[14–18] At least one study has shown a direct relationship between weight reduction and prolonged survival.[19] We believe that the importance of obesity as a risk factor for NIDDM and for coronary heart disease may not be given adequate emphasis in the decision to use insulin in treating obese patients with NIDDM.

We present two case reports that demonstrate the potential problem of insulin treatment in obese patients with NIDDM.

Case History 1

A 39-year-old married woman, mother of four, had been a patient of the family practice center for about 5 years. She was obese and had associated low back pain and arthritis involving both knees. In 1987, NIDDM was diagnosed following symptoms of polyuria and polydypsia. Her weight at that time was 250 lb (height, 5 ft 2 in.). She was referred to a dietitian, and glyburide therapy was initiated.

Over the next year, the patient was monitored monthly and encouraged to follow appropriate dietary recommendations, yet there was no change in weight or glycemic control. Although dietary recommendations were recorded clearly, there is no objective verification that the patient was following the diet as directed. This patient's fasting blood glucose levels were usually approximately 200 mg/dL (11.1 mmol/L). In association with a family crisis in 1989, the patient's fasting blood glucose levels rose (400 to 500 mg/dL [22.2 to 27.8 mmol/L]). Glyburide was increased to the maximum dose, and a second referral was made to the dietitian. Despite these efforts, blood glucose levels remained elevated, and no weight reduction occurred. Insulin treatment was begun.

Initial low doses of insulin had little effect on the blood glucose levels. Insulin was gradually increased from 16 to 250 units per day over 1 year. With a total of 250 units of insulin split into three injections per day, the patient's blood glucose level dropped to the 200 to 250 mg/dL range. The patient's weight gradually increased more than 75 lb (from 250 lb to 327 lb) during the year following initiation of insulin (Figure 1). She had no symptoms of other medical problems such as congestive heart failure or thyroid dysfunction that might have accounted for the weight gain.

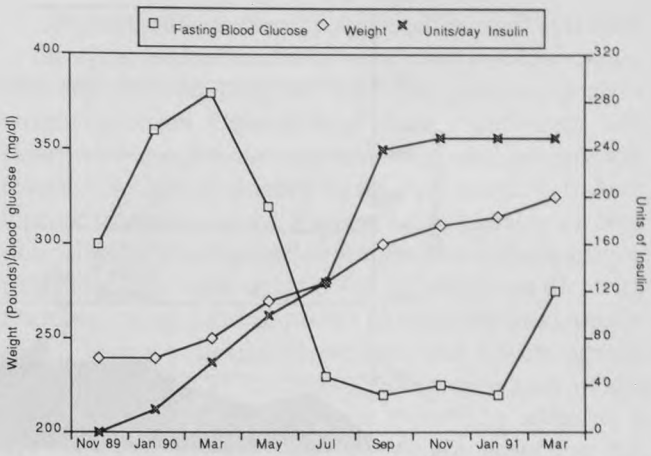

Figure 1. Case history 1. Response of patient's fasting blood glucose and weight to initiation of insulin therapy.

Case History 2

A 47-year-old divorced, unemployed mother of a physically disabled child received care in the family practice center beginning in September 1989. She was followed by one primary care provider for her medical problems, which included obesity and arthritis involving both knees. Clinical findings did not indicate congestive heart failure or other significant medical problems. Her baseline weight in May 1990 was 241 lb (height, 5 ft 5 in.).

In April 1990, the patient's blood glucose level was reported to be in the 200 to 300 mg/dL range. A program of exercise and nutrition counseling was implemented to address the underlying problem of obesity and glucose intolerance. Two months later, little progress had been documented either with weight reduction (244 lb) or glucose control. Glyburide, 2.5 mg per day, was started and a whole blood glucose monitor was ordered. Over the next 6 months, the dose of glyburide was increased to 10 mg per day, but there was no improvement in glucose control. The patient's weight did not change significantly (246 lb), despite continued nutrition counseling.

In January 1991, insulin therapy was instituted and glyburide was discontinued. The initial insulin dosage was 15 units of human insulin (Humulin 70/30) given every morning. The dose of insulin was increased with each subsequent visit in an attempt to improve glycemic control. By March 1990, the dose was 45 units in the morning and 30 units in the evening.

In spite of these large doses (75 units per day) of insulin, there was little improvement in the patient's

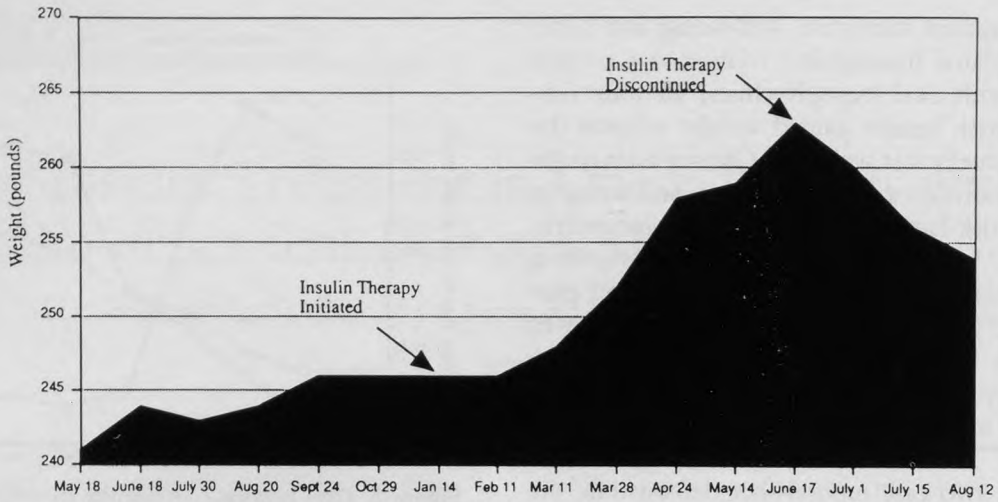

Figure 2. Case history 2. Patient's weight response to initiation and then discontinuation of insulin therapy.

glucose control. In addition, following initiation of insulin therapy, and particularly while receiving higher doses of insulin, the patient's weight increased to 263 lb, a gain of 22 lb over her baseline weight (Figure 2).

In July 1991, given the lack of improved glucose control and persistent weight gain, a decision was made to discontinue the insulin therapy and return to glyburide. The patient's glucose level remained uncontrolled, but her weight decreased by 11 lb over the next 6 weeks.

Discussion

The basic mechanisms underlying the phenomenon of insulin resistance in the obese patient are related to the increased fat mass in these patients. This increased fat mass is associated with increased lipolysis and a concomitant increase in plasma free fatty acids (FFA). The FFA serve as substrate for increased lipid oxidation, which directly opposes insulin actions. In the liver this results in increased gluconeogenesis. At the same time, the increased lipid oxidation inhibits insulin-mediated glucose disposal in both the muscles and the liver.[20] Additionally, preferential shunting of substrate away from muscles to adipose tissue is a factor contributing to a self-perpetuating cycle of obesity in these patients.[21]

The blunted insulin effect causes increased insulin secretion, essentially producing a state of hyperinsulinemia. This hyperinsulinemia is the trigger for downregulation of both insulin receptor number and the intracellular glucose transport system, which contributes to insulin resistance. In susceptible persons, pancreatic beta cells may be unable to produce adequate insulin levels. This results in a relatively hypoinsulinemic state. The result is an increased glucose intolerance leading to overt diabetes with fasting hyperglycemia (Figure 3).

In lean patients with NIDDM, the probable underlying pathophysiology is a beta-cell insufficiency causing an insulin deficiency. The resultant hyperglycemia may cause a faster exhaustion of the remaining functional capacity of the beta cells.[22] Glucose toxicity,[20,22–24] which is insulin resistance secondary to elevated serum glucose levels, is probably common to both entities.

Obese patients on weight-reducing diets can achieve good glycemic control after attaining desired weight loss. If the individual patient has been treated with insulin before losing weight, insulin therapy may actually become unnecessary as long as weight loss is maintained.[23,25–27] On the other hand, lean patients do not respond to weight reduction with a decreased dependence on insulin, and most will still need insulin even after rigorous dieting.[28] The two subgroups also differ in their response to oral hypoglycemic medications. Secondary failure of oral hypoglycemic agents occurs more commonly in lean patients (6.2% per year) than in obese (20% above ideal body weight) patients with NIDDM (1.2% per year).[29]

The pathophysiological differences between obese patients with NIDDM and lean patients mandate different treatment strategies. Elevated blood glucose levels in association with insulin deficiency in these patients may justify earlier insulin treatment in an attempt to prevent complications. This situation is in contrast to the metabolic abnormality in obese patients with NIDDM in whom secondary hyperinsulinemia results in further insulin resistance.

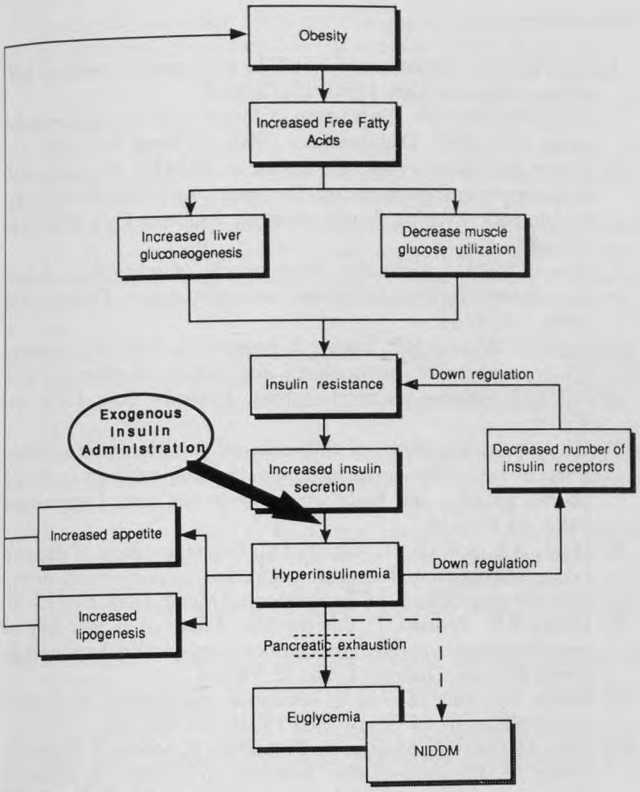

Figure 3. Flow chart illustrating the mechanism whereby exogenous insulin given to control hyperglycemia may actually contribute to hyperinsulinemia and increased insulin resistance.

Although the findings of a recently published trial involving older men established only borderline significance for hyperinsulinemia as an independent risk factor for coronary artery disease (CAD),[30] an earlier well-controlled study showed a stronger association between hyperinsulinemia and macrovascular disease.[31] The patients in the latter study did not differ with respect to body weight or fasting blood glucose, yet exhibited higher daily insulin doses and fasting-free insulin levels. The Helsinki Policemen Study also showed a high plasma insulin level to be predictive of CAD risk independent of other risk factors including blood glucose levels.[32] Despite this evidence suggesting that hyperinsulinemia may have an impact on CAD risk, at a pathophysiologic level, the interaction of hyperlipidemia, hyperinsulinemia, and obesity is not completely defined.[33]

Nonetheless, when attempting to improve overall glucose control in these patients, it is important to remember that obesity does constitute an independent risk factor for cardiovascular disease[14–17] and that mortality from CAD in obese patients is higher than in nonobese patients.[14] This is of particular importance in patients with NIDDM because 80% to 90% are obese, and cardiovascular events account for most fatalities in this group.[17,34]

A reasonable treatment approach toward NIDDM in the obese patient would be adherence to a low-calorie diet and exercise program with the primary goal of weight reduction. Up to 85% of obese, middle-aged, and elderly diabetic patients can achieve normal glucose tolerance if weight is reduced to its ideal range.[35] In fact, glucose tolerance can be improved considerably or even normalized with only modest weight loss without having to achieve ideal body weight.[25,26] A low-calorie diet with associated weight loss improves glucose and lipid metabolism, increases insulin sensitivity, and lowers arterial blood pressure with a corresponding reduction of the cardiovascular risk-factor profile.[28,36–39] In addition, a low-calorie diet that results in weight reduction has additional beneficial effects caused by changes in fat metabolism.[38] Decreasing plasma FFA concentrations may improve insulin resistance and eliminate hyperinsulinemia.[37,39,40] Weight reduction should be accompanied by increased physical activity.[41] Increased exercise increases caloric expenditure, thereby helping to reach an isocaloric state. Exercise itself has a direct impact in that it reduces insulin resistance. Because this effect is of short duration, however, exercise should become a regular component of lifestyle.[42]

The addition of oral hypoglycemics can be of benefit in obese patients with NIDDM.[6,29] Oral hypoglycemics enhance the effectiveness of endogenous insulin and decrease the level of hyperinsulinemia. Since the failure rate of these medications in obese patients is low, many of these patients may benefit over an extended period. If the obese patient with NIDDM has poor glycemic control and is maintaining or gaining weight, renewed emphasis on dietary adherence and intensified patient education is needed. Although there are ways to predict which patients will be most likely to achieve improvement in glycemic control with weight reduction,[43] one study of obese patietns with NIDDM showed that the only significant factor associated with more than 10% weight loss is the number of clinic visits.[44] The physician may have to accept suboptimal glycemic control for some patients, particularly patients who are not compliant with follow-up or diet and exercise recommendations.[23,45]

Dissatisfaction with suboptimal glycemic control can tempt the physician to start insulin treatment. The existing treatment options include the use of sulfonylureas, insulin, or a combination of both. There is no convincing evidence that the combination approach is better than either treatment alone.[1,2,6,7,12,23] In fact, sulfonylureas in combination with insulin may actually accelerate hyperinsulinemia.[6,13]

There are two potential drawbacks associated with insulin therapy in these patients: behavioral and medical. Although some patients are willing and able to master

the complexities of insulin administration, blood glucose monitoring, and frequent dosage adjustment, a number of these patients may display less interest in the important dietary or activity changes necessary to optimally treat their diabetes. In these persons, insulin use may become a substitute for substantive lifestyle change.

From a medical point of view, the insulin dose required to maintain glycemic control in some obese patients is often very high, with a number of authors describing the need for daily dosages in excess of 100 units.[23,45] The insulin given may cause additional weight gain and may actually increase the potential for morbidity and mortality from CAD.

Although successful weight reduction through diet and exercise is more challenging for the physician than simply initiating insulin therapy, diet and exercise are better from a physiological perspective. Physical activity also appears to protect against the development of NIDDM.[41,46] This effect is strongest in persons at highest risk for NIDDM.

The risks and benefits of insulin therapy should be assessed before initiation of treatment. Although obesity should not be considered a contraindication to the use of insulin in patients who fail oral hypoglycemics,[47] the benefits of striving to decrease blood glucose levels in these patients must be weighed against the risk of hyperinsulinemia and its potential complications as well as the risks of increasing obesity itself.[45,46]

The report of the long-term follow-up of patients in the UK prospective diabetes study[7] is expected to be published in 1995.[3] The goal of the study is to determine whether improved glucose control aiming for basal normoglycemia is advantageous, and whether sulfonylurea or insulin therapy has any advantages. Although obesity should not be considered a contraindication to the initiation of insulin therapy in the patient with NIDDM,[4–7] conservative efforts remain the cornerstone of therapy in these patients. Even modest weight loss and increased activity can have long-term beneficial effects and are possible with appropriate support.[26,43,46,48]

In summary, adjustment of diet and exercise should be the treatment of choice in the obese patient with NIDDM, with the addition of oral hypoglycemics when necessary. Insulin should generally be reserved for lean patients, those with ketoacidosis, or those with significant persistent hyperglycemia refractory to other treatment. Insulin may improve glycemic control and patient well-being, yet insulin has not been shown to reduce complications or increase longevity in these patients. At the same time, insulin may increase the risk for vascular disease as well as cause mild weight gain in many and severe weight gain in some.

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