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PERSPECTIVE

Diabetes Guidelines May Delay Timely Adjustments During Treatment and Might Contribute to Clinical Inertia

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Abstract

Clinical inertia and poor knowledge by many physicians play an important role in delaying diabetes control. Among other guidelines, the Position Statement of the American Diabetes Association/European Association for the Study of Diabetes on Management of Hyperglycemia in Type 2 Diabetes is a respected guideline with high impact on this subject in terms of influencing physicians in the definition of strategic approach to overcome poor glycemic control. But, on the other hand, it carries a recommendation that might contribute to clinical inertia because it can delay the needed implementation of more vigorous, intensive, and effective strategies to overcome poor glycemic control within a reasonable time frame during the evolution of the disease. The same is true with other respected algorithms from different diabetes associations. Together with pharmacological interventions, diabetes education and more intensive blood glucose monitoring in the initial phases after the diagnosis are key strategies for the effective control of diabetes. The main reason why a faster glycemic control should be implemented in an effective and safe way is to boost the confidence and the compliance of the patient to the recommendations of the diabetes care team. Better and faster results in glycemic control can only be safely achieved with educational strategies, structured self-monitoring of blood glucose, and adequate pharmacological therapy in the majority of cases.

The dimension of poor glycemic control in Brazil is a matter of deep concern. A study conducted by 12 diabetes centers in different regions of the country showed that only 10.4% of subjects with type 1 diabetes and 26.8% of those with type 2 diabetes (T2D) were considered as ideally controlled, defined by a glycated hemoglobin (A1C) level below 7.0%.[1] Another study by a leading population health management company in the United States with data extracted from electronic databases on more than 23,000 diabetes patients showed that 57.5% of these patients presented a A1C level above 9.0% in their first test; results of this study also showed that long intervals between tests increase the probability that the next test result continues to be above 9.0%.[2] How can we reverse this situation? What strategies can be implemented to promote a better diabetes control in an effective and safe way?

The analysis from the original data from the Steno-2 study and after a follow-up of 3.8 years, published in 1999, showed that intensified multifactorial interventions in patients with T2D were able to slow progression to nephropathy, to retinopathy, and to autonomic neuropathy, but at that time the benefits of intensive intervention on macrovascular complications and mortality were not yet well defined.[3]

The analysis of cost-effectiveness of intensified versus conventional multifactorial intervention in T2D patients from the Steno-2 study indicated that ''from a health care payer perspective in Denmark, intensive therapy was more cost-effective than conventional treatment.''[4]

Further analysis of results from the Steno-2 study confirmed the superiority of the intensive approach in comparison with conventional treatment, as shown by different studies that demonstrated the benefits of intensive approach in relation to the following: a 50% reduction of cardiovascular and microvascular events[5]; a reduction in cardiovascular complications and rates of death from any cause or from cardiovascular causes[6]; the maintenance of the benefits of intensive approach after 19 years of follow-up, with a decrease in mortality and in the need for dialysis in patients with T2D and microalbuminuria[7]; and reduction in the risk of end-stage renal disease by 65%, of microalbuminuria by 9%, and in macroalbuminuria by 30%.[8]

Clinical inertia is a serious threat to diabetes control because it results from two converging negative components: (1) poor compliance of the patients to the treatment and recommendations from healthcare professionals due to ignorance or

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lack of motivation related to repeated and unsuccessful efforts to reach adequate glycemic control or (2) lack of better knowledge or even lack of courage from physicians to implement more intensive treatment approach. A recent article including more than 80,000 subjects published in *Diabetes Care* evaluated the time to treatment intensification in people with T2D treated with one, two, or three oral antidiabetes drugs and associated glycemic control; results of this study showed that time to treatment intensification varied from a minimum of 1.6 years to a maximum of 7.2 years, depending on the treatment schedule, confirming that a substantial proportion of people with diabetes remain in poor glycemic control for several years before intensification with oral antidiabetes drugs and insulin.[9]

The Position Statement of the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) certainly is one of the best of all the guidelines of its kind released during the past decade. The Statement outlines an innovative approach to management of hyperglycemia according to specified clinical parameters for decision-making to determine appropriate efforts to achieve glycemic targets, together with the concept of stressing the utmost importance of treatment individualization, both of these conditions highlight and justify the impact of these guidelines in clinical practice.[10]

And it is exactly for the potential of these recommendations in terms of greatly influencing healthcare professionals in the definition of therapeutic strategies that, in our opinion, we must reconsider and reformulate a concept inserted in the ADA/EASD proposed algorithm. The issue can be summarized as follows: the algorithm suggests a rational sequence for introducing/replacing/intensifying different pharmacological options for the treatment of diabetes, distributed in four sequential steps, from changes in lifestyle plus or minus metformin in monotherapy (step 1), up until full insulinization (step 4). The problem is that before moving to step 2 and before moving to step 3 afterward there is a recommendation of waiting 3 months before proceeding to the next step. Worse yet: it is recommended that before proceeding from step 3 to step 4 we should wait an additional 3–6 months before concluding that the therapeutic approach of step 3 did not work. It is a fact that the ADA/EASD guideline considers the implementation of three-drug combinations other than metformin in case metformin cannot be used or as therapeutic strategy proceeds. However, the key message in the algorithm illustration reinforces the need to wait 3 months before changes in pharmacological therapy should be made.

In other words, the algorithm suggests that we should wait 9–12 months to find out that our therapeutic strategy is not adequate for that particular patient, which characterizes clinical inertia. What kind of patient would be willing to wait that long to have his or her diabetes treatment still undefined and in poor control? What will be the consequences for the unfortunate patient in terms of losing motivation and increasing frustration and guilt feeling with one more defeat against diabetes? In fact, the ADA and EASD are not alone in terms of this apparently strange recommendation because the same suggestion is being repeatedly presented by many diabetes associations throughout the world, on the grounds that the full impact of any treatment strategy over A1C levels can only be evaluated 3 months after implementation. This is true, but the trend of the partial impact of treatments can be safely evaluated by measuring A1C levels after the first and second month from treatment implementation.

Another excellent guideline for the treatment of T2D is the algorithm proposed by the American Association of Clinical Endocrinologists (AACE) in 2013. This is a very didactic, richly illustrated, and informative guideline that considers three different levels of A1C at the initial visit and is much more explicit in terms of recommending dual or triple oral antidiabetes drugs or insulin administration/intensification. But, again, the problem is that the AACE algorithm also recommends waiting 3 months before migrating from one step to the next.[11]

A short-term, randomized, pilot study carried out by our group and published[12] in *Diabetes Technology & Therapeutics* in October 2011 indicated that a rapid improvement of glycemic control in T2D can be achieved in an effective and safe way by using weekly intensive multifactorial interventions, like structured glucose monitoring, patient education, and weekly adjustment of therapy. Compared with the standard care control group, patients in the intensive group showed dramatic improvement of weekly mean glycemia (WMG), glycemic variability (SD), and A1C in just 6–12 weeks. At week 6, compared with week 0, WMG was reduced by -76.7 mg/dL versus -20.5 mg/dL, SD was reduced by -16.3 mg/dL versus -5.0 mg/dL, and A1C was down by -1.82% versus -0.66%, reaching a reduction of -2.2% by week 12. To be considered under control, patients should reach both targets: a WMG of <150 mg/dL (equivalent to an A1C of 6.9%) and an SD of <50 mg/dL, without any significant changes in frequency of hypoglycemia or weight. Patients in the control group were seen only on weeks 0, 6, and 12, and those in the intensive group were seen in on a weekly basis from week 0 to week 6 and from then on at week 12. Data of structured, intensive glucose monitoring were downloaded at each visit and subjected to computerized analysis and generation of glycemic profile and calculation of WMG and SD.

It should be pointed out that the focus of our study was to evaluate the viability of an intensive, yet safe, approach to control diabetes on a short-term basis, which includes the first 6–12 weeks. To maintain the good results obtained during the acute phase of this study, it is obvious that effective strategies of diabetes education and control should be made available to the patients in a long-term basis. As an example, one of our patients had a WMG of 342 mg/dL and an SD of 60 mg/dL at baseline (week 1). During the first 4 weeks she refused to accept insulin treatment, was placed on different oral treatments, and did not show any significant improvement. As of week 4 she was placed on insulin therapy plus oral treatment and 3 weeks later (at week 7) presented a WMG of 112 mg/dL and an SD of just 25 mg/dL, with no hypoglycemic episodes.

In summary, the best way to promote adequate glycemic control is the implementation of intensive, effective, and safe therapeutic strategies, including intensive monitoring of blood glucose, intensive education by an interdisciplinary team of well-trained healthcare professionals, and a rational, individualized pharmacological approach that can be adjusted weekly during the acute phase of the process. It is really expected that this strategy will be more time consuming and perhaps more costly during just a few weeks, but considering its benefits, we might speculate that it could certainly be cost-effective in a long run. It is a fact that chronic complications of diabetes take several years to develop, and therefore some experts might

consider that there is no hurry in reaching the best possible glycemic control. But it should be kept in mind that a faster intervention approach, whenever possible, has the major objective of improving a patient's compliance and motivation as essential tools to provide the patient with the needed strength to face the challenge of diabetes control within a reasonable period of time. Most of our patients in the age bracket of 50–60 years reported that for the first time in their lives they were able to reach the blessing of an adequate glycemic control.

Last, but not least, we want the stress the concept that intensification of therapy can only be carried out in an effective and safe way when both the patient and the doctor are fully convinced that self-monitoring of blood glucose (SMBG) is a very important source of information to evaluate diabetes control when practiced the right way. Unfortunately, very few healthcare professionals utilize the informatics resources that would allow a systematic analysis and the correct interpretation of the glycemic profile by providing automatic calculation of newer parameters such as average glycemia and glycemic variability (SD) and by generating the glycemic profile during the observation period. Data from computerized methods can be easily obtained and can help the diabetes care team in the definition and/or adjustment of the therapeutic strategy.[13]

Isolated, randomly performed glycemic tests are of little or no value at all for the correct evaluation of glycemic control and for properly orienting the doctor in the choice of the best available therapeutic options. Only a structured practice of SMBG can offer adequate guiding for both the patient and the doctor. In an article published in 2011, Polonsky et al.[14] reported the significant results of the implementation of a structured SMBG program that did not utilize computerized resources, with the results being evaluated just with the help of graphic methods recorded by the patients in a special printed plotting card. Patients were seen every 3 months during a whole year when glycemic results were checked and treatment adjustments were made as needed. Before each visit, patients performed seven tests per day over 3 consecutive days (three tests before meals, three tests 2 h after meals, and one test at bedtime). Patients were randomly assigned to one of two groups: the structured testing group and the active control group. The first group presented a reduction of -1.2% in A1C levels, compared with just -0.9% in the second group. The authors concluded that appropriate use of structured SMBG significantly improves glycemic control and facilitates more timely/aggressive treatment changes in non–insulin-treated T2D patients.[14]

Author Disclosure Statement

The authors declare that they have no competing interests in relation to this subject. Both authors discussed the practical importance and implications of this comment. A.P.-N. produced the text, and M.T.Z. revised it. Both authors read and approved the final manuscript.

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