Importance of glycemic control

Edward J. Shahady, MD

TAKE-HOME POINTS

- Early treatment of hyperglycemia may improve β-cell function and prevent β-cell death.
- The target A1C level must be individualized for factors such as duration of diabetes, presence and extent of comorbidities, and life expectancy.
- FPG contributes progressively more to a patient's A1C level as A1C rises to ≥8.5%, while PPG contributes progressively more as A1C drops to <8.5%.
- Balancing treatment effectiveness, safety, and cost, and patient acceptance of the treatment regimen, comprise the cornerstones of successful treatment.

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Type 2 diabetes (T2DM) is characterized by increasing insulin resistance and declining ability of the β-cell to compensate.[1] By the time fasting hyperglycemia is present, β-cell secretory capacity is reduced by ≥50% and usually continues to decline despite treatment with glucose-lowering medications.[2] This environment of increasing insulin resistance and worsening glycemic control leads to the diabetes complications of neuropathy, retinopathy, nephropathy, and cardiovascular disease.[3] Accumulating evidence suggests, however, that the decline in β-cell function may be slowed or even reversed, particularly if addressed early in the course of the disease.[4] Long-term exposure to hyperglycemia, hyperlipidemia, and inflammatory cytokines may be factors that lead to β-cell decline and death. Early treatment to reduce that exposure may be the key to β-cell survival.[4,5] Several studies indicate that some medications, such as insulin, the thiazolidinediones, and incretin-based therapies, improve β-cell function and may prevent β-cell death.[6-9] Results of investigations with metformin and sulfonylureas have provided conflicting results,[10-14] perhaps as a result of differences in duration of T2DM or of unappreciated differences in the surrogate markers of β-cell function.[15,16] Furthermore, the Diabetes Prevention Program demonstrated a 58% reduction in the incidence of diabetes over 3 years with lifestyle changes in individuals with impaired glucose tolerance.[17]

Effect of glycemic control on cardiovascular disease in diabetes

Diabetes is considered a cardiovascular disease risk equivalent, as people with diabetes but no prior myocardial infarction (MI) have been shown to have a 3- to 4-fold greater risk of MI than those who do not have diabetes.[18] Reducing hyperglycemia has been associated with a reduction in cardiovascular events in some but not all clinical studies.

The United Kingdom Prospective Diabetes Study (UKPDS), which investigated newly diagnosed middle-aged patients with T2DM, revealed a reduction in cardiovascular events after 10 years in the group receiving intensive treatment.[19] This long-term benefit has been called the legacy effect, to emphasize the importance of intensive early treatment in patients newly diagnosed with T2DM. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[20-22] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study,[23] and the Veterans Affairs Diabetes Trial (VADT),[24,25] however, demonstrated either no effect or an increased incidence of cardiovascular events with intensive glucose-lowering therapy. These differences in outcomes may be explained by the fact that the patients in the ACCORD and VADT studies were older, had a longer duration of diabetes, and had had a prior cardiovascular event. Subanalyses of the 3 studies revealed a reduction in cardiovascular events in patients who were

Dr. Shahady is Medical Director of the Diabetes Master Clinician Program for the Florida Academy of Family Physicians in Jacksonville, Florida.

younger, had a relatively short duration of T2DM, and had no known cardiovascular disease.

These studies have led to current recommendations to individualize treatment, with aggressive lowering of glycosylated hemoglobin (A1C) to <7% for those with little comorbidity and a long life expectancy.[19,20] However, less aggressive lowering is recommended for patients who are older, have significant comorbidities, and have had diabetes for 10 to 15 years.[26,27] It is also important to remember that the duration of the ACCORD, ADVANCE, and VADT studies was 5 years or fewer, while the average follow-up in the UKPDS was 10.7 years. In addition, the UKPDS involved patients newly diagnosed with T2DM. This is an important distinction, since more aggressive lowering of blood glucose early in the disease has been shown to reduce the risk of cardiovascular events. It is also important to remember that reducing blood glucose levels reduces the incidence of microvascular complications in T2DM.[28]

Achieving glycemic goals

The target A1C goal recommended by the American Diabetes Association (ADA) is <7.0%,[26] whereas the A1C goal of the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) is ≤6.5%.[29] When selecting therapy to achieve the target A1C goal, it is important to keep in mind that A1C levels of 8.5% or higher are determined to a greater extent by the fasting plasma glucose (FPG) level than by the postprandial plasma glucose (PPG) level.[30] As the A1C level falls to <8.5%, it is the PPG level that becomes the determinant of the A1C level such that at an A1C level <7.3%, PPG contributes approximately 70% to the A1C level.[30] Therefore, while focusing on FPG reduction may be appropriate in most patients with T2DM when initiating treatment, PPG becomes an important treatment target as the A1C level declines.

Balancing treatment goals and barriers

Early identification and treatment of T2DM and effective use of medications can help reduce diabetes-related complications.[31-33] Empowerment of the patient and office team, as well as diabetes registries to measure success of treatment, can also promote reduction of diabetes-related complications.[34,35] However, patients and clinicians face multiple barriers when they attempt to establish this foundation. Lack of time, financial reimbursement issues, low health literacy and numeracy, and limitations associated with many current therapies often result in suboptimal treatment. Many patients do not achieve current glycemic, lipid, and blood pressure goals,[19] and treatment-related side effects such as hypoglycemia and weight gain can lead to nonadherence.[36] When the right medications are chosen for the right patient at the right time and are used in the right way, however, patient health outcomes can be significantly improved. Balancing treatment effectiveness, safety, and cost, and patient acceptance of the treatment regimen, comprise the cornerstones of successful treatment. ■

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