No Need for the Needle (at First)

In this issue of Diabetes Care, Chen et al. (1) describe an approach to the initial treatment of newly diagnosed type 2 diabetic patients with severe hyperglycemia (fasting plasma glucose [FPG] concentrations >300 mg/dl or random plasma glucose concentrations >400 mg/dl) entailing intensive insulin therapy during 10 to 14 days of hospitalization. Following this, half of the patients were randomized to continued insulin treatment and the other half to oral antidiabetes drugs (OAD), starting with metformin in overweight and obese patients and a sulfonylurea (SU), gliclazide, in lean patients. If satisfactory control was not obtained with a single OAD, a combination of metformin and the SU was used. Doses of insulin and the OAD were adjusted at each outpatient visit every 2 weeks during the first 2 months and every 4 weeks for another 4 months. Oral glucose tolerance tests were performed after the intensive insulin therapy: once just before randomization and again 6 months later. At that time, patients in the insulin group were switched to OAD and all patients were followed for another 6 months.

As expected, FPG concentrations were no different at randomization: however, they were significantly increased in the OAD group compared with those maintained on insulin. A1C levels were significantly lower at 3 and 6 months in patients maintained on insulin compared with those given OAD. They also remained significantly lower 6 months after the insulin patients were switched to OAD.

Glucose and insulin responses among the insulin and OAD groups to the oral glucose tolerance tests were compared at randomization and 6 months later. To their credit, the authors compared only those patients who had achieved an A1C level <7.0% (22 of 24 in the insulin group and 8 of 18 in the OAD group). As expected, glucose responses were significantly improved in both groups compared with those at randomization, although there were no differences between groups. Conversely, insulin responses (assessed by homeostasis model assessment of β-cell function, insulinoenic index, and insulin area under the curve) were all significantly higher not only in both groups at 6 months compared with randomization but also in the insulin group compared with the OAD group at 6 months.

So, should there be a rush to insulin as the initial therapy in newly diagnosed type 2 diabetic patients? I think not. Just as one should not rush to judgment, one should carefully examine clinical evidence when deciding on treatments for type 2 diabetes. First of all, hospitalization for implementing insulin treatment of newly diagnosed patients is not recommended (2) and is simply impractical, at least in the U.S. and Europe. Achieving excellent control after starting insulin therapy in office or outpatient settings will take much longer than 2 weeks (probably more like 2 months). Furthermore, even after quickly achieving excellent control and maintaining it for 6 months, most of these patients still required OAD. The authors postulate that perhaps a 2-week course of intensive insulin therapy in patients with less severe hyperglycemia (in contrast to the severely hyperglycemic patients in their study) might induce long-term glycemic control. Given the much greater efforts on the part of both patients and physicians to initiate treatment with insulin (see below), we need evidence, not hypotheses, to recommend this course.

The question arises (and the authors discuss) whether the improved insulin secretion in the insulin group is due to decreased glucose toxicity or to insulin per se. Although they cite an in vitro paper (3) to support the latter possibility, Peter Butler discussed the issue of insulin affecting apoptosis of the β-cell at a symposium during the recent ADA Scientific Sessions and stated that there was no human evidence that this was so. Furthermore, the presence of significantly higher FPG concentrations after starting patients on OAD supports suppression of glucotoxicity as an explanation. OAD dosing is an important issue in this paper, as patients not achieving an A1C level <7.0% were taking only half the maximal dose of the SU (see the supplementary Table in the online appendix of ref. 1, available at http://dx.doi.org/10.2337/dc08-0075). Because doses of the OAD at 12 months were not provided, it is not possible to ascertain whether the significant A1C differences at that time might also be related to the continuation of submaximal doses of the SU in patients who had not achieved an A1C level of <7.0%.

Even allowing for the possibility that initial intense insulin therapy might have a direct effect (independent of glucose toxicity) on β-cell function because only patients with A1C levels <7.0% were compared, how clinically important is this? Given that there is virtually no clinical development or progression of microvascular complications at A1C levels <7.0% (4–8), this, not surrogate measures of insulin secretion, should be our primary goal. Indeed, this goal can be achieved in almost all severely hyperglycemic, newly diagnosed type 2 patients by initial treatment with high doses of SU (9). (Note that A1C levels in this study were measured by a boronate affinity rather than an electrophorosis method, with the former yielding values ~1% higher.)

Moreover, patients have diabetes for many, many years. How important and how practical is initial insulin therapy that might preserve some β-cell function during the first year or so after the diagnosis? As in the study by Chen et al. (1), initial insulin therapy in all studies supporting this approach was administered by either insulin pumps (9–12) or multiple daily injections (12,13)—modalities of treatment not easily accomplished, especially quickly, in the office or outpatient setting. Furthermore, whatever the amount of β-cell function preserved, it is not enough to preclude the need for OAD when insulin is discontinued in a substantial proportion of these patients (9–13). To judge the utility of initial insulin therapy, consider what is required from both patients and providers when either insulin or OAD is started (Table 1). Given the cost to patients and their physicians and the very limited and unproven clinical benefit of some possible brief preservation of β-cell function that might lead to improved control for a short initial period during the many years of diabetes, it seems to me that there is little clinical evidence that insulin should be the initial treatment for type 2 diabetes.

In my view, OAD should be the initial treatment for type 2 diabetes as long as...
A1C levels of <7.0% can be achieved. This is much easier for both patients and providers. OAD should be increased as necessary to maintain this well-supported A1C goal. However, as soon as OADs are unable to maintain this target, insulin should be initiated. This is not being done. For instance, the A1C level of nearly 1,000 patients on combination OAD in a large HMO was, on average, 9.2% when insulin was started (14). While on combination OAD, these patients spent 30 months with A1C levels >9.2% and 58 months with A1C levels >7.0% before starting insulin therapy. Therefore, our biggest challenge is to overcome the insulin resistance of patients and, probably more importantly, of providers. Unfortunately, clinical inertia is alive and well and, in my opinion, is the main reason why so many type 2 diabetic patients' diabetes remains uncontrolled.

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