Self-Mixed/Split Insulin Regimen: A Serious Omission in the ADA/EASD Position Statement

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Diabetes Care 2014;37:3–4 | DOI: 10.2337/dc13-1665

It has been over a year since the recommendations by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the management of hyperglycemia in type 2 diabetes were published (1). Since then, there have been a significant number of articles published about newer insulins and insulin formulations in development. But the recommendations on insulin therapy put forth in the report, in my opinion, have a serious omission. The section on insulin treatment discusses only three regimens: basal insulin alone when patients fail a combination of other agents, a basal/bolus regimen when patients fail basal insulin, and premixed insulins (in which there is a fixed amount of intermediate-acting and short- or rapid-acting insulin—usually in a 70–75% to 25–30% ratio, respectively). In the interest of full disclosure, I was a reviewer of these recommendations. The original rendition failed to mention the self-mixed/split regimen (in which the amounts of intermediate and short- or rapid-acting insulins can be adjusted independently of each other). I had questioned this approach, but the response was that the self-mixed/split regimen was too difficult for patients and physicians. After some persistence on my part, the following statement was added to the discussion of premixed insulins: "An older and less commonly used variation of this two-injection strategy is known as 'split-mixed,' involving a fixed amount of intermediate insulin mixed by the patient with a variable amount of regular insulin or a rapid analog. This allows for greater flexibility in dosing" (1). I feel this statement is in error as the dose of the intermediate-acting insulin is not fixed but is also adjusted as is the routine practice of those using this insulin regimen.

The basal/bolus insulin regimen is no panacea. It requires four injections of insulin per day, including a midday one. The latter is fairly easy with pens, but many patients do not have insurance coverage for these expensive items and thus have to use a syringe and insulin vial for the prelunch injection, which is inconvenient to say the least. It would be possible to prefill prelunch insulin syringes, but many patients are not that well-organized. I work in an inner-city clinic, and when patients are given a choice between self-mixed/split and basal/bolus insulin regimens after bedtime insulin fails, almost all of our patients opt for the two-injection regimen.

To limit the necessity for four injections, it has been recommended that the regimen starts with a single preprandial injection of a short- or rapid-acting insulin and increases to injections before the second and possibly all three meals, only as necessary (2,3). This approach, while logically appealing, can lead to long delays in reaching target A1C levels. First, the target level of glucose must be achieved, either postprandially or before the subsequent meal (or bedtime snack in case dinner is the meal in question). Then at least 3 months must elapse before the A1C level will accurately reflect overall glycemia. This period will be doubled if an injection before the second meal is required and tripled if injections before all three meals are deemed necessary. Since only 25–30% of patients who achieve target fasting glucose concentrations with bedtime glargine insulin and subsequently receive a single preprandial dose of a rapid-acting insulin achieve an A1C level of $<$7.0% (4,5), there will be long delays in reaching A1C goals in the majority of patients.

There is a further potential difficulty in evaluating the effect of preprandial short- or rapid-acting insulin injection. The most important determinant of postprandial glucose concentrations is the preprandial assessment and the increments over preprandial levels are similar regardless of the starting preprandial values (6–8). Therefore, postprandial hyperglycemia is initially best treated by lowering preprandial glucose levels. In a situation where a preprandial injection before a single meal has controlled the postprandial glucose concentrations but A1C levels have not reached target, a second

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injection must be introduced. However, when the second injection lowers the preprandial values before the initial meal, the short- or rapid-acting insulin dose given before that first meal may be too high leading to postprandial hypoglycemia. The same potential problem occurs when a third injection is introduced.

It is not our practice to use premixed insulins because of the challenges of achieving tight control with them due to the fact that one cannot adjust their components separately. For instance, a common situation is elevated before-bedtime glucose levels that occur following dinner, usually the largest meal of the day, accompanied by fasting values that are within the target range. Increasing the predinner dose of a premixed insulin to lower the elevated before-bedtime values can be problematic because of the potential for inducing overnight hypoglycemia caused by the proportionally higher dose of the intermediate component (70–75%) of the premixed insulin preparation.

Self-mixed/split insulin regimens can be very effective (9). In a head-to-head comparison carried out many years ago in type 1 diabetic patients, glycemic responses were similar between basal/bolus and self-mixed/split insulin regimens (10). Likewise, in a more recent head-to-head comparison between self-mixed/split and basal/bolus insulin regimens in hospitalized patients, the glycemic responses were virtually identical (11). In my inner-city outpatient clinic, I train midlevel providers (registered nurses, nurse practitioners, physician assistants) to adjust insulin doses on their own. In a separate family medicine clinic at an associated off-site county facility, a trained registered nurse using a self-mixed/split insulin regimen lowered A1C levels from 11.1 to 7.3% within 9–12 months in 132 patients referred to her by their primary care physicians (12). Eighty-five percent of these patients were Latino with an average education level of 6 years of school. Therefore, the difficulty of teaching self-mixing should not be the problem; perhaps practitioners feel that they cannot afford to take the initial extra time required.

In addition to the time of initial teaching, there are two potential drawbacks to a self-mixed/split insulin regimen. The first issue is that the amounts of the intermediate-acting and short- or rapid-acting insulins in the syringe are not exactly the same for each injection. Clinically, this is not an important issue because of the intraindividual variability of responses to injected insulin. The glycemic response to a repeat injection of the same amount of short-acting insulin by the same nurse at the same abdominal site on two separate days can vary up to 25% (13). Thus, small differences in the amounts of each insulin in the syringe from injection to injection will not have an important impact on the glycemic response. The second issue—which is valid—is the relative lack of flexibility in eating (and exercise) patterns when using a self-mixed/split insulin regimen (which also applies to premixed insulins). A basal/bolus regimen is an advantage for patients with highly variable eating (and exercise) patterns. However, these patients are in the minority in my practice, especially those with type 2 diabetes.

In my view, it was a serious omission not to include a self-mixed/split regimen as insulin treatment for type 2 diabetic patients in the ADA/EASD recommendations. They are effective, can be easily taught, and are preferred by many patients.

Acknowledgments. The incisive review of the commentary by Stanley Hsia, Charles R. Drew University, is gratefully acknowledged.

Funding. M.B.D. received partial salary support from National Institutes of Health (NIH)/National Institute on Minority Health and Health Disparities grant US54-MD-007598 (AXIS grant, formerly U54-RR-026138), and NIH/National Center for Advancing Translational Sciences grant UL1-TR-000124.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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