HbA1C in Management of Type II Diabetes Mellitus: A Cross-sectional Survey of Indian Physicians

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Abstract
Objectives: Hemoglobin A1C (HbA1C) estimation is the standard and commonly used method for diagnosis and monitoring of diabetes therapy. We conducted a questionnaire based survey to understand the Indian physician’s adherence to HbA1C for effectively managing Type 2 diabetes mellitus (T2DM) patients and its influence on the decision making process.

Methods: A validated questionnaire comprising of 10 questions was administered to physicians/endocrinologists at the 44th Annual Conference of RSSDI-2016, Hyderabad. The questions of the survey were designed to understand average cutoff HbA1C level for physicians to start the mono-therapy or combination therapy with or without insulin along with preferred class of Oral anti-diabetic drugs (OAD) in Indian T2DM patients.

Results: 41% physicians selected HbA1C level in between 7.0-7.4% to start mono-therapy while 94.5% chose metformin as the first line OAD. In metformin uncontrolled patients, 56.8% responders chose to start a DPP4 inhibitor. To initiate dual therapy 42.9% responders chose HbA1c level of 8.0-8.4% while for triple therapy 37.1% responders selected HbA1c level of 9.0-9.4%.

Conclusion: This survey shows the management patterns of T2DM patients by Indian physicians are in line with western guidelines especially AACE. Though guidelines do not offer stringent recommendation on first/second add-on class of OADs, DPP4i emerged as preferred choice for mono-therapy in metformin-intolerant patients and as first add-on in patients uncontrolled on metformin alone.

Introduction
Diabetes is one of the leading cause of premature morbidity and mortality globally, mainly due to the increased risk of cardiovascular disease (CVD). Worldwide more than 415 million adults are suffering from the diabetes which is estimated to reach around 642 million by 2040. Nearly 80% of total adult diabetics are in low or middle income countries.

In India 69 million person are suffering from diabetes. WHO estimates every 26 per 100,000 person die due to diabetes in India. Almost every tenth adult (9.3%) in India is estimated to be affected by diabetes. Increasing evidence shows that nearly half of the patients with Type 2 Diabetes mellitus (T2DM) are not aware of their condition. T2DM in India poses a daunting challenge to Indian health care system and its sustainable development. Early diagnosis is crucial as careful diabetes management can reduce long term complications like retinopathy, renal failure, cardiovascular disease and limb amputation.

Hemoglobin A1C (HbA1C) estimation is the standard and commonly used method for diagnosis and monitoring of diabetes therapy. It relates well to both post prandial blood glucose and fasting Plasma glucose (FPG). Guidelines have recommended HbA1c as reference to monitor, intervene or diagnose the disease. The American Association of clinical endocrinologists and American college of Endocrinology (AACE) supports an HbA1C goal of < 6.5% for most patients and a liberal goal of >6.5% if the lower target cannot be achieved without adverse outcomes in T2DM patients. American diabetes association (ADA) supports HbA1C <7.0% in most patients as glycemic goal but HbA1C < 6.5% in some patients such as young patient with relatively shorter history of the disease, if it can be achieved without adverse outcome.

Though guidelines specify definitive values of HbA1C in T2DM patients for diagnosis, management and monitoring, the extent to which these guidelines that are followed in real life scenario is unknown.

The rationale of this questionnaire based survey is to understand the adherence of HbA1C to effectively manage Indian T2DM patients by Indian physician/diabetologist/endocrinologist and its influence on the treating physician’s decision making during the management of Indian T2DM patients.

Methodology
This was a questionnaire-based survey of physicians seeing patients of T2DM across different parts of
Delegates attending RSSDI conference were approached, explained the objective of doing the survey and those willing to participate were asked to fill up the questionnaire. The completed questionnaires were collected and analyzed. Number of responses to each question was categorized as percentages for all the responses were calculated. Data were expressed in n (%). Missing data was not considered for calculating percentages.

Results

A total of 337 questionnaires were filled, out of which 310 were included for analysis. 27 questionnaires were not included because of incomplete or illegible responses.

HbA1C value in the newly diagnosed T2DM patients at the time of presentation to the physicians was in the range of 8.5 to 8.9% as opined by 31.3% of surveyed physicians, closely followed by patients presenting with HbA1C value of >9% (Figure 1).

In response to the HbA1c level at which the pharmacotherapy should be started 41% physicians preferred HbA1C level in between 7.0-7.4% to start the mono therapy, followed by HbA1C level of 6.6 to 6.9% (18.4%). Around 17% chose the option to start the dual therapy in all the patients in all patients irrespective of HbA1C value (Figure 2).

Majority of the responders chose metformin as first line Oral hypoglycemic agent (OHA) (94.5%). In metformin intolerant (contraindicated) patients, majority of surveyed physicians preferred to start a DPP4 inhibitor (56.1%) followed by alpha glycosidase inhibitors (5.5%) and thiazolidinedione (5.5%), in patients uncontrolled on metformin (56.8%) responders preferred a DPP4i option, followed by option opted SU with (33.9%) responders choosing SUs as option.

In response to cut off value to initiate dual and triple therapy 42.9% responders chose the HbA1c level of 8.0-8.4% as cut off to initiate dual therapy, followed by HbA1c level of 7.5-7.9% (23.2%) while 37.1% responders selected option of HbA1c level of 9.0-9.4% to initiate the triple therapy and more than 10.0% of HbA1c level to start the basal insulin (37.7%).

More than half (52.6%) responders believed in initiating basal insulin in patients uncontrolled on combination of metformin and a DPP4i. More than a third of responders (37.7%) chose 10.0-10.4% of HbA1c level to initiate the insulin therapy followed by 26.1% responders choosing the HbA1c level of 9.0-9.4% to initiate the insulin therapy.

Discussion

It is well established that microvascular and macrovascular complications are related to hyperglycaemia and good glycemic control remains the foundation of the management of T2DM. The level of HbA1c value < 7.0% is said to be appropriate for reducing the risk of cardiovascular complications.8

The Diabetes complications and control trial (DCCT) established HbA1c as the gold standard tool for monitoring
glycemic control. The amount of HbA1c reflects the glycemic control of a patient during the past 6–8 week’s period. The amount of HbA1c correlates well with fasting and postprandial blood glucose levels. At present, HbA1c is the most commonly used surrogate marker for setting goals of treatment.9

Interestingly, in case metformin being intolerable, survey showed that majority of the responders chose to initiate therapy with a DPP4i. Even when tolerability of metformin is not a concern a healthy proportion of responders (46.8%) chose DPP4i as the second add on to metformin and SU.

Multiple sites of actions and glucose dependent lowering are the hallmarks of incretin based therapy. DPP4is other than being effective in lowering the blood glucose level, have considerably raised the curiosity of the researchers because of their pleotropic effects including potential role in modifying the course of inflammation. DPP4 inhibitors pleotropic effect may result from their action on multiple factors including insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, dysfunctional immunity, and anti-apoptotic properties of these agents in the heart and vasculature.10

ADA and EASD combined position statement states that if mono-therapy alone does not achieve/maintain an HbA1c target over ~3 months, the next step would be to add a second agent.11,12 It also recommends the addition of one of five anti-hyperglycemic drugs beyond metformin when A1C is above target in a step-wise manner acknowledging their side effects and safety.13

However, DeFrenzo et al14 talks about the pathophysiology approach. It states that in most newly diagnosed diabetic patients, mono-therapy will not reduce HbA1c <6.5–7.0% or, most optimally, <6.0%, and combination therapy will be required.

It further goes on to state that, underlying pathogenic abnormalities if not corrected by anti-diabetic drugs will not achieve long term glycemic control OHA prescribed as combination therapies should have an synergistic effect. Three years into the UKPDs trial (designed as a monotherapy study) it became clear that neither metformin nor SU can prevent the progressive β-cell dysfunction and hence cannot stabilize the HbA1c.17

American association of clinical endocrinologists (AACE) in its glycemic control algorithm extensively uses the presenting HbA1c as a parameter to initiate the pharmacotherapy (mono or in combinations).18 It is recommended by AACE to start mono-therapy when the entry HbA1c is less than 7.5%, dual therapy at the entry HbA1c level of more than 7.5%. This survey has shown that most Indian physicians initiate pharmacotherapy at HbA1c level of 7.0% and above however a significant proportion of physicians (28.1%) preferred the initiation of pharmacotherapy in patients with HbA1c levels between 6.5%-6.9%. Similarly for dual therapy most physicians preferred chose entry level HbA1c of 8.0-8.4% where as a sizeable portion of respondent preferred 7.5%-7.9% entry HbA1c which is more or less in line with AACE recommendations.

If glycemic control is not achieved in 3months with dual therapy AACE recommends further intensification of therapy or addition of insulin. For patients presenting with HbA1c of 9.0% without symptom AACE warrants the triple therapy initiation. In course of this survey for initiating triple therapy most physicians preferred the option of HbA1c entry level of 9.0-9.4%

It shall be noted in context that Indian T2DM patients differs significantly from their global counterparts, in terms of presentation, entry HbA1c level and duration of disease before diagnosis. However, the finding of this survey are more or less in line with AACE glycemic control algorithm as far as the therapy based on entry level HbA1c is concerned.

Though the guidelines do not offer much distinction on the class of OHAs to be preferred especially as first and the second add on. This survey has shown that the preference of Indian physicians in metformin intolerant patients as well as add on to metformin therapy in others is a DPP4 inhibitor.

Being a questionnaire based survey with multiple options to choose against each question this analysis has few limitations including that the actual prescription patterns were not tracked and analyzed based on HbA1C cut-off values. For practical purposes, the survey included direct questions relying on HbA1c level rather than the complete clinical profile and that HbA1c can’t be the only basis for the direction of therapy.

However, whether the approach suggested by majority of responders to start combination therapy based on HbA1c level is beneficial than the stage wise addition of anti-diabetic agents remains to be a subject of debate unless an adequately powered randomized controlled trial (RCT) is carried out to answer this question.

Conclusion

This survey has shown that despite of Indian T2DM patients being significantly different from their western counterparts, the management patterns of Indian T2DM patients by Indian physicians are in line with western guidelines especially AACE and though these guidelines do not offer recommendation on class of OHAs as first and second addition to therapy, DPP4 inhibitors have emerged as preferred choice amongst Indian physicians as combination therapy

Fig. 4: Preferred alternate OHA options patients intolerant to metformin
and as mono-therapy in metformin intolerant patients.

References


