

# Early Insulin Therapy for Type 2 Diabetic Patients: More Cost Than Benefit

Let me start by summarizing what we (think we) know and don't know that pertains to this issue. In the mid-1960s (when I was a fellow), the conventional wisdom was that the complications of diabetes were unrelated to glycemic control; they were genetically determined. Therefore, the clinical goal was simply to keep diabetic patients asymptomatic. Fifteen years later, animal and some retrospective human studies convinced some (1) that near euglycemia would have a beneficial effect on diabetes complications. Controversy surrounding this issue raged until the results of the Diabetes Control and Complications Trial (DCCT) were published (2). Some controversy remained regarding extending the DCCT results to type 2 diabetes (3,4), but with the publication of the U.K. Prospective Diabetes Study (UKPDS) (5,6), the beneficial effects of near euglycemia on microvascular complications were irrefutably established for both type 1 and type 2 diabetic patients. In the past decade, five studies evaluating >2,000 patients with both type 1 (7–9) and type 2 (10,11) diabetes over 6–9 years have demonstrated that development or progression of retinopathy and microalbuminuria were minimal or absent if A1C levels were maintained below 7%, increased only slightly if A1C levels were between 7 and 8%, but increased markedly at values exceeding 8%.

It is important to distinguish between the micro- and macrovascular complications when considering the impact of near euglycemia on diabetes complications because they are often lumped together in arguments for tight control. The relationship between glycemia and these two types of complications differs. Although the association between glycemia and macrovascular disease is well established (12–15), to date there is no convincing evidence from intervention studies that lowering glycemia has a beneficial effect on macrovascular complications (16,17). One potential exception to this statement often cited is the DIGAMI (Diabetes Mel-

litus, Insulin Glucose Infusion in Acute Myocardial Infarction) study (18), in which patients receiving the insulin glucose infusion had decreased mortality compared with the control group that did not. A1C levels fell in both groups during the first year, with a 0.7% greater decrease in the infusion group at 3 months and 0.5% greater at 12 months (19). However, although there was a difference in mortality after 1 year between the two groups, two-thirds of the deaths were due to congestive heart failure (19). Reinfarctions were virtually identical (19). Mortality from cardiovascular causes was statistically different between the two groups after a mean of 3.4 years of follow-up, but no A1C data were available after the first year (20).

One reason for the apparent lack of a well-documented effect of near euglycemia on cardiovascular disease may be the quantitative relationships between A1C levels and micro- and macrovascular complications provided by the UKPDS (21). A 1% change in A1C levels was associated with a 37% change in the risk of microvascular complications but only a 14% change in the risk of myocardial infarction. Furthermore, the risk of coronary artery disease is increased in the upper half of the normal glycemic range (22). Men between the ages of 40 and 79 years with A1C levels between 5.0 and 5.4% had a 2.7-fold increased chance of dying from ischemic heart disease over the subsequent 4 years compared with men with A1C levels <5.0%. Thus, since A1C levels in the lower half of normal are very unlikely to be achieved in diabetic patients, reducing the glycemic risk for macrovascular disease (if there really is a direct causal relationship) is less likely to be as effective as reducing the glycemic risk for microvascular complications. Even though abnormal heart findings are present in 20–25% of type 2 diabetic patients at the time of diagnosis (23,24), given the relationship between glycemia and macrovascular disease, it seems very unlikely that early insulin treatment (or

any glycemic therapy for that matter) will positively impact cardiovascular disease in these individuals.

The second established fact is the continued gradual decrease in  $\beta$ -cell function in type 2 diabetes. Insulin secretion assessed indirectly by the HOMA- $\beta$  formula (25) is ~50% diminished at the time of diagnosis of type 2 diabetes and continues to fall, at least in those treated with diet, metformin, or a sulfonylurea agent (26).

A third relatively recent documented phenomenon, especially important in the context of this discussion, is the effect of hyperglycemia per se on insulin secretion and, to a lesser extent, on insulin action, i.e., glucotoxicity (27). Regardless of the level of intrinsic insulin secretion, hyperglycemia will depress it further. Lowering the elevated glucose concentrations restores insulin secretion (and action) to its intrinsic level.

I have no quarrel with the argument that intensive insulin treatment early in the course of type 2 diabetes improves subsequent insulin secretion (28–30), no doubt by lowering glucose toxicity. However, more than half of these patients require pharmacological therapy within a year to maintain near euglycemia (30,31). It does not require insulin treatment to reduce glucose toxicity and improve insulin secretion. For instance, even in markedly symptomatic type 2 diabetic patients (on no other antidiabetes medications), maximal sulfonylurea agent therapy accomplished the same thing (32). These patients presented with plasma glucose concentrations >400 mg/dl, involuntary weight loss, ketosis (in some), and mild compensated acidosis (in a few). In the first 55 patients so treated, the fasting plasma glucose was 202 mg/dl after 1 week and 120 mg/dl after 4 months. The fasting glucose-to-insulin ratio rose significantly by threefold at 1 week, with a further (nonsignificant) 70% increase at 4 months. At that time, 6 patients remained on a maximal dose of glyburide, 29 were taking a submaximal dose, 11 were on

diet therapy alone, 3 had been placed on insulin (metformin and glitazones were not available when this study was carried out), and 6 had been lost to follow-up. Since that time, our unit has treated >100 similar markedly symptomatic patients, with <10% requiring insulin.

There is a definite “cost” to both patient and provider with insulin therapy. For the patient, besides initially needing to learn how to use insulin and measure blood glucose, there is the ongoing lifestyle adjustments of balancing food intake and exercise with insulin dosing to avoid hypoglycemia and hyperglycemia. For the provider, besides the intensive initial education, contact with the patient is much more frequent in the beginning as the insulin doses are adjusted appropriately and ongoing education takes place. Compared with patients taking pills, subsequent contact with the patient after the initial insulin doses are stabilized should also remain more frequent, albeit not as much as in the first several weeks to months. Most of these recent-onset patients will eventually require decreasing doses of insulin as they are brought under control.

The current evidence clearly indicates that near euglycemia has beneficial effects on microvascular complications. Currently, there is no good evidence that briefly improving insulin secretion with insulin therapy provides any additional long-term benefit. Furthermore, it can be accomplished by any therapeutic approach that lowers glycemia, thus reversing glucose toxicity. Although preserving  $\beta$ -cell function is the argument used for early insulin therapy, within a relatively short period the majority of patients require treatment with a pharmacological agent. Treating to target is the crucial goal. It doesn't seem to matter how we get 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 do it as simply as possible.

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