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Review Article

Indian consensus on durability of glycemic control in type 2 diabetes management and role of oral antidiabetic drugs

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ABSTRACT

The prevalence of type 2 diabetes mellitus (T2DM) is increasing in an alarming way in India as well as across the globe. In order to minimize complications, there is a need to maintain good glycemic control in patients with T2DM and long-term durable glycemic control remains a challenge. Clinically, this challenge was addressed by step-wise intensification of therapy with additional antidiabetic drugs to maintain glycemic control. Various disease and patient-related factors as well as different antidiabetic agents influenced the durability of glycemic control differently. While understanding of the factors that influenced therapeutic outcomes had evolved, there was paucity of information about the durability of glycemic control and the role of oral antidiabetic drugs (OADs) in achieving it. With an objective to understand the role of durability of glycemic response in the management of Indian patients with T2DM, 4 advisory board meetings attended by 48 physicians from across the country were conducted in Mumbai, Delhi, Kolkata and Bengaluru. There was consensus to consider durability of glycemic control as an important goal in the management of T2DM. Personalized approach in T2DM management along with early initiation of dual combination therapy were recommended to achieve durability. Age group of patients, body mass index, glycated hemoglobin levels at diagnosis, presence or absence of comorbidities and complications are important factors that need to be considered before initiating dual combination therapy for patients with T2DM.

Keywords: Diabetes mellitus, Durability of glycemic control, Metformin, Dipeptidyl peptidase-4 inhibitors

INTRODUCTION

The prevalence of diabetes in India is steeply rising and is expected to grow from 8.8% of the adult population today to around 10% by 2035 and approximately 87% to 91% of all people with diabetes are estimated to have T2DM.[1] What is more concerning is that compared to western countries, diabetes in India occurs at a younger age and the incidence is also high among individuals with low body mass index (BMI). Other characteristics of Indian diabetes include an equal affect in both urban and rural population and individuals from all socioeconomic strata. Due to lack of adequate screening programs, the disease is diagnosed at a later stage, generally when it presents with some complication, moreover, the diagnosed population remains largely uncontrolled with glycosylated hemoglobin (HbA1c) levels reaching up to 9.0% owing to nonuniform management strategies.[2]

As demonstrated by epidemiological studies, uncontrolled diabetes and hyperglycemia pose a significant risk in the development of cardiovascular disease (CVD), hence, attaining a target HbA1c level of <7.0% is essential to prevent the onset and progression of macrovascular diseases including CVD.[3-5]

Diagnosed patients are usually prescribed monotherapy with metformin as first-line therapy and the control of

glycemic levels is assessed during follow ups. However, for a population with uncontrolled diabetes at high risk of complications and mortality like in India, monotherapy may often be inadequate.

Long-term durable glycemic control to minimize the risk of several complications remains a challenge. Gradual loss of pancreatic β cells, β cell dysfunction and insulin resistance are among the main reasons for glycemic failure in patients.[6] Clinically, this challenge is addressed by step-wise intensification of therapy with additional antidiabetic drugs to maintain glycemic control. Various disease and patient-related factors as well as different antidiabetic agents influence the durability of glycemic control differently.[7] With the evolution of science around diabetes, understanding about the factors that influence therapeutic outcomes has significantly increased. However, there is paucity of information on the durability of glycemic control and the role of OADs.

Methodology

With an objective to understand the role of durability of glycemic response in the management of Indian patients with T2DM, 4 advisory board meetings were conducted across in Mumbai, Delhi, Kolkata and Bengaluru. In all, 48 physicians from across the country attended these meetings and provided recommendations based on their clinical experiences, on various topics such as causes of failure of OADs, initiation of therapy in newly diagnosed patients (monotherapy versus combination therapy), role of various OADs and their durability. International guidelines were also discussed along with their applicability to the Indian scenario. Here, we summarized the recommendations based on these discussions.

Durability of glycemic response

Glycemic durability is defined as the maintenance of optimal glycemic control (HbA1c <7.0%) for 2 years without substitution or adding other glucose-lowering agents. Long-term glycemic durability is important and should be considered among the goals of diabetes management. Higher baseline BMI and lower HbA1c have been associated with better durability.[6]

Key determinants of durability of glycemic control include diet; co-morbidities; adherence to therapy or compliance; HbA1c levels at the time of diagnosis and at first follow up visit; level of insulin resistance and physical activity of patient or sedentary lifestyle.[6]

Consensus recommendations

Factors to be considered for improving durability of glycemic control in patients with T2DM were enforcement of lifestyle modifications; early initiation of combination therapy (dipeptidyl peptidase inhibitors [DPP4i]+metformin); addition of insulin therapy, if required; personalized approach and improving patient compliance by counselling, pill reminders, compliance packs.

Lifestyle modification, especially appropriate exercise, is the key to improve durability and hence, more focus needs to be paid on training patients to learn appropriate exercise and ensure compliance to it.[6] The durability of glycemic control also varies based on the drug prescribed. DPP4 inhibitors and thiazolidinediones are proven to show high glycemic durability among all the oral hypoglycemic drugs.[8,9]

Treatment initiation with monotherapy versus dual therapy

The main objective while prescribing combination therapy was to reduce glucotoxicity and achieve durable glycemic control. OAD failure was a major challenge in the management of T2DM. Monotherapy was more prone to fail than combination therapy, especially in patients with high HbA1c and obesity.[10]

Table 1: Guideline recommendations for initiation of dual therapy in newly diagnosed patients with T2DM.

Guidelines	HbA1c recommendations (%)
ADA 2019	>9.0
ICMR 2018	>9.0
AACE/ACE 2019	>7.5
ADA-EASD 2019	≥1.5 (12.5 mmol/mol) above the glycemic target

AACE/ACE, American association of clinical endocrinology; ACE, American college of endocrinology; ADA, American diabetes association; EASD, European association for the study of diabetes; HbA1c, glycated hemoglobin; ICMR, Indian council of medical research.

Initial dual therapy established better glycemic control, eventually translating into delayed progression of the disease and limiting the complications.[10] In patients with high HbA1c (>9%), the concept of dual therapy was already established. One school of thought believed in early intensified treatment even for treatment-naïve patients with HbA1c <8% to benefit from delayed the progression (via metabolic memory) and reduced the risk of complications. Attainment and maintenance of near-normal glycemic levels decreased the risk of microvascular complications and mortality as well.[11,12]

There were differences among guideline recommendations with respect to initiation of dual therapy for newly diagnosed patients with T2DM (Table 1). American diabetes association (ADA) guidelines and Indian council of medical research (ICMR) 2018 guidelines recommended initiation of dual combination therapy if HbA1c at diagnosis was >9.0%, whereas the American association of clinical endocrinology (AACE) and American college of endocrinology (ACE) guidelines recommended >7.5% as the cutoff for initiating dual combination therapy.[13-15] The ADA and European society

for study of diabetes (ADA-EASD) joint consensus guidelines recommended initiating combination therapy if HbA1c was >1.5% above the desired target for a particular patient.[16]

One of the known causes of deteriorating glycemic control was the gradual failure of β-cell function. This was conventionally addressed by adding additional agents over a period of time, often years, to maintain acceptable glycaemia. Different agents may modify the progression of glycemic failure differently.

Consensus recommendations

Factors to be considered while advising combination (dual or triple drug) antidiabetic therapy to achieve durable glycemic control were age of the patient; duration of diabetes; level of glycemic control-HbA1c, fasting and postprandial glucose levels; presence and severity of comorbidities; cost of medications; route of drug administration; family and social situations; diet and physical activity of the patient and liver and renal functional status.

Durable glycemic control with metformin, sulfonylurea and thiazolidinediones

Metformin was recommended as first-line agent over other drugs until it was contraindicated or not tolerated by patients.[13-16] It was safe for patients with cardiovascular diseases. Monotherapy with metformin was often inadequate in patients with high HbA1c, comorbidities, inadequate dietary patterns or lack of exercise.[17] In the United Kingdom prospective diabetes study (UKPDS), metformin did not decrease the rate of loss of β-cell function, which suggested that it may not provide durable glycemic control.[18] The diabetes outcome progression trial (ADOPT) measured glycemic durability of rosiglitazone, metformin or glyburide monotherapy during a median period of 4 years in 4360 recently diagnosed patients with T2DM.[19,20] This trial observed superior durability of glycemic control and less monotherapy failure with rosiglitazone than with metformin and glyburide. Another trial that compared glycemic durability of glypizide and dapagliflozin over 2 years observed greater glycemic durability, sustained reductions in weight and systolic blood pressure and a low hypoglycemia rate with dapagliflozin relative to glipizide.[21]

Durable glycemic control and gliptins

DPP4 inhibitors or gliptins were important second-line agents recommended by most guidelines as an add-on to metformin therapy because of their advantages like minimal hypoglycemia, weight neutrality and cardiovascular safety.[13-16] In meta-analysis and systematic reviews, DPP4 inhibitors have shown better glycemic durability compared to other class of anti-diabetic agents.

A systematic review and meta-analysis of DPP4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) involving 12 long-term randomized trials and 14829 participants with a minimum treatment duration of 76 weeks showed that glycemic control with DPP4 inhibitors was sustained for a year and started decreasing in the second year.[22] Meta-analysis of long-term randomized trials with patients assigned to either an oral DPP4 inhibitor or an oral sulfonylurea, which included 8 trials with treatment duration of at least 2 years (104 weeks), showed that treatment with DPP4 inhibitors was associated with significantly smaller changes in HbA1c levels compared with sulfonylureas, suggesting better durability of glycemic control with DPP4 inhibitors.[23]

The VERIFY trial evaluated whether early combination of vildagliptin 50 mg twice daily with metformin resulted in better durability of glycemic control than sequential intensification of therapy (with initial metformin monotherapy followed by combination of vildagliptin and metformin), in treatment-naive people with T2DM.[24] In this large trial, 2001 participants were randomized to receive either early combination therapy or stepwise intensification therapy and were followed up for 5 years. The study observed that an early combination treatment strategy significantly reduced the relative risk of time to initial treatment failure by 49% versus initial monotherapy strategy. Median time to failure was 3 years with the initial monotherapy strategy compared to over 5 years with early combination strategy. When all patients were receiving combination therapy, the risk of time to second treatment failure reduced by 26% in the early combination group. The results explained the importance of durability of glycemic control and role of early combination therapy with metformin and vildagliptin.

Consensus recommendations

Initiation of dual combination therapy with metformin and DPP4 inhibitors like vildagliptin needed to be considered for newly diagnosed diabetes patients if HbA1c levels were >7.5% and <9.0%; patient was not obese; patient belonged to any age group especially elderly age group (>60 years); patient did not have any associated cardiovascular, hepatic and renal comorbidities; patient was not pregnant and patient was prone for hypoglycemia.

DISCUSSION

The experts recommendeded that dual therapy should be endorsed for treatment initiation in treatment naïve patients with high HbA1c (>9.0%). Late detection of T2DM was a common phenomenon in India, patients were often diagnosed with HbA1c >8.0%.[25] Experts concurred with the current international guidelines for recommendations on initiation of dual therapy, namely HbA1c >9.0% for ADA 2019 and >7.5% for AACE/ACE 2019.[13,15] The attending physicians emphasized on a

personalized approach, which was in line with the ADA-EASD 2019 guideline recommendation, that is, considering initiation of dual therapy in patients with newly diagnosed T2DM who have HbA1c ≥1.5% above their glycemic target.[16] This concept was apt as target HbA1c level varied based on age and associated comorbidities.

Dual therapy can be initiated in patients with uncontrolled T2DM on metformin or those who were intolerant to high doses of metformin. Dual therapy was also initiated in patients with HbA1c >8.5% (or 1.5% more than the target HbA1c).[16] Clinically, combination therapy should be initiated in patients specially to reduce glucotoxicity and to improve durability. Comorbid conditions also played a role in determining whether treatment should be initiated with dual therapy. Gliptins have a definite role in the management of T2DM and they were frequently prescribed in non-obese patients with HbA1c levels of 7.5-9.0% without associated comorbidities. Vildagliptin and other gliptins have shown good durability of glycemic control in clinical studies.[7,8,22-24] However, there was a requirement of robust studies to establish the same.

The panel also recommendeded a way forward for management of T2DM; routine screening for T2DM using random blood sugar can be done in all patients above 30 years of age, especially for high-risk patients such as those with a family history of diabetes. The Indian diabetes risk score (IDRS) can be displayed at prominent places in clinics to increase diabetes awareness, thereby encouraging voluntary screening for diabetes.[26] HbA1c is the gold standard for diagnosis but fasting and postprandial blood sugar were equally important in initiation and titration of treatment drugs. HbA1c levels should be tested at least twice a year.

CONCLUSION

Durability of glycemic control needs to be considered as an important goal in the management of T2DM as better durability minimizes the incidence of complications. Early initiation of combination therapy with metformin and DPP4 inhibitors like vildagliptin has shown to provide durable glycemic control. Factors such as HbA1c level at diagnosis, patient age group, BMI and presence or absence of co-morbidities and complications need to be considered while choosing a particular therapy given that the choice of therapy is expected to play a critical role in achieving durable glycemic control.

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