

A Case for Introducing Insulin Early in the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is characterized by insulin resistance and insulin deficiency. The majority of patients with type 2 DM will eventually require insulin therapy. The traditional paradigm for starting insulin has been to use it after therapy with oral antidiabetic agents has failed. However, changing this paradigm and introducing insulin therapy early in the course of treatment may have advantages beyond improving glycemic control.

Objective: The goal of this article was to describe the rationale and potential benefits of using insulin therapy early in the course of type 2 DM.

Methods: Materials used for this article were identified through a search of MEDLINE from 1966 to 2006. English-language articles were chosen using the search terms *diabetes mellitus type 2*, *insulin resistance*, and *islets of Langerhans*.

Results: The pathogenesis of type 2 DM is characterized by 2 major processes: insulin resistance (which results in increased glucose production by the liver and decreased glucose disposal by peripheral tissues) and a progressive impairment of β -cell function (which leads to a corresponding decline in insulin secretion with time). Studies in patients with newly diagnosed type 2 DM have shown that short-term intensive therapy with insulin that achieves near-normal glycemic control may lead to prolonged periods of good glycemic control, without the need for pharmacologic therapy. Early, aggressive use of insulin therapy may improve β -cell function, which in turn could delay, halt, or even possibly reverse the natural progression of type 2 DM.

Conclusions: With a more aggressive approach to starting and intensifying insulin therapy, patients may be more likely to achieve and maintain glycemic goals, thereby reducing the development of DM complications. Over time, this intervention may lead to healthier and longer lives for patients with type 2 DM. (*Insulin*. 2006;1:65-69) Copyright © 2006 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, insulin resistance, insulin deficiency, insulin therapy.

INTRODUCTION

Type 2 diabetes mellitus (DM) is associated with substantial morbidity and mortality due to microvascular and macrovascular complications. It is clear that glycemic control decreases the risk of retinopathy, nephropathy, and neuropathy in patients with type 2 DM.¹ Therefore, treatment regimens that maintain good glycemic control in these patients for as long as possible are essential for reducing the burden of complications.

Insulin has traditionally been viewed as the last pharmacologic option to use in a patient with type 2 DM.² However, starting insulin early in the course of the disease is an effective way to achieve good glycemic goals. The objective of this article was to discuss the rationale for introducing insulin early in the treatment of type 2 DM based on what is

known about the pathophysiology of the disease. Evidence supporting the value of such a strategy is also presented.

MATERIALS AND METHODS

Materials used for this article were identified through a search of MEDLINE from 1966 to 2006. English-language articles were chosen using the search terms *diabetes mellitus type 2*, *insulin resistance*, and *islets of Langerhans*.

THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

The pathogenesis of type 2 DM is characterized by 2 major processes: insulin resistance (which results in increased glucose production by the liver and decreased glucose disposal by peripheral tissues) and a progressive impairment of β -cell function (which leads to a corresponding decline in insulin

secretion with time).³ Prospective studies of Pima Indians have shown that both of these problems begin well before the onset of type 2 DM.⁴ An underlying insulin resistance increases the demand for insulin from the β -cell. The inability of the β -cell to continue to compensate adequately for this demand is what leads to the onset of hyperglycemia; it also separates those who develop type 2 DM from those who do not develop type 2 DM and instead have impaired glucose tolerance.⁴ Therefore, the onset of β -cell dysfunction is the key event in the development of type 2 DM.

Data from the United Kingdom Prospective Diabetes Study (UKPDS), a trial of >4000 subjects newly diagnosed with type 2 DM, demonstrated that an ongoing decline of β -cell function occurred at a constant rate after the onset of type 2 DM in patients treated with diet, metformin, or a sulfonylurea.⁵ β -Cell function was determined through homeostasis model assessment (HOMA), a method that utilizes fasting glucose and insulin levels. Therefore, patients on insulin therapy could not be analyzed. These patients had lost ~50% of their β -cell function at the time of diagnosis.⁵ A regression line that incorporated the data for 6 years of study showed that the β -cell dysfunction may have started 10 years before the diagnosis of DM. Thus, the onset of β -cell dysfunction associated with type 2 DM may start many years before the disease is recognized.

Other studies that have examined insulin secretion in the course of type 2 DM have reported that insulin secretion decreases with time after the diagnosis of DM.^{6,7} The Belfast Diet Study, using the HOMA method to analyze insulin secretion, found a progressive decline in β -cell function in 233 recently diagnosed patients with type 2 DM who were followed up over a 10-year period.⁷ Both the UKPDS and the Belfast Diet Study demonstrated that this progressive drop in β -cell function was associated with progressive deterioration in glycemic control. In the UKPDS, although the initial glycosylated hemoglobin (A1C) values were successfully lowered with diet or pharmacologic interventions, improvements in A1C values deteriorated over time, and the proportion of patients who continued to maintain their target glycemic control declined over the duration of the study.⁸ About 50% of these patients were able to maintain their target glycemic control at 3 years, whereas only ~25% of these patients were able to maintain glycemic control at 9 years.⁸ Thus, the progressive loss of β -cell function that occurs with the natural course of type 2 DM appears to be largely responsible for the documented failure to maintain efficacy over the long term that is seen with diet and oral antidiabetic agents.

Multiple factors have been implicated in the pathogenesis of the β -cell failure that develops in type 2 DM. These include: β -cell exhaustion due to the increased demand for insulin secretion that arises from insulin resistance; desensitization of the β -cell due to elevations in glucose; adverse effects of lipids on insulin secretion and action; and a reduction in the β -cell mass.³ Butler et al⁹ examined pancreatic tissue from autopsies and determined that obese people with

type 2 DM had a 63% deficit in β -cell volume compared with obese people without DM. They also reported an increased frequency of apoptosis in individuals with type 2 DM compared with controls, which would suggest that the mechanism underlying the loss of β -cell mass was apoptosis. Deng et al¹⁰ examined pancreatic islets from cadaver donors and found an inverse linear relationship between the islet cell mass and the duration of type 2 DM. In addition, the function of these islets was impaired compared with islets from people without DM.¹⁰ The results of these studies provide the physical evidence of the quantitative and qualitative abnormalities of the β -cells in individuals with type 2 DM.

On a molecular level, chronic exposure to hyperglycemia can have adverse effects on insulin secretion and insulin action.¹¹ This concept is referred to as *glucotoxicity*. Exposure to elevated glucose levels, especially over long periods of time, can be harmful to β -cell function and perhaps even β -cell viability.¹¹ Thus, hyperglycemia may be both the consequence and the cause of continued β -cell deterioration seen in type 2 DM. In addition, high levels of free fatty acids, which are associated with type 2 DM, may further aggravate insulin resistance and may adversely affect β -cell function.¹² This concept is referred to as *lipotoxicity*.

THE TRADITIONAL ROLE OF INSULIN IN TYPE 2 DIABETES MELLITUS

The traditional pathway for pharmacologic management of type 2 DM has been to start with an oral antidiabetic agent. If a patient's glycemic goal is not met or if glycemic control deteriorates, a second agent is added. If 2 oral antidiabetic agents fail to meet or maintain the patient's glycemic goal, a third agent is often added. Insulin is generally the last therapeutic step.² It is typically used when maximum doses of oral antidiabetic agents are inadequate, and it is usually started in combination with these agents.

A major flaw in this treatment paradigm is that failure occurs at one step before moving on to the next step. Treatment intervention regains glycemic control, but then the control is allowed to slip away again. A large study by Brown et al¹³ of patients with type 2 DM (N = 7208) confirmed that this traditional stepwise approach exposes patients to substantial periods of hyperglycemia and is unsuccessful at sustaining good glycemic control. They examined the pattern of using oral antidiabetic agents in the treatment of type 2 DM and found that patients were started on monotherapy after having had A1C levels >8.0% for a mean of 8.7 months. A second agent was added to the sulfonylurea therapy after a mean of 20.5 months when A1C values were >8.0%, and a second agent was added to treatment with metformin after a mean of 14.5 months when A1C values were >8.0%. By the time insulin therapy was finally started, the average patient had accumulated ~5 years of experiencing A1C values >8.0% and ~10 years of experiencing A1C values >7.0%. Exposure to such long periods of hyperglycemia places these patients at risk for developing DM complications.

Besides allowing for prolonged periods of hyperglycemia, this treatment approach—that is, delaying initiation of insulin therapy until the last step—is flawed because it does not recognize the underlying pathophysiology of type 2 DM. Defects in insulin secretion are present at the outset of type 2 DM, and deterioration of β -cell function progresses with the duration of DM. Thus, early, rather than later, use of insulin would be a more logical approach.

POSSIBLE BENEFITS OF EARLY INSULIN USE ON β -CELL FUNCTION

Brief periods of intensive therapy with insulin leading to near euglycemia can lead to immediate improvement of endogenous insulin secretion in patients with type 2 DM.¹⁴⁻¹⁶ This would suggest that β -cell dysfunction resulting from glucotoxicity may be at least partially reversible when hyperglycemia is corrected. Furthermore, several studies in patients with newly diagnosed type 2 DM have shown that short-term intensive treatment with insulin that achieves near-normal glycemic control may lead to prolonged periods of good glycemic control, without the need for pharmacologic therapy.¹⁷⁻¹⁹

In a study by Ilkova et al,¹⁷ 13 severely hyperglycemic, newly diagnosed patients with type 2 DM (mean baseline A1C value, 11.0%) were treated intensively for 2 weeks with continuous subcutaneous insulin infusion (CSII). After the treatment, 9 patients maintained good glycemic control with diet alone for a median of 26 months. Ryan et al¹⁸ used a 2- to 3-week course of intensive treatment with human neutral protamine Hagedorn (NPH) and regular insulin in 16 patients newly diagnosed with type 2 DM (mean baseline A1C value, 11.8%). After 1 year of following this treatment, 7 patients were maintaining glycemic control with diet alone. Using a 2-week course of CSII treatment, Li et al¹⁹ achieved optimal control in 126 patients with newly diagnosed type 2 DM (mean baseline A1C value, 10.3%). At 24 months after this treatment, 42% of these patients were maintaining euglycemia without pharmacologic therapy. Li et al also noted that patients in this study who were able to maintain control for at least 12 months had a greater recovery of β -cell function when this was measured right after the course of insulin treatment. Thus, the mechanism responsible for such long-term “remissions” is an improvement in β -cell function that, at least in some patients, is able to be preserved for at least 2 years.

Twenty patients with type 2 DM who had failed to achieve and/or maintain glycemic control with oral antidiabetic agent therapy were studied.¹⁶ A significant correlation ($P < 0.001$) was observed between the baseline fasting C-peptide value before intensive therapy with insulin was undertaken and the improvement in β -cell function, as assessed by C-peptide responses to glucagon, that occurred after the treatment: the higher the level, the better the response.¹⁶ Other research has reported that success in being able to remain off pharmacologic therapy after intensive insulin therapy depends on the duration of DM.²⁰ Patients who were able to continue without pharmacologic therapy had had the diagnosis for a

shorter amount of time.²⁰ These observations support the belief that the extent of such treatment's success in type 2 DM depends on the patient's stage of disease progression. A patient in the early stages of type 2 DM would be expected to be more responsive to therapeutic interventions because additional β -cell function should be intact compared with someone with a longer duration of the disease. Early insulin therapy—as early as at the diagnosis of type 2 DM—may be an effective way of attenuating the loss of β -cell function that characterizes the natural course of type 2 DM, thus delaying the progression of the disease. In turn, this would be expected to help sustain good glycemic control and therefore prevent or at least delay the development of DM complications.

Insulin therapy exerts a better protective effect on β -cell function than sulfonylurea therapy.²¹ A trial of 39 patients recently diagnosed with type 2 DM compared a BID regimen of 70% NPH/30% regular insulin with the sulfonylurea glibenclamide.²¹ At the end of the second year of treatment, the mean A1C value had deteriorated in the sulfonylurea group but not in the group treated with insulin, and fasting insulin levels were higher in the insulin-treated group compared with the sulfonylurea-treated group ($P = 0.02$). The C-peptide response to glucagon increased significantly in the insulin-treated group during the study ($P = 0.02$); the response in the sulfonylurea-treated group was unchanged. Glycemic control was therefore better in patients who received early insulin therapy, and it appeared that endogenous insulin secretion was better preserved in this group.

Thus, compared with oral antidiabetic agents, insulin therapy would appear to have an advantage. These oral agents often have limitations in their glucose-lowering efficacy, whereas an insulin dose can be increased as high as necessary to achieve the desired result. Therefore, insulin has a more potent ability to lower glucose levels.

THE EFFECT OF INSULIN THERAPY ON INSULIN RESISTANCE

Intensive insulin therapy has been shown to reduce insulin resistance in patients with type 2 DM.^{14,22-24} One mechanism by which exogenous insulin exerts this effect is by reversing the postreceptor defect in insulin action in the periphery.^{14,22} Peripheral insulin resistance can be overcome if exogenous insulin is given in large enough doses to achieve target glycemic goals. These benefits are seen even when taking into account the weight gain that occurs with insulin therapy.²³

POTENTIAL ADVERSE EFFECTS OF EARLY INSULIN THERAPY

Hypoglycemia and weight gain are potential adverse effects associated with the use of insulin early in the course of type 2 DM; these are the same issues that may emerge when insulin is used at any stage of type 2 DM. Intensive insulin therapy is associated with an increased risk of hypoglycemia.^{25,26} The UKPDS observed hypoglycemia in intensively treated patients with type 2 DM that was described as mild to moderate.²⁵ The risk of severe hypoglycemia in the

UKPDS was less than what had previously been reported for intensively treated patients with type 1 DM.²⁶

Patients starting insulin therapy should be educated about how to recognize the symptoms of hypoglycemia and how to manage such episodes. The risk of hypoglycemia with intensive therapy may be less with the newer insulin analogues, which have more physiologic insulin profiles compared with older insulin preparations. Prandial insulin (such as lispro or aspart) and basal insulin (such as glargine) have been shown to be associated with less hypoglycemia than regular and NPH insulin, respectively, in patients with type 2 DM.^{27,28}

Weight gain is commonly observed with insulin therapy, especially with more intensive insulin regimens. In the UKPDS, weight gain was 5% greater in the group intensively treated with insulin than in the group conventionally treated.²⁵ The UKPDS demonstrated, however, that the insulin-treated group did not have any increased risk for adverse cardiovascular consequences, despite this weight gain. Because of the benefits of tight glycemic control, the potential for weight gain should not be a deterrent to introducing insulin early in the course of type 2 DM. One possible treatment option is to combine metformin with insulin therapy, as this approach might attenuate the weight gain seen with insulin alone.²⁹

Epidemiologic studies have found an association between high levels of endogenous circulating insulin and cardiovascular disease.^{30–32} However, clinical evidence does not support the theory that exogenous insulin therapy is associated with cardiovascular disease. The UKPDS showed no increase in cardiovascular mortality with the use of insulin in patients with type 2 DM.²⁵ The Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction Study showed that patients with type 2 DM who received an insulin–glucose infusion at the time of an acute myocardial infarction and were managed with intensive insulin therapy afterwards had a reduced risk of mortality.³³ Recently, data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study demonstrated that intensive insulin therapy decreased the risk of cardiovascular disease among patients with type 1 DM.³⁴ These observations should dispel any concern about a link between exogenous insulin therapy and risk of cardiovascular disease.

INITIATING INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

There are a variety of ways to initiate insulin therapy in a patient with type 2 DM. These options range from the relatively simple strategy of having the patient take a single injection of NPH or glargine at bedtime (along with therapy using oral antidiabetic agents) to a more complex regimen of using basal injections of a long-acting insulin along with prandial injections of a short-acting insulin.³⁵ Other possibilities include using regimens of premixed insulin or fixed-dose combinations of insulin, as well as using prandial insulin along with oral antidiabetic agents.³⁵ All of these options can be successful in achieving good glycemic control; they each have advantages and disadvantages.

In studies that found intensive insulin therapy had beneficial effects on β -cell function, insulin was used early in the course of type 2 DM to achieve glycemic control.^{17–20} Thus, although the best way to initiate insulin therapy in patients with type 2 DM may be debatable, the critical factors are to introduce insulin therapy before the patient has had prolonged periods of hyperglycemia; to use insulin therapy optimally so that glycemic targets are reached; and to intensify insulin therapy as needed to sustain glycemic control.

CONCLUSIONS

Study findings suggest that the early—rather than later—use of aggressive insulin therapy in the course of type 2 DM has advantages beyond improving glycemic control. Early use of insulin therapy may improve β -cell function, which can delay, halt, or even possibly reverse the natural progression of type 2 DM. With a more aggressive approach to starting and intensifying insulin therapy, patients may be more likely to achieve and maintain glycemic goals, thereby reducing the development of DM complications. Over time, this intervention may lead to healthier and longer lives for patients with type 2 DM.

ACKNOWLEDGMENT

Dr. Westphal is a consultant and speaker for Bristol-Myers Squibb Company, New York, New York, and The sanofi-aventis Group, Bridgewater, New Jersey.

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