Review Article

Optimizing the treatment of newly diagnosed type 2 diabetes mellitus with combination of dipeptidyl peptidase-4 inhibitors and metformin: An expert opinion

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Abstract

The expanding burden of Type 2 Diabetes Mellitus (T2DM) in today's world, with respect to incidence, prevalence, and cost incurred, is an existential risk to society. Various guidelines recommend individualization of treatment. This expert opinion aims to review the recent evidences and reach a consensus on the preferable combination therapy for use in newly diagnosed Indian T2DM patients with HbA_{1C} >7.5%. The core committee included seventeen diabetes specialists. Three statements were developed, discussed, and rated by specialists and recommendations were noted. Specialists were requested to rate the statements using a 9-point Likert's scale with score of 1 being "Strongly Disagree" and 9 being "Strongly Agree". Statement-specific scores of all the specialists were added and mean score of ≥7.00 was considered to have achieved a consensus. Statements used to meet the consensus were: Statement 1. Majority of newly-diagnosed Indian diabetics have HbA_{1C} >7.5%; Statement 2. Patients with HbA_{1C} >7.5% may be initiated with dual therapy of dipeptidyl peptidase-4 inhibitors (DPP4Is) + Metformin; and Statement 3. In Indian patients with HbA_{1C} >7.5% at diagnosis, DPP4Is + Metformin may be considered as a first-line therapy. Literature review revealed that HbA_{1C} level at the time of diagnosis in majority of Indian T2DM patients is >7.5%. Consensus was reached that dual anti-diabetic therapy should be initiated in patients with HbA_{1C} >7.5%. DPP4Is + Metformin is the preferred cost-effective option and may be considered as a first-line therapy in Indian T2DM patients with HbA_{1C} >7.5% at diagnosis.

Keywords: Combination therapy, DPP4 inhibitors, HbA_{1C}, Metformin, T2DM

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Received: 03-12-2020 **Revised:** 20-02-2021
Accepted: 09-07-2021 **Published:** 27-12-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_2378_20

How to cite this article: Das AK, Gandhi P, Saboo B, Reddy S, Chawla R, Zargar AH, *et al*. Optimizing the treatment of newly diagnosed type 2 diabetes mellitus with combination of dipeptidyl peptidase-4 inhibitors and metformin: An expert opinion. J Family Med Prim Care 2021;10:4398-409.

Introduction

Diabetes mellitus (DM) is considered as one of the major health challenges for the 21st century and expanding burden of DM possesses a pragmatic risk to society.[1] Estimates of International Diabetes Federation (IDF) Diabetes Atlas show that India is a significant contributor to global burden of Type 2 DM (T2DM), as suggested by a tenfold rise in prevalence over past four decades.[2] It is evident from Global Burden of Disease data illustrating prevalence of 26 million in 1990, which increased to 65 million in 2016.[3] This figure is anticipated to rise to 134.3 million by 2045.[2,4] The ICMR-INDIAB study, involving 15 Indian states, reported overall prevalence of diabetes to be 7·3%, with prevalence being higher in urban (11·2%) than rural areas (5·2%), and significantly higher in mainland (8·3%) than North-Eastern states (5·9%).[5]

According to American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2018 consensus statement,[6] American Diabetes Association (ADA) 2018 consensus report,[1] and Research Society for the Study of Diabetes in India (RSSDI) 2017 guidelines,[7] Metformin is first line therapy for newly diagnosed T2DM patients, based on baseline HbA_{1C} at diagnosis. If Metformin is contraindicated or not tolerated, other alternative oral anti-diabetics (OADs) can be considered as first line therapy, which include Dipeptidyl Peptidase-4 Inhibitors (DPP4Is), Glucagon-like Peptide 1 (GLP-1) Agonists, Sulfonylureas (SUs), Thiazolidinediones (TZD), Alpha-glucosidase Inhibitors (AGIs), Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2Is), and Glinides [Figures 1-3].[1,6,7] If HbA_{1C} at diagnosis is higher (>7.5%), initial dual OAD combination therapy can be considered.[6] RSSDI guideline (2017) states, first line dual therapy is considered, if single agent is not able to achieve glucose targets.[7]

Aim of this expert opinion was to deliver important and reasonable proposals for management of T2DM with dual therapy of DPP4Is and Metformin, as an initial OAD combination therapy, if entry HbA_{1C} is >7.5%. It will form a significant decision-making tool for clinicians in various Indian healthcare settings. In this expert opinion, we review glycemic, metabolic effects, and cardiovascular outcomes, and provide rationale for recommendation of combination of DPP4Is + Metformin.

Methodology and Approaches for Developing the Expert Opinion

The core committee of subject experts for framing expert opinion included 17 specialists. Position statements (2012, 2015) and consensus statement (2018) given by ADA/ESAD,[4,8] AACE/ACE (2018),[6] and RSSDI guidelines (2017)[7] were used as reference points. Thorough review of literature was directed towards evaluating efficacy and safety of combinations involving DPP4Is + Metformin and existing treatment algorithms. Subject specialists assessed underlying draft proposals and provided pertinent recommendations to reach at an agreement and then proposals were consolidated, as deemed appropriate. This expert opinion has been framed using available evidences and where strong reinforce did not exist, by utilizing experience and knowledge of specialists and extensive review by additional experts.

Key principles of expert opinion

These important principles incorporate elements of managing T2DM with combination of DPP4Is + Metformin which include:

- All therapeutic decisions should be based on comprehensive assessment and risk stratification.
- A clear focus on available evidence on efficacy and safety of DPP4Is + Metformin.

We hope that this expert opinion forms a platform for all clinicians, as part of renewed emphasis on explicit management approaches to T2DM with combination of DPP4Is and Metformin.

Expert Opinion: Use of DPP4Is + Metformin as first line therapy in patients with HbA_{1C} >7.5%.

Purpose of the Expert Opinion

Management of hyperglycemia in T2DM is highly intricate with an augmented cluster of available pharmacological agents. However, there is an apprehension regarding their possible adverse events (AEs) and ambiguity regarding actual advantages of tight glycemic control on macrovascular complications.[1] The expert opinion aims to -

- Provide an improved and up-to-date understanding on management of T2DM from context of Indian diabetic patients.
- Identify key treatment algorithms in T2DM patients, based on baseline HbA_{1C}.
- Address key inquiries on initial combination of therapy, to help clinical practice.
- Discuss combination therapy using DPP4Is + Metformin: Highlighting its mechanism, rationale, and clinical evidences to provide clinical recommendations categorically in Indian patients with entry HbA_{1C} >7.5%.
- To discuss out-of-all available options, the preferred choice of DPP4Is from context of Indian diabetic patients.

Developing an expert opinion through modified Delphi method

Eligible specialists having related background and experience concerning target issue were considered and invited for discussion. These specialists could contribute and were willing to give decisions in order to reach consensus.

The meeting was initiated by Working Group Members, and 17 Indian specialists were involved in discussion. The **expert opinion** context was set as:

DPP4Is + Metformin may be used as 1st line therapy in Indian diabetic patients with HbA_{1C} >7.5% at the diagnosis.

The modified Delphi method was used for developing expert opinion by drafting statement related questions and circulating to all specialists. There were three statements and each specialist was requested to rate statements using a 9-point Likert's scale, with a score of 1 being "Strongly Disagree" and 9 being "Strongly Agree". For each statement, scores of all specialists were added and then mean score was derived.[9]

Reaching the consensus

Statements achieving mean score of ≥7.00 were considered to have achieved consensus; mean score of ≥6.50 were considered to have achieved a near consensus; and statements achieving mean score of <6.50 were considered to have achieved no consensus.

Following statements were used to develop consensus among specialists for use of dual therapy containing DPP4Is and Metformin:

Statement 1. Majority of newly diagnosed Indian diabetic patients (NDIDP) have HbA_{1C} >7.5%

In a retrospective analysis (CINDI 2) of 1500 Indian patients with newly diagnosed young onset diabetes (YOD), mean HbA_{1C} was found to be 9.86 ± 2.43% at the time of diagnosis.[10] Another study reported overall prevalence of patients with a mean HbA_{1C} of 7.5 ± 0.33% and above to be 10.4%, in Newly Diagnosed Diabetics (NDD).[11]

Wani *et al.* reported that T2DM patients with HbA_{1C} >7.5% had more microvascular complications (neuropathy, nephropathy, and retinopathy) than patients with HbA_{1C} in the range of 6.5-7.5% demonstrating an association between raised HbA_{1C} and increased risk of microvascular complications.[12]

Based on available evidences and individual clinical experience, majority of specialists agreed that majority of NDIDPs have HbA_{1C} >7.5%. Mean consensus score achieved on the Likert's scale was 7.76 ± 0.60 (Mean ± SEM) and hence, this statement was accepted.

Statement 2. Patients with entry HbA_{1C} >7.5% may be initiated on dual therapy of DPP4Is + Metformin

Glycemic management and monitoring in newly diagnosed T2DM

Combination therapy

T2DM is a progressive disease generally ascribed to steady decline in insulin secretion and rise in insulin resistance. Gradual loss of beta cell secretion significantly affects glycemic control with monotherapy. This theory is supported by report of ADA-EASD (2018) which endorses step-wise addition of anti-hyperglycemic agents, and also considers initiating a dual therapy in patients with newly diagnosed T2DM who have A_{1C} ~ 1.5% (17 mmol/mol) above their glycemic target.[1]

AACE/ACE (2018) consensus statement algorithm considered Metformin as first line drug and second line drugs recommended are SUs, DPP4Is, GLP1-RA, SGLT2Is, AGIs, TZDs, and Glinides. It states that patients with HbA_{1C} >7.5% at diagnosis should be prescribed Metformin + another agent and addition of any second-line agent is generally associated with further decrease in HbA_{1C} by ~ 0.5 to 1%.[6] Latest ADA-EASD consensus report recommends, considering cardiovascular and renal risk when initiating second line drugs after Metformin, wherein, SGLT2I and GLP1As are recommended because of their established cardio-renal benefits.[1] However, there are limitations for usage of SGLT2Is and GLP1As, due to adverse events. Various publications have pointed out adverse events mainly associated with SGLT2Is,[13,14] GLP1RAs[6,15,16] and sulfonylureas.[4] Compared to other OADs, considering efficacy, safety, and cost, DPP4Is are preferred add-on oral therapies to Metformin.[17,18] Moreover, current trend is to initiate therapy with combination of drugs rather than sequential addition.[19]

Rationale for combining DPP4Is with Metformin

DM is characterized by impaired secretion of insulin, insulin resistance, and glucagon hypersecretion. Metformin acts by decreasing hepatic glucose yield and enhances insulin sensitivity, while DPP4Is act by stimulating insulin secretion and inhibiting glucagon hypersecretion. Hence, additive or synergistic activity is predicted through possibly enhanced distinctive mechanism. Moreover, Metformin increases GLP-1 levels which would be potentially additive to action of DPP4Is.[20,21] Thus, combined use of these two classes of drugs is justified.

Clinical evidence of combination therapy of DPP4Is and Metformin

Initial combination therapy

A 24-week randomized trial (RT) showed maximum reduction in HbA_{1C} (2.1%), fasting glucose (3.8 mmol/l), and post-prandial glucose (15.9 mmol/l) in patients receiving initial combination therapy of Sitagliptin (50 mg) + Metformin (1000 mg) twice daily with 66% patients achieving HbA_{1C} <7.0%.[22]

A study by Haak *et al.* evaluated efficacy and safety of Linagliptin + Metformin as an initial combination therapy in patients with inadequate glycemic control through 24 weeks double-blind, RT in 791 patients. Mean change in HbA_{1C} from baseline was significantly ($p < 0.001$) higher in combination arms compared to their respective monotherapy arms.[23]

In 12-week controlled trial of newly diagnosed T2DM patients with severe hyperglycemia, significant reduction of HbA1c was observed in patients receiving Saxagliptin + Metformin combination therapy as compared with Glipizide monotherapy.[24]

The post-trial observations of UKPDS and DCCT trials have suggested the importance of early tight glycemic control for the prevention of future complications of diabetes. These post-trial

observations have been called legacy effects or metabolic memory (Laiteerapong N, *et al.*, 2019).

VERIFY study, assessed glycemic durability of an early initial combination therapy with Vildagliptin and Metformin versus Sequential Metformin monotherapy in newly diagnosed T2DM patients. Treatment failure incidence was comparatively lesser in combination group (43.6%) than monotherapy group (62.1%), concluding that early intervention with combination therapy provides significant long-term benefits compared with initial metformin monotherapy.[25]

Thorough literature search revealed, initial treatment of severe hyperglycemia with DPP4Is + Metformin in newly diagnosed patients with HbA_{1C} >7.5% resulted in significant change in HbA_{1C} and this combination therapy was effective [Table 1].[22,26-30]

Sequential addition of anti-hyperglycemic agents

DPP4Is + Metformin vs Monotherapy:

In a clinical study on T2DM, addition of DPP4I LAF237 (50 mg o.d.) to Metformin (1,500–3,000 mg/day) resulted in reduction of HbA_{1C} by 0.6 ± 1% in 12 weeks.[31]

Numerous studies have revealed better improvements in glycemic control with combination of DPP4Is and Metformin [Table 2].[32-37]

DPP4Is + Metformin vs Metformin + Other agents:

Various studies demonstrated that addition of DPP4I to Metformin monotherapy is non-inferior to combination of Metformin with other OAD agents. Comparable reduction in mean HbA_{1C} was observed. Moreover, when adverse effects (hypoglycemia, GI disturbances, and weight gain) were considered, DPP4I was better tolerated [Table 3].[34,38-41]

Currently, approved indications of DPP4Is and Metformin combination are:

- Adjunctive to diet and exercise, to enhance glycemic control in T2DM patients with insufficiently controlled diabetes with Metformin hydrochloride alone.[42,43]
- As triple combination therapy, in insufficiently controlled T2DM patients with Metformin and Sulfonylureas, in addition to diet and exercise.[42]
- An add-on to Insulin, to improve glycemic control, when adequate doses of Insulin and Metformin do not result in enough glycemic control.[42]

Patient-focused perspectives

Route of administration, adverse event profile, patient preference, and cost of therapy are factors considered for choosing adjunctive therapy. Considering safety, DPP4Is + Metformin combination is associated with minimal or no risk and thus effective in achieving better glycemic control and minimizing pill burden in T2DM.[44]

Pharmacoeconomic profile of DPP4Is compared to other second-line agents

As second-line therapy in T2DM, long-term cost-effectiveness of DPP4I + Metformin was compared with SU + Metformin and incremental cost-effectiveness ratio (ICER) was estimated using Markov model. Incremental cost of DPP4I + Metformin was found to be $11,849 with 0.61 incremental life-years gained compared to SU + Metformin resulting in an ICER of $19,420 per life-year gained.[45]

Other similar studies also demonstrated cost-effectiveness of DPP4Is as second-line therapies.[46-49]

From the evidences, DPP4Is are preferred hypoglycemic agent for patients who are uncontrolled on Metformin monotherapy. Safety profile and cost-effectiveness analysis of DPP4Is + Metformin

Table 1: Clinical studies on DPP-4 Inhibitors + Metformin as initial combination therapy

Study Drug	Baseline HbA1C	Mean diabetes duration	No. of patients (*n*)	Mean change from baseline (%)	Ref. no.
Metformin 1,000 mg b.i.d. + Sitagliptin 100 mg b.i.d	11.2%	4.5 years,	117	HbA1C reduction by-2.9%	[22]
Linagliptin 2.5 mg + Metformin 1,000 mg b.i.d.	11.8%	≤1 years 23 >1-5 years 23 >5 years 20	66	HbA1C reduction by-3.7%	[26]
Metformin 500-2,000 mg b.i.d. + Saxagliptin 5-10 mg	≥9.0%	1.7-2.0 years	991	HbA1C reduction-1.7 to -2.5%	[27]
Sitagliptin/Metformin 50/500, 50/1000 mg bid, Metformin 500 mg bid	9.9%	3.3 years	1250	HbA1C reduction by −2.4% for sitagliptin/metformin −1.8% for metformin	[28]
Sitagliptin 100 mg once and Metformin 500 mg twice daily	8.7%	6.1 years	150	HbA1C reduction by -1.5%	[29]
Tenegliptin 20 mg + Metformin 1000 mg	8.0%	-	450	HbA1C reduction after 12 weeks -1.2% after 24 weeks -1.6% after 48 weeks -1.0%	[30]

Table 2: Clinical studies on DPP-4 Inhibitors + Metformin vs monotherapy

Study Drug	Baseline HbA1C/ Fasting glucose	Mean diabetes duration	Study duration	Key efficacy results	Ref. no.
Vildagliptin 50 mg OD added to Metformin 2.1 g daily	8.4%/9.7 mmol/l	6 years	24 weeks	HbA1C reduction by in Metformin alone - 0.2% Vildagliptin alone - 0.5% Combination - 0.9% Fasting glucose, Metformin alone - increased by 0.7 mmol/l Vildagliptin alone - reduced by 0.8 mmol/l Combination - reduced by 1.7 mmol/l Significant reduction in GI adverse events with combination	[32]
Sitagliptin 100 mg OD added to Metformin >1.5 g daily	7.7%/8.4 mmol/l	6.6 years	4 weeks	Fasting glucose reduced by, Metformin alone - 0.4 mmol/l Combination - 1.3 mmol/l	[33]
Sitagliptin 100 mg OD or Placebo added to Metformin >1.5 g daily	8.0%/9.5 mmol/l	6.2 years	24 weeks	Target HbA1C <7% reached by, 47% in combination group 18.3% in Metformin alone group	[34]
Sitagliptin 50 mg BD. + Metformin 1,000 mg BD or Sitagliptin 50 mg BD + Metformin 500 mg BD or Metformin 1,000 mg BD or Metformin 500 mg BD or Sitagliptin 100 mg q.d.	8.7%	-	54 weeks (788 patients) f/b extension of 50 weeks (517 patients)	HbA1C reduction by, 1.7% in group 1 1.4% in group 2 1.3% in group 3 1.1% in group 4 1.2% in group 5	[35]
Sitagliptin 100 mg + Metformin 500 mg BD (titrated to 50/1000 mg BD) vs Pioglitazone 15 mg (titrated to max. 45 mg daily)	9.0%	-	40 weeks	Change in HbA1C from baseline to 40 weeks, Sitagliptin/Metformin: -1.7% Pioglitazone: 1.4% Proportion of patients achieving HbA1C <7% and <6.5% were, 55% with combination 31.2% with Pioglitazone	[36]
Sitagliptin 100 mg + Metformin OR Placebo + Metformin	9.2%/200 mg/dl	-	30 weeks	Patients on combination were more likely to achieve HbA1C <7% at week 18 and week 30 (p=0.012 and p<0.001)	[37]

are comparable with other dual combination therapies. Combination of DPP4Is and Metformin results in reduction of HbA_{1C} level below 7.5% in T2DM. Thus, specialists agreed that Indian patients with HbA_{1C} >7.5% at diagnosis may be initiated on dual therapy of DPP4Is + Metformin. Mean consensus score achieved on the Likert's scale was 7.00 ± 0.61 (Mean ± SEM) and hence, this statement was accepted.

Statement 3. In Indian diabetic patients having HbA_{1C} > 7.5% at diagnosis, DPP4Is + Metformin may be considered as a 1st line therapy

RSSDI (2017) guidelines state dual combination therapy of DPP4Is + Metformin is more effective in reducing HbA_{1C} (1%) than metformin monotherapy.[7] Moreover, ICMR (2018) guidelines for management of T2DM states, DPP4Is are first choice after SU and preferred over other OAD agents, when treating asymptomatic individuals with HbA_{1C} >9%.[50]

DPP4Is are divided into peptidomimetics (Vildagliptin, Saxagliptin, and Teneligliptin) and non-peptidomimetics (Sitagliptin, Alogliptin, and Linagliptin).[51,52] Various DPP4Is + Metformin combinations, as dual therapy, are widely used and are available in India [Table 4].[53-56]

A survey questionnaire involving 502 physicians and endocrinologists reported that 59.9% physicians preferred DPP4Is + Metformin. Additionally, DPP4Is (54%) are preferred choice of drugs than other OADs in T2DM patients not controlled on combination of SU + Metformin.[57]

DPP4Is + Metformin: FDC versus co-administered dual therapy: Efficacy and compliance

Bajaj *et al.* assessed HbA_{1C} change in Fixed-dose combination (FDC) versus co-administered dual therapy (CDT) of DPP4Is + Metformin. Switching to FDC of DPP4I + Metformin was associated with significant improvement in HbA_{1C} especially in patients with high pill burden.[58] American College of Physicians (ACP) practice guideline updated recommendation states that, combination treatment is superior to Metformin alone for decreasing A_{1C} levels, weight, and blood pressure in T2DM.[17]

Comparison among various DPP4Is in terms of efficacy and selectivity

A study by Agrawal *et al.* observed no significant difference between Teneligliptin and other DPP4Is. Teneligliptin was equally efficacious to other available DPP4Is in maintaining HbA_{1C} levels.[59]

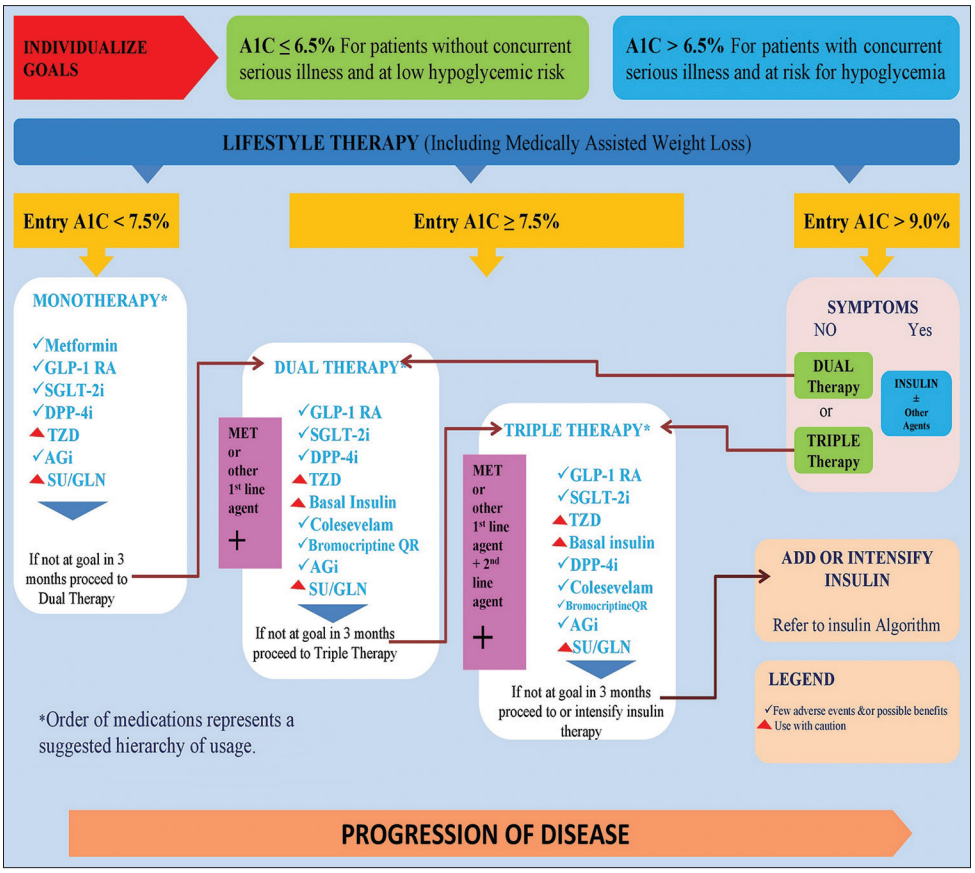

Figure 1: Glycemic Control Algorithm by AACE/ACE 2018 (*Adapted from AACE/ACE 2018)*[6]

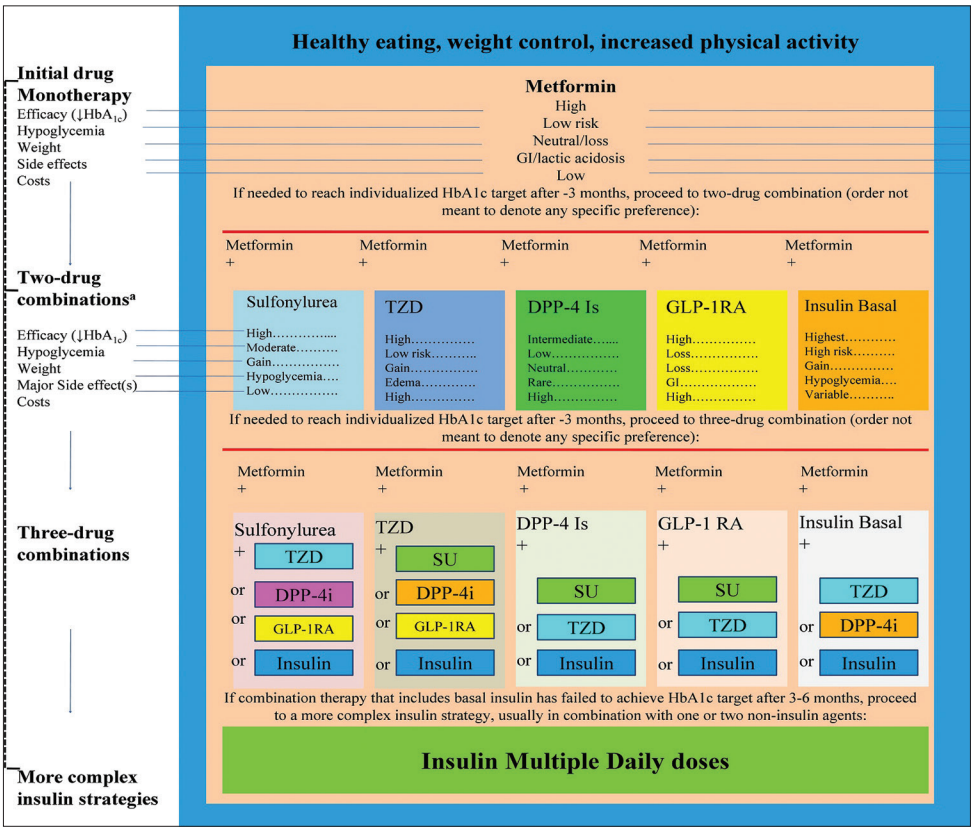

Figure 2: Glycemic Control Algorithm by ADA/EASD 2018 (*Adapted from ADA/EASD 2018)*[1]

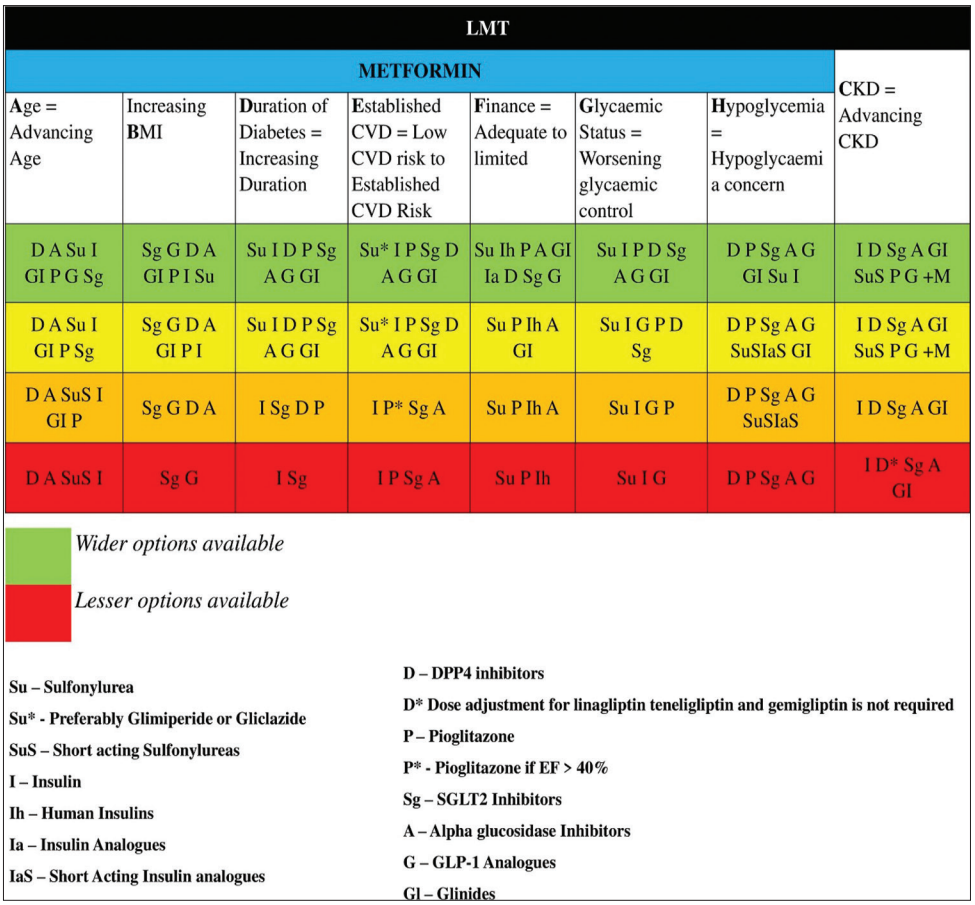

Figure 3: Research Society for the Study of Diabetes in India (RSSDI's) Patient-centric approach or ABCD (EFGH) approach for diabetes management representing therapy *(Adapted from RSSDI 2018)*[7]

Jayanthi *et al.* evaluated glycemic, non-glycaemic effects of Teneligliptin versus Sitagliptin. Statistically significant ($p < 0.001$) decrease in FBS and PPBS at week 8, week 12, and reduction in HbA_{1C}, LDL-CH, TC from baseline in Teneligliptin group, as compared to Sitagliptin group was observed.[60]

In a study, Teneligliptin co-administered with Metformin monotherapy demonstrated dose-related and statistically significant ($p < 0.001$) reductions in HbA_{1C} after 24 h, increased proportion of responders achieving HbA_{1C} <7.0% and maintenance of response throughout 28 weeks with Teneligliptin (20 mg).[61]

Data from real-world, retrospective study (Treat-India) suggests that Teneligliptin significantly ($p < 0.001$) improves glycemic control in T2DM patients, when prescribed either as monotherapy or in combination with Metformin compared with SU combination therapy.[62,63]

Cardiovascular safety of DPP4Is

Cardiovascular (CV) safety is the major focus of anti-diabetic therapy and it was mandated by USFDA in 2008 to establish cardiovascular safety of newer OADs. CV safety of DPP4Is is proved in several clinical trials. They reduce CV risk factors (weight gain and hypoglycemia).[64]

Multiple clinical trials (SAVOR-TIMI 53, EXAMINE, TECOS, CARMELINA) have evaluated the CV safety and efficacy of DPP4Is in patients with T2DM and reported improved glycemic control with DPP4Is and favorable CV safety as compared to placebo or other OAD agents.[65-69]

Safety profile of DPP4Is in T2DM patients with respect to QTc prolongation

Multiple studies have demonstrated significant reduction in FPG, PPBG and HbA_{1C} with no significant effects on QT/QTc interval prolongation by Teneligliptin.[70,71]

A thorough QT/QTc study has shown no clinically significant QTc interval prolongation with 40 mg dose of teneligliptin as per data submitted to Pharmaceuticals and Medical Devices Agency, Japan.[72]

Pharmacoeconomic profile of various DPP4Is

Choice of DPP4Is is based on clinical characteristics of patient, inclination, insurance or paying capacity of patient, and existing co-morbidities. Cost of drugs and affordability of overall therapy are basis for decision making while selecting proper treatment option.[73] Average cost per day for DPP4Is was reduced to INR 9 after switching to Teneligliptin as observed in a cost effectiveness study.[59]

Table 3: Clinical studies on DPP-4 Inhibitors + Metformin vs Metformin + Other agents

Study Drug	Baseline HbA1C/ Fasting glucose	Mean diabetes duration	Study duration	Key efficacy results	Ref. no
Sitagliptin 100 mg q.d. added to Metformin ≥1.5 g daily Vs Glipizide 5 mg/day added to Metformin ≥1.5 g daily	8%/ 9.5 mmol/l	6.2 years	30 weeks extension phase	Change in HbA1C from baseline to 30 weeks, Sitagliptin-0.7% Glipizide-0.9% Hypoglycemia reported as, Glipizide group 16% Sitagliptin 1%, respectively Changes in body weight Sitagliptin -0.9 kg Glipizide + 1.5 kg	[34]
Sitagliptin 100 mg OD OR Rosiglitazone 8 mg daily OR Placebo All 3 groups: Met* 1,500-3,000 mg/day	7.7%, 158 mg/dl	4.9 years	18 weeks	Changes in HbA1C by, Sitagliptin -0.73% Rosiglitazone -0.79% placebo. -0.22% BW† decreased by, Sitagliptin (-0.4 kg) placebo (-0.8 kg) BW increased Rosiglitazone (+1.5 kg)	[38]
Sitagliptin 100 mg OD or Saxagliptin 5 mg daily Both groups: Met* 1500-3,000 mg/day	7.5-10.0%	-	18-week	Change in mean HbA1C: Sitagliptin/Metformin group: 7.69% to 7.07% (adjusted mean, -0.62%; -0.69% to -0.54%) Saxagliptin/Metformin group: 7.68% to 7.16% (adjusted mean, -0.52%; -0.60 to -0.45%). FPG levels decreased Sitagliptin 16.2 mg/dl Saxagliptin10.8 mg/dL	[39]
Exenatide 2 mg/week + oral placebo once daily Sitagliptin 100 mg oral/day + injected placebo once weekly Pioglitazone 45 mg q.d. + injected placebo once weekly All 3 groups: Met* 1,500-2,000 mg/day	8·5%/9·1 mmol/L	6 years	26 weeks	The groups experienced the greatest HbA1C reductions from baseline to 26 weeks Exenatide (1.5%). Sitagliptin (0.9%) Pioglitazone (1.2%). Improvements in FPG Exenatide (-1.8 mmol/L) Sitagliptin (-0.9 mmol/L) Pioglitazone (-1.5 mmol/L).	[40]
Sitagliptin 100 mg q.d. added to Metformin ≥1.5 g daily Vs Glipizide 5 mg/day added to Metformin ≥1.5 g daily	7.5%/15 mmol/l	6.5 years	52 weeks	HbA1C reduction by in 0.51% with Sitagliptin 0.56% with Glipizide Fasting glucose, 0.56% with Sitagliptin 0.42% with Glipizide Hypoglycemia episodes Glipizide (32%) Sitagliptin (5%) weight loss with Sitagliptin (1.5 kg) weight gain with Glipizide (1.1 kg)	[41]

*Met, Metformin; †BW, body weight

Table 4: DPP4Is plus Metformin dual combinations currently available and marketed in India

Drug Combination	Brand Name	Company Name	Dose	Ref. no
Vildagliptin + Metformin	Galvus Met	Novartis India (Mumbai, Maharashtra, India)	50 mg + 500-1000 mg	[42]
Sitagliptin + Metformin	Janumet XR	MSD Pharmaceuticals (Mumbai, Maharashtra, India)	100 mg + 1000 mg	[43]
Alogliptin + Metformin	Kazano	Takeda Pharmaceutical Company (Mumbai, Maharashtra, India)	12.5 mg + 500 mg	[53]
Linagliptin + Metformin	Jentadueto	Boehringer Ingelheim and Lilly (Mumbai, Maharashtra, India)	2.5 mg + 500-1000 mg	[54]
Saxagliptin + Metformin	Kombiglyze XR	Bristol Myers Squibb India Private Limited (Mumbai, Maharashtra, India)	5 mg + 1000 mg	[55]
Teneligliptin + Metformin	Zita Met Plus	Glenmark Pharmaceuticals (Mumbai, Maharashtra, India)	20 mg + 500 mg	[56]

Based on these evidences, Teneligliptin is the most preferred DPP4I used in combination with Metformin in newly diagnosed T2DM patients as per efficacy, safety, and cost-effectiveness.

Based on results of various studies, DPP4Is co-administered with Metformin produce significant reductions in HbA_{1C} (<7.5%) in T2DM without increasing risk of hypoglycemia and thus,

specialists agreed that this combination may be considered as first line therapy. Mean consensus score achieved on the Likert's scale was 7.09 ± 0.41 (Mean ± SEM) and hence, this statement was accepted.

Advantages of Using Combination of DPP4Is and Metformin in T2DM

- With distinct advantages of oral administration, weight neutrality, and no hypoglycemia, DPP4Is are recommended as second-line therapy, and as an alternative first line therapy when Metformin is contraindicated or not tolerated.[1,7]
- DPP4Is are also recommended as an add-on therapy to Metformin and as an add-on therapy to SU and Metformin, TZD and Metformin, Metformin plus Insulin and Insulin monotherapy in patients not adequately controlled on monotherapy or dual therapy.[1,6,74,75]
- DPP4Is carry an insignificant risk of hypoglycemia, when used as either monotherapy or combination therapy with Metformin.[39]
- DPP4Is and Metformin do not affect the pharmacokinetics of each other.[20]
- FDC of DPP4Is and Metformin allows physicians to modify treatment regimens of patients with inadequately controlled glucose levels without increasing pill burden.[44]
- DPP4Is + Metformin treatment is cost-effective as compared to SU + Metformin, as long-term second-line therapy in treatment of T2DM.[45]
- Availability of extended/sustained release FDC of Metformin with Teneligliptin results in fewer gastrointestinal adverse events and improved compliance as compared to immediate release metformin FDC formulations.[43,54,55,56]

Conclusion

Evidence from various studies revealed that majority of Indian T2DM patients have HbA_{1C} level >7.5% at diagnosis. This expert opinion provides a comprehensive summary of existing clinical trials and best evidence for managing T2DM using a combination of DPP4Is + Metformin. The consensus was reached amongst specialists that at time of diagnosis, dual oral anti-diabetic therapy in the form of DPP4Is + Metformin needs to be initiated in patients with HbA_{1C} >7.5%. Moreover, DPP4Is + Metformin is preferred option and may be considered as a 1st line therapy in Indian T2DM patients with HbA_{1C} >7.5% at diagnosis. The consensus reached among specialists depicts best professional judgment and is based on currently available evidence and practical experience of specialists.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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