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Pro's and Con's of the Early Use of Insulin in the Management of Type 2 Diabetes: A Clinical Evaluation

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Abstract

Purpose of Review—Recently, there have been increasing calls for insulin to be used as the initial treatment of type 2 diabetes, and if not then, soon after its onset. The underlying reason given is that insulin will slow apoptosis of pancreatic β -cells which is increased in type 2 diabetes. This review will examine the clinical evidence supporting this recommendation.

Recent Findings—Several observational studies in which newly diagnosed type 2 diabetic patients are intensively treated for a short time with insulin which is then stopped have shown that approximately half of these patients retain good control without pharmacological therapy for up to a year. However, Hb A1c levels in patients who have to be started on oral anti-diabetic drugs (OAD) are similar to the values in those who do not. Hb A1c levels are similar in patients randomized to initial therapy with insulin or OAD. There is no clinical evidence yet for an effect of insulin on β -cell apoptosis.

Summary—The primary goal is to achieve and maintain Hb A1c levels of $<7.0\%$. Given the extra demands on both patients and physicians when starting insulin compared to OAD and the many subsequent years in which patients have diabetes, the arguments for using insulin initially, or in patients who have achieved the target Hb A1c level, are not convincing. However, as soon as OAD therapy cannot meet this goal, insulin must be introduced.

Keywords

Initial insulin therapy; early insulin therapy

INTRODUCTION

There is an increasing chorus of people recommending insulin as “early” treatment of type 2 diabetes in both print [1] and at national meetings [2]. A subtext of this recommendation is to use insulin as the *initial* treatment for newly diagnosed patients with type 2 diabetes. The hope (in the absence of firm evidence) is that this approach will have a favorable effect on apoptosis of pancreatic β -cells and thus help preserve β -cell function. Initiating insulin treatment requires much time, effort and inconvenience on the part of both the patient and the provider. Before embarking on this course, a careful examination of the evidence supporting this recommendation is required. Moreover, if insulin is not selected as the initial treatment, consideration of when it should be used “early” in the course of diabetes is also important. The clinical evidence for using insulin initially or “early” is discussed, and based on this analysis, recommendations made.

REVIEW OF PERTINENT LITERATURE

Using insulin early in the course of type 2 diabetes is problematic because patients have varying periods of asymptomatic hyperglycemia, i.e., undiagnosed diabetes, before the diagnosis is made. This has been shown to be 4–7 years and estimated to be as long as 9 to 12 years [3]. Furthermore, insulin secretion at diagnosis is already reduced by approximately 50% [4,5]. Therefore, one can only speak of using insulin “early” in relation to when the diagnosis is made. Currently, the standard clinical parameter of disease resolution is the glycemic response to therapy. Insulin secretion continues to deteriorate in spite of improving glycemia [4,5]. Therefore, in this discussion, the timing of insulin therapy can only be related to the diagnosis and the response can only be evaluated by glycemic changes and the need for subsequent therapies (Table 1).

Ilkova and colleagues [6] hospitalized 13 newly diagnosed patients who failed to achieve fasting plasma glucose (FPG) concentrations of <160 mg/dl and postprandial glucose concentrations of <200 mg/dl after three to six weeks of diet and exercise for two weeks of continuous subcutaneous insulin infusion (CSII). At hospitalization, their mean FPG and postprandial glucose concentrations were 218 mg/dl and 304 mg/dl, respectively, and glycated hemoglobin levels by affinity chromatography were 11.0%. One patient could not be controlled satisfactorily on CSII and was an early failure. The mean FPG and postprandial glucose concentrations at discharge in the remaining 12 patients were 119 mg/dl and 133 mg/dl, respectively, when CSII was discontinued. Satisfactory control was defined as FPG and postprandial glucose concentrations of <160 mg/dl and <200 mg/dl, respectively. At six months and one year, seven and six patients were still in satisfactory control, respectively. Changes in body weight did not predict success or failure.

Park and colleagues [7] hospitalized 91 patients and treated them for two to eight weeks with CSII. Prior to hospitalization, 47 had been treated with diet alone, 25 with oral hypoglycemic agents, 11 with NPH insulin alone and 8 with a combination of NPH insulin and oral hypoglycemic agents. The mean duration of diabetes was 7.2 years and the mean Hb A1c level when hospitalized was 13.2%. The criteria for remission was achieving and maintaining FPG and postprandial glucose concentrations of <108 mg/dl and <180 mg/dl, respectively, without medication. This occurred in 34% after the initial CSII therapy, 32% at six months and 31% at one year. Not unsurprisingly, the most important determinant of remission was the duration of diabetes. Remissions occurred in 62%, 53%, 22%, 20% and 0% for durations of ≤1 year, 2–5 years, 6–10 years, 11–15 years and ≥16 years, respectively.

Ryan and colleagues [8] treated 16 newly diagnosed patients with FPG concentrations >200 mg/dl as outpatients for two to three weeks with a basal (NPH insulin)/bolus (regular insulin) regimen. They were in daily phone contact with the study physician for dose adjustments. The mean FPG and Hb A1c levels before insulin therapy were 239 mg/dl and 11.8%, respectively. The mean FPG concentration when insulin therapy was discontinued was 126 mg/dl. After one year, seven patients remained off of medications, six were taking glyburide, two glyburide plus metformin and one was receiving insulin again. The FPG and Hb A1c levels for the entire group were 121 mg/dl and 6.6%, respectively. The only predictors for those who remained off of medications were a smaller dose of insulin (0.32 vs. 0.73 units/kg) and a lower attained FPG concentration (106 vs. 139 mg/dl) at the end of insulin treatment.

Li and colleagues [9] hospitalized 138 newly diagnosed patients with FPG concentrations >200 mg/dl and treated them with CSII for two weeks. Their mean FPG, postprandial glucose and Hb A1c levels before hospitalization were 245 mg/dl, 342 mg/dl and 10.1%, respectively. The goals of CSII therapy were FPG and postprandial glucose concentrations of <110 and <144 mg/dl, respectively. Twelve patients failed to achieve these targets. At discharge, FPG and

postprandial glucose concentrations in the 126 successfully treated patients were 113 and 155 mg/dl, respectively. All medications were stopped and the patients followed on diet and exercise alone. Relapse was defined as either a FPG or postprandial glucose concentration of >126 and >180 mg/dl, respectively, which had to be confirmed on a separate day. At six months, 91 patients were still being followed, 67% of whom remained off of medication. At one year, 68 patients were still being followed, 47% of whom remained off of medication. Only a slightly, but significantly ($P = 0.035$), lower FPG concentration after CSII predicted remission at one year (110 ± 22 [SD] vs 121 ± 20 mg/dl). There was no difference in the insulin doses.

Chen and colleagues [10] hospitalized 50 consecutive newly diagnosed type 2 diabetic patients whose FPG glucose concentrations were >300 mg/dl or random glucose concentrations were >400 mg/dl and treated them intensively with insulin for 10 to 14 days. At discharge, 30 of the 50 subjects were randomly assigned to continue insulin treatment (more than half because of the concern that some patients would refuse longer term insulin therapy) and 20 randomly assigned to treatment with oral anti-diabetes drugs (OAD), metformin in obese patients and gliclazide-MR in lean ones. At six months, the insulin-treated group was also switched to OAD. Upon initial hospitalization, glycemic status was similar in the patients subsequently maintained on insulin for six months and in those switched to oral medications at discharge as follows: peak FPG concentrations, 345 vs. 329 mg/dl, respectively; peak random glucose concentrations, 527 vs. 483 mg/dl, respectively; and Hb A1c levels, 11.9 vs 11.3%, respectively. FPG and Hb A1c levels were significantly lower in the patients treated with insulin during the first six months after discharge and remained so during the subsequent six months after they were switched to OAD. However, during the first six months, the mean dose of gliclazide-MR was only 54.5 mg per day, less than half of the maximal dose of 120 mg per day. No information was given concerning the doses during the subsequent six months for either group.

Two studies compared initial treatment with insulin to an SU with or without metformin on subsequent maintenance of near euglycemia without medications. Weng and colleagues [11], in a multi-center study, randomized newly diagnosed patients to be initially treated with CSII, of whom 124 completed the study, or multiple daily injections (MDI) of insulin, of whom 113 completed the study, or oral medications (gliclazide and/or metformin), of whom 94 completed the study. Doses were adjusted daily in the insulin groups and every three days in the SU/metformin group. Glycemic status at randomization was comparable in the CSII, MDI and oral medication groups as follows: Hb A1c levels (%), 9.8, 9.7 and 9.5, respectively; FPG concentrations (mg/dl), 203, 207 and 194, respectively; and 2-hour postprandial glucose concentrations (mg/dl), 290, 315 and 299, respectively. Successful initial therapy was defined as FPG or 2-hour postprandial glucose concentrations of <110 mg/dl and <144 mg/dl, respectively, which needed to be achieved within two weeks. After the initial therapy, glycemic control was again comparable among the three groups as follows: FPG concentrations (mg/dl), 119, 122 and 117, respectively; 2-hour glucose concentrations (mg/dl), 135, 146 and 148, respectively. Therapy was continued for two more weeks at which time all treatment was stopped and the patients kept on diet and exercise alone. Relapse was defined as a FPG or a 2-hour postprandial glucose concentration of >126 mg/dl and >180 mg/dl, respectively, which had to be confirmed one week later. Remissions in the three groups at six months (estimated from a graph) were 56%, 48% and 32%, respectively. At one year, the remissions (stated in the text) were 51%, 45%, and 27%, respectively. Those who relapsed were shifted to standard therapy. However, Hb A1c levels at one year were no different among patients originally randomized to the three groups as follows: 6.4%, 6.6% and 6.7%, respectively [12].

Chandra and colleagues [13] explained treatment options and the possibility of long term benefits of insulin therapy to newly diagnosed type 2 diabetic patients with fasting blood glucose (FBG) concentrations >200 mg/dl and allowed them to choose between an SU or

insulin, enrolling 30 in each group. Patients selecting the SU were started on 60 mg of gliclazide-MR once a day and advised to perform self monitoring of blood glucose (SMBG) before breakfast and at bedtime. The dose was reduced to 30 mg if the FBG was <90 mg/dl for two consecutive days and stopped if on that dose the FBG remained <90 mg/dl for at least one week. FBG's were then measured every third day and gliclazide restarted if values were >110 mg/dl on more than two occasions. The insulin regimen was premixed 70/30 insulin given twice a day, starting with 10 units before breakfast and 6 units before supper. Patients were instructed to perform SMBG before each injection and decrease the dose by two units if the preprandial value was <100 mg/dl on two consecutive days (in consultation with a study physician who was available around-the-clock by telephone). When the daily dose reached 4 units and euglycemia, defined as a FBG <110 mg/dl, was maintained for over a week, or the patient experienced hypoglycemia, the insulin was discontinued. It was restarted if the FBG concentration increased to >110 mg/dl. Remission was defined as "euglycemia" off drug treatment for a minimum of one month. Initial glycemia was comparable in the insulin and SU groups with Hb A1c levels of 10.4% and FBG concentrations of ~250 mg/dl in each. FBG concentrations normalized within 2–6 weeks in both groups and remained similar throughout the study with data available up to two years. Consistent with the FBG data, Hb A1c levels were similar at six months, 6.8% in patients originally assigned to insulin and 6.2% in the SU group. However, at six months, only one of 30 patients (3%) taking gliclazide was in remission while 24 of 30 (80%) originally assigned to insulin were. At one year, one of 20 (5%) in the SU group remained in remission while 10 of 16 (62%) in the insulin group did.

In the United Kingdom Prospective Diabetes Study Group (UKPDS), patients with newly diagnosed diabetes were treated initially with diet alone for three months [14]. Those who still had hyperglycemic symptoms or whose FPG concentrations were >270 mg/dl after this initial treatment were randomized to receive either insulin (N = 178) or an SU (N = 231). Ultralente insulin was started but if preprandial or bedtime glucose concentrations were >126 mg/dl, short-acting insulin was added two or three times a day or twice daily injections of intermediate- and short-acting insulin were used. The initial FPG concentrations (284 mg/dl) were identical in the two groups while the Hb A1c levels were almost so (10.6% vs 10.5%). There was little difference in the Hb A1c levels between the insulin and SU groups at one year (7.0% vs 6.8%).

Alvarsson and colleagues [15] followed 39 randomized type 2 diabetic patients within two years of diagnosis who were being treated with diet alone for at least one month and had not received more than six months of pharmacological therapy before entry and followed them for two years. Initial Hb A1c levels in those allocated to insulin (N = 18) and glibenclamide (glyburide) (N = 21) were 7.3% and 6.9%, respectively. They remained slightly, but significantly, lower one and two years later in the insulin group with the mean values in both groups <7.0%. However, the average dose of the SU was only 3.0 mg/day, far below the maximal amount. Furthermore, the guideline for the need to switch to insulin in this study was a Hb A1c level >3% above the upper reference limit.

DISCUSSION

In general, approximately half of newly diagnosed type 2 diabetic patients who were initially treated intensively with insulin were able to achieve near euglycemia without medications for at least a year after the insulin was discontinued (Table 1). Should these results now turn us to initiating treatment with insulin in newly diagnosed type 2 diabetic patients? I think not for several reasons. First, patients started on insulin were either hospitalized [6,7,9,10] or contacted their physicians daily [8,11] or every several days [13]. This is simply not feasible in current western medical care systems. Second, newly diagnosed type 2 diabetic patients treated with OAD achieved and maintained goal Hb A1c levels ([11,13–15]. Third, although insulin will certainly bring a patient under control, compare what is required from physicians and patients

when insulin or OAD are started (Table 2). Quite a difference for both parties. Although analogue insulins were not used in most of studies discussed, these do not change the requirements of initiating insulin therapy. Fourth, patients have diabetes for many, many years, usually for the remainder of their lives. How clinically important might a short period of no medications after initial intensive insulin therapy be given the length of time patients will have to have pharmacological treatment?

Note that I have restricted these comments to glycemic outcomes, not physiological ones. The rationale for initial therapy with insulin is the belief that this treatment will reverse the increased apoptosis of pancreatic β -cells seen in type 2 diabetic patients [16] and thus allow improved metabolic control over a longer period without more intensification of therapy. Peter Butler discussed this issue during the Scientific Sessions of the 2008 American Diabetes Association (ADA) national meeting in which he confirmed that the frequency of β -cell apoptosis is increased in people with type 2 diabetes. However, a sub-analysis of the cases with type 2 diabetes when divided into those on insulin versus those on OAD did not show that the insulin-treated patients had lower β -cell apoptosis. On the other hand, these small numbers of observations do not resolve this issue because those receiving insulin probably had a longer duration of diabetes and more β -cell dysfunction.

Although a number of the studies utilizing initial intensive insulin therapy described above have also shown some temporary preservation of insulin secretion, this is of unproven clinical benefit. This is in marked contrast to the virtual absence of the development or progression of diabetic retinopathy and nephropathy in over 2000 patients whose average Hb A1c levels were maintained <7.0% over six to nine years [17–21]. Finally, even though the ADA recommends insulin therapy in severely hyperglycemic, symptomatic type 2 diabetic patients [22], it really isn't necessary under these circumstances. High doses of a SU will quickly bring these patients under control [13,14,23] as rapidly as insulin [13,14]. Severely hyperglycemic, newly diagnosed type 2 diabetic patients are often hospitalized and started on insulin at my county institution and invariably have near euglycemia (and often hypoglycemia) when first seen in our diabetes clinic. We then have to discontinue the insulin and place them on metformin as recommended by the ADA [22].

One must keep in mind that the risk benefit profiles of different OAD are not equal, and furthermore, that these profiles compared to insulin over time remain incompletely understood. However, at this time, there is no evidence that the early use of insulin provides sufficient physiologic advantage to warrant the money, time and resources of patients and providers that are necessary to implement this treatment in a successful, timely manner. Although most studies of the early use of insulin did not use glargine or other longer acting analogues, use of these insulins would not address the issues raised in Table 2.

CONCLUSION

In my view, OAD should be the initial treatment for type 2 diabetes and continued as long as Hb A1c levels are kept below 7.0%. This is much easier for both physicians and their patients and control is not compromised. When a combination of two [24] or three [25–29] OAD that had been successful finally fail, that is the time for the “early” use of insulin. Too often, insulin treatment at this point is not happening. For instance, the Hb A1c level of nearly 1000 patients on combination OAD in a large HMO was 9.2% when insulin was started [30]. While on combination OAD, these patients spent 30 months with Hb A1c levels >8.0% and 58 months with Hb A1c levels >7.0% prior to insulin therapy. Therefore, our biggest challenge is to overcome the “insulin resistance” of patients, and frankly and probably more important, of physicians. Unfortunately, clinical inertia is alive and well and, in my opinion, is the main reason why so many type 2 diabetic patients remain uncontrolled. Treating to target is the

crucial goal. It doesn't seem to matter how we arrive there (absent troubling side effects of the therapeutic approach). Why make it harder on our patients and ourselves as long as we get (and stay) there? Let's just do it as simply as possible.

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Table 1
Effect of intensive initial insulin or oral drug therapy on subsequent treatment without medications

Reference	N	BMI	Baseline A1C (%)	Type of Initial Rx	Duration (Days)	“Euglycemia” (%)	
						6 months	12 months
3	13	NA	11.0	CSII	14	54	46
4	91	“Nonobese”	13.2	CSII	53	32	31
5	16	30.8	11.8	Basal/bolus	14–21	NA	44
6	138	25.0	10.1	CSII	14	67	47
8	124	25.1	9.8	CSII	28	NA	51
	113	24.4	9.7	MDI	28	NA	45
	94	25.1	9.5	SU/metformin	28	NA	27
10	30	24.7	10.4	Pre-mixed insulin SU	~3 months in 24/30 *	80	62 (n=16)
	30	25.5	10.4			3	5 (n=20)

* 29/30 did not reach euglycemia without drug

Table 2

Physician and patient responsibilities at the initiation of treatment

PHYSICIANS	PATIENTS
Insulin	
<u>Teach the following:</u> <ol style="list-style-type: none"> Different insulin preparations Time course of actions How to draw up (and mix) insulins How and where to inject Recognition of hypoglycemia Treatment of hypoglycemia SMBG* (and all that entails) <u>Do the following:</u> <ol style="list-style-type: none"> Maintain frequent interactions with patient after initiating therapy to establish appropriate dose Maintain close follow-up to reduce dose after decreased glucose toxicity restores baseline insulin secretion 	<u>Do the following:</u> <ol style="list-style-type: none"> Learn taught material Inject suggested insulin doses Perform SMBG at appropriate times Maintain frequent contact with physician
Oral Antidiabetes Drugs	
<u>Teach the following:</u> <ol style="list-style-type: none"> Recognition of hypoglycemia (SU's) Treatment of hypoglycemia (SU's) <u>Do the following:</u> <ol style="list-style-type: none"> Measure FPG concentrations every 2–3 weeks initially to adjust doses Maintain patient contact 	<u>Do the following:</u> <ol style="list-style-type: none"> Learn taught material (SU's) Swallow suggested doses at appropriate times Have FPG concentrations measured at the suggested times

* Self monitoring of blood glucose