EDITORIAL (SEE CHEN ET AL., P. 1927)

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, insulinogenic 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

Table 1—*Provider and patient responsibilities at the initiation of treatment*

Provider	Patient
Insulin	
Teach the following:	Learn what is taught.
Different insulin preparations	Inject suggested insulin doses.
Time course of actions	Perform SMBG at appropriate times.
How to draw up insulin	Maintain frequent contact with provider.
How and where to inject	
Recognition of hypoglycemia	
Treatment of hypoglycemia	
SMBG (and all that entails)	
Maintain frequent interactions with patient after initiating insulin therapy to establish appropriate dose.	
Maintain close follow-up to reduce dose after decreased glucose toxicity restores baseline insulin secretion.	
OAD	
Teach recognition and treatment of hypoglycemia (not necessary for metformin).	Swallow suggested doses at appropriate times.
Measure FPG concentrations initially every 2–3 weeks to adjust doses as necessary.	Have FPG concentrations measured at suggested times.
Maintain patient contact.	

SMBG, self-monitoring of blood glucose.

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 >8.0% 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.

MAYER B. DAVIDSON

From Charles Drew University, Los Angeles, California.

Corresponding author: Mayer B. Davidson, mayerdavidson@cdrewu.edu.

DOI: 10.2337/dc08-1283

Acknowledgments— M.D. was supported by National Institutes of Health Grant U54 RR014616.

References

1. Chen H-S, Wu T-E, Jap T-S, Hsiao L-C, Lee S-H, Lin H-D: Beneficial effects of insulin on glycemic control and β-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 31:1927–1932, 2008
2. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 29:1963–1972, 2006
3. Kilpatrick ED, Robertson RP: Differentiation between glucose-induced desensitization of insulin secretion and β-cell exhaustion in the HIT-T15 cell line. *Diabetes* 47:606–611, 1998
4. Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
5. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
6. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L Krolewski A: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
7. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
8. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
9. Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 20:1353–1356, 1997
10. Park S, Choi AB: Induction of long-term normoglycemia without medication in Korean type 2 diabetes patients after continuous subcutaneous insulin infusion therapy. *Metab Res Rev* 19:124–130, 2003
11. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng JP: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. *Diabetes Care* 27:2597–2602, 2004
12. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, Liu J, Li M, Fu Z, Cheng H: Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomized parallel-group trial. *Lancet* 371:1753–1760, 2008
13. Ryan EA, Imes S, Wallace C: Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 27:1028–1032, 2004
14. Brown JB, Nichols GA, Perry A: The burden of treatment failure in type 2 diabetes. *Diabetes Care* 27:1535–1540, 2004