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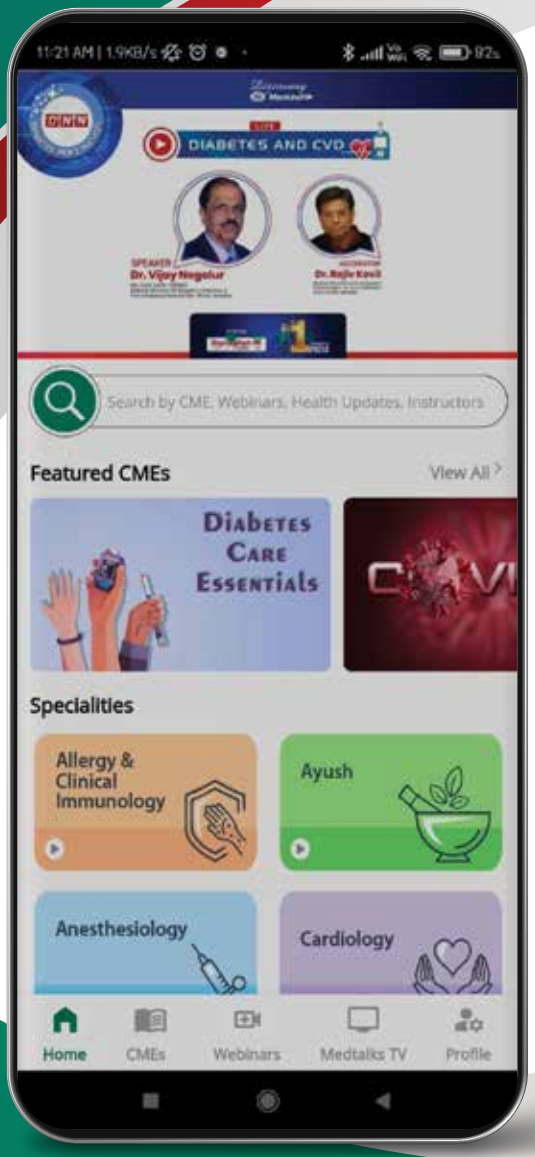

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GUEST EDITORIAL

ORIGINAL ARTICLE

REVIEW ARTICLE

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Diabetes Management: Dynamism Ahead

Type 2 diabetes is a complex disease, with multiple etiologies, presentations, and trajectories. At the same time, diabetes care is equally dcomplicated: research has helped develop effective, as well safe, means of managing the disease which need to be chosen and prescribed carefully.

In this issue of the *Asian Journal of Diabetology*, we explore various evidence-based medical interventions used in diabetes care. 'Old is gold', goes the age-old adage, and Jain et al[1] write about the usage of low-dose glimepiride (0.5 mg) and metformin combination in persons with type 2 diabetes. Modern sulfonylureas are the backbone of type 2 diabetes management, along with metformin, and smart usage. Jain et al demonstrate that this is possible, by collating evidence from across India.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have revolutionized not only diabetes praxis, but also the prevention and treatment of heart and kidney disease. In their comprehensive review, Unnikrishnan et al[2] describe how SGLT2i are being used in diabetology, cardiology and nephrology. The concept of endocrine exaptation[3] is evident from the discussion about the pleiotropic benefits of this class of drugs.

Glucagon-like peptide 1 receptor agonists (GLP-1RA) are another class of glucose-lowering drugs with proven cardiovascular and renovascular safety and benefit. Till recently, only injectable GLP1-RA preparations were available, and this limited their acceptance and uptake. Baidya et al[4] report on an oral formulation of semaglutide, and explain how it will be a game-changer in the management of type 2 diabetes. The authors cover the basic as well as clinical pharmacology of oral semaglutide, and share evidence and experience regarding its usage in clinical practice. Newer drugs are also being developed and imeglimin is the first of its class of oxidative phosphorylation inhibitors. Approved for use in Japan, this molecule has demonstrated effective glucose-lowering efficacy in type 2 diabetes. Kalra et al[5] review its pharmacology and clinical trial data, and propose pragmatic ways for its appropriate placement in type 2 diabetes management algorithms.

The diabetes pandemic shows no signs of slowing down.[6] Rather, it seems to be gaining momentum. This is true for the *Asian Journal of Diabetology* as well. We strive to improve diabetes care across Asia, and across the world. Through the evidence and experience published in our pages, our expert authors share best practices, which can help enhance the quality of our practice. Feel free to share your comments and criticism, to help us improve further. We look forward to learning together.

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Insulin is Essential: The National List of Essential Medicines, India, 2022

Introduction

Insulin is essential for life. While most persons produce adequate amounts of insulin, not everyone is lucky enough. Persons living with type 1 diabetes, with pancreatic diabetes, and with severe or long-standing type 2 diabetes need exogenous insulin for survival.[1] Many persons with type 2 diabetes and comorbidities such as renal or hepatic impairment, severe sepsis or infection, also require insulin. Insulin is also the drug of choice for glycemic control during pregnancy. Unfortunately, however, insulin is expensive, and may be out of reach of many people who need it.[2] One way of ensuring affordable insulin is to declare it an essential drug.

India's National List of Essential Medicines

The National List of Essential Medicines (NLEM), India reflects this thought process. Successive editions of the NLEM have included various preparations and strengths of insulin.[3,4] This year's NLEM lists four insulins: soluble, NPH (neutral protamine Hagedorn) premixed insulin and glargine, irrespective of delivery device.[5] It is assumed that all strengths (40 IU/mL and 100 IU/mL for human insulin, and 100 μ/mL for glargine) are included in the essential list. The 50:50 premixed insulin preparation is not included in NLEM, though it must be admitted that it is not as commonly prescribed as the 30:70 preparation.

The addition of insulin glargine in the Indian NLEM is a welcome development. This underscores the acceptance of the need to provide safe and effective medication to persons living with diabetes at an affordable cost. The updated NLEM highlights India's commitment towards providing world-class treatment to its citizens, and towards ensuring that the noncommunication disease epidemic is addressed aggressively. The Indian pharmaceutical industry has contributed immensely to the production of economical and efficient insulin, not only for the domestic, but also for the global market.[6] An Indian insulin glargine brand has received a label for interchangeability with originator brands from the United States Food and Drug Administration (US FDA),[7] it implies the quality, robustness in clinical data and more importantly "a make in India product to the

global need" which addresses two key barriers, i.e., affordable and accessible insulin to all. US FDA defines Interchangeable if the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient."[8] The 'interchangeable' status can prompt faster and wider uptake of insulin biosimilars and keep the insulin expenditure under control, especially for patients who otherwise practice nonadherence or rationing of life-saving insulin.

National Lists of Essential Devices and Essential Diagnostics

Persons living with diabetes need much more, however. Just as insulin preparations are essential, so are insulin delivery devices like syringes, pens and pumps.[9] Insulin monitoring systems, such as glucose monitors, urine sugar strips, ambulatory/continuous glucose monitoring systems are equally essential to ensure safe and accurate therapy. Equal emphasis should therefore be placed on diabetes care in the National Lists of Essential Devices and Essential Diagnostics.

Noninsulin Medications

The 2022 NLEM contains a brief, yet comprehensive, list of noninsulin oral medications.[5] Their listing reflects the increasing disease burden of diabetes, as well as the efficacy, safety and cost-effectiveness of the drug. Teneligliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor has been added this year. The sulfonylurea glimepiride, and the insulin sensitizer, metformin, complete the list. No sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonists (GLP-1RA) figure in the list, however.

Summary

As we work towards becoming the Diabetes Care Capital of the world (Prof BK Sahay, personal communication), each and every stakeholder's involvement is important. Diabetes care cannot be achieved without ensuring availability, accessibility and affordability of diabetes related diagnostics, drugs and devices. The NLEM 2022 demonstrates the commitment of the Indian government towards achieving this goal. Sustained and concerted efforts will be needed in the future as well, to accomplish our goals.

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ORIGINAL ARTICLE

Usage of Low-dose Glimepiride (0.5 mg) and Metformin Combination in the Management of Type 2 Diabetes Continuum in Indian Setting

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ABSTRACT

Background: To understand the approach of clinicians about the treatment pattern, dosage, efficacy and safety of the combination of low-dose glimepiride (0.5 mg) and metformin fixed-dose combination (FDC) in the management of type 2 diabetes mellitus (T2DM) continuum in Indian settings. **Methods:** This case-based questionnaire survey included health care professionals (n = 112) across India, who were prescribing glimepiride and metformin FDC. Data were collected from the medical records and analyzed. **Results:** The data of 1,403 patients with T2DM were included. The mean age was 49.1 years and 68.4% of patients were males. The median duration of T2DM was 36 months. A total of 86.7% of patients received glimepiride and metformin FDC as first-line therapy. The most commonly prescribed (71.5%) dosage of glimepiride and metformin was 0.5 mg/500 mg. The titration of the dose was performed in 231 patients, of which 82.7% required up-titration and 17.3% required down-titration. The mean glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels reduced significantly (mean change: 1.2%, 36.5 mg/dL and 50.2 mg/dL, respectively) post-treatment. The hypoglycemic event and weight gain were reported in 7.7% and 9.5% of patients, respectively. Overall physician's global evaluation of efficacy and tolerability was rated good to excellent in the majority of patients (>85%). **Conclusion:** Results demonstrate low-dose (0.5 mg) glimepiride and metformin FDC is effective in achieving glycemic control through lowering HbA1c, FPG and PPG levels with acceptable safety outcomes.

Keywords: Low-dose, fixed-dose combination, glycemic control, tolerability

Background

Type 2 diabetes mellitus (T2DM) is one of the most important public health concerns worldwide, affecting 537 million people in 2021. This number is expected to increase to 783 million by 2045.[1] India harbors the second largest T2DM population – of 74.2 million cases in 2021 which is estimated to increase to 124.9 million cases by 2045.[1]

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The primary goal of T2DM management is to achieve and maintain a good glycemic control to limit the long-term micro- and macrovascular complications.[2] Therefore, early diagnosis and management are particularly important to lower blood-glucose levels aggressively and to reduce diabetes-related morbidity and mortality.

There are a number of antidiabetes agents available for managing T2DM.[3] The choice of antidiabetes agents is based on efficacy along with drug safety. Metformin has been the most recommended monotherapy for the initial treatment of T2DM.[4-6] However, many diabetic patients eventually require more than one drug, due to treatment failure with monotherapy over time.[7] Combined regimens are effective to minimize the dosage of antihyperglycemic agents and thereby their unwanted effects. Among various medications, combination therapy using modern sulfonylurea, (glimepiride) and metformin has shown to be effective in improving glycemic control.[8,9]

Early implementation of combination therapy using submaximal doses of glimepiride and metformin could improve glycemic control with marginal micro- and macrovascular complications.[10] Glimepiride and metformin fixed-drug combination (FDC) has a complementary mechanism that promotes insulin secretion and improves insulin resistance,[11] and its use has seen a rise worldwide.[12] Glimepiride and metformin FDC is widely used in Indian clinical settings due to its efficacy and cost-effectiveness in improving glycemic control.[8,13]

Among glimepiride and metformin FDCs, the low-dose combination (0.5 mg + 500/1000 mg) is widely used and well-accepted.[14,15] The glimepiride and metformin FDC (0.5 mg + 500 mg) is useful in patients with early-stage T2DM. The therapy was well-tolerated with no reports of hypoglycemia or weight gain.[14] Evidence suggests that treatment with low-dose glimepiride (0.5 mg) and metformin can improve glycemic control in newly diagnosed patients and those with diabetes duration <5 years with a lower risk of hypoglycemic events and weight gain.[8,15,16]

However, data is lacking about the real-life practice of low-dose (0.5 mg) glimepiride and metformin FDC in treating Indian patients with T2DM. Therefore, the present study aimed to understand the clinician's approach regarding the treatment pattern, the dosage used, and the efficacy and safety of low-dose glimepiride and metformin FDC in the management of the T2DM continuum in Indian settings.

Materials and Methods

Study design

This case-based questionnaire survey study included 112 health care professionals (HCPs) [general physician, endocrinologist, diabetologist, cardiologist and neurologist] who participated in online surveys, across India and prescribed glimepiride and metformin FDC for their patients with T2DM. This study was conducted between June 2020 and June 2021. Here, the HCPs provided information on these patients retrospectively.

Study population

The study population included patients of either sex aged >18 years who were diagnosed with T2DM and were taking or newly started glimepiride and metformin FDC. The data was collected from the medical records of all eligible patients from selected clinics.

Data collection

The questionnaire included questions regarding demographic characteristics (age, sex, education, occupation, weight, height, heart rate and blood pressure), risk factors, history of diabetes complications, biochemical measures (fasting plasma glucose [FPG] and postprandial plasma glucose [PPG], levels of glycated hemoglobin [HbA1c]), comorbidities, use of glimepiride and metformin FDC (first-line/second-line), the dosage of glimepiride and metformin FDC (0.5/500 mg or 0.5/1000 mg), frequency, initiation of a combination of glimepiride and metformin FDC at the levels of HbA1c, FPG and PPG, concomitant and antidiabetic medications (treatment pattern), dosage up-titration, and down-titration, reasons for up- and down-titration, lipid parameters, glycemic parameters changes, weight changes and hypoglycemic episodes during therapy. Patients having incomplete data files or with any condition that according to the discretion of the investigator indicated that the patient were not suitable for inclusion in the study, were excluded.

Outcomes

The primary objective was to study the demographics of patients receiving a dosage of glimepiride and metformin FDC and/or with other antidiabetic drugs in the management of T2DM. This study also assessed different doses of glimepiride and metformin FDC (0.5/500 mg or 0.5/1000 mg), HbA1c levels, up-titration and down-titration, weight changes, hypoglycemic episodes and comorbidities and complications during antidiabetic therapy.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 23.0. Qualitative data were presented as numbers and percentages, while quantitative data were presented as mean (standard deviation [SD]) or median (range), depending on the normal or skewed distribution of data. A paired sample *t*-test was used for comparing the pre- and post-treatment HbA1c, FPG and PPG levels. A $p < 0.05$ was considered statistically significant.

Results

A total of 1,403 patients were included in the study, of which 68.4% of patients were males. The mean (SD) age was 49.1 (11.9) years and 54.8% of patients were aged between >41 to ≤60 years. The demographic characteristics are summarized in Table 1. The median duration of T2DM was 36.0 months. Sedentary lifestyle (59.2%), obesity (48.4%) and emotional stress (39.2%) were the most common risk factors observed among these patients (Fig. 1). A family history was noted in 1,073 patients; of these, 671 patients were the first-degree relatives. Neuropathy was the most common complication observed in 21.7% of the patients. A total of 113 patients were current smokers while 59 were former smokers (Table 1). A total of 645 patients reported comorbid conditions, of these hypertension (59.5%) was the most common comorbidity, followed by dyslipidemia (34.0%) (Fig. 2).

A total of 86.7% of patients received glimepiride and metformin FDC as first-line therapy. The strength of glimepiride 0.5 mg and metformin 500 mg (71.5%) was the most commonly prescribed combination followed by glimepiride 0.5 mg and metformin 1000 mg combination (28.5%). Once a day was the preferred dosing frequency in 733 (58.7%) patients with T2DM, while twice a day was prescribed in 515 (41.3%) patients with T2DM. The median duration of treatment of low-dose glimepiride and metformin FDC therapy was 23.4 months. Titration of the dose was performed in 231 patients and of these, 82.7% required dosage up-titration and the remaining required dosage down-titration (Table 2). The mean HbA1c levels significantly decreased post-treatment with glimepiride and metformin FDC – with a mean change of 1.2% (95% confidence interval [CI], 1.0-1.3; $p < 0.001$) (Fig. 3A). Similarly, the mean FPG (mean change: 36.5 mg/dL; 95% CI, 32.3-40.7; $p < 0.001$) and PPG (mean change: 50.2 mg/dL; 95% CI, 43.8-56.6; $p < 0.001$) levels were significantly reduced post-treatment with glimepiride and metformin FDC therapy (Fig. 3B and 3C). Hypoglycemic events were reported in 7.7% of patients and weight gain was

Table 1. Demographic Characteristics

Parameters	Number of responses (n = 1,403)*
Age (years), mean (SD)	49.1 (11.9)
Age groups (years)	
≤40	405 (28.9)
>41-≤60	769 (54.8)
>61	229 (16.3)
Sex	
Male	960 (68.4)
Female	443 (31.6)
Weight (kg)	74.4 (11.2)
Height (cm)	1.7 (0.1)
BMI (kg/m^2)	27.1 (4.1)
Education (n = 1,287)	
Up to 10th standard	138 (10.7)
Up to 12th standard	277 (21.5)
Graduate	679 (52.8)
Postgraduate	193 (15.0)

Table 1. Demographic Characteristics

Parameters	Number of responses (n = 1,403)*
Occupation (n = 1,253)	
Private service	268 (21.4)
Self-employed	246 (19.6)
Government servant	232 (18.5)
Unemployed	214 (17.1)
Professional	119 (9.5)
Semi-skilled	64 (5.1)
Manual laborer	49 (3.9)
House-wife	47 (3.8)
Retired	14 (1.1)
Area of stay (n = 1,256)	
Semi-urban	544 (43.3)
Urban	489 (38.9)
Rural	200 (15.9)
Metropolitan	23 (1.8)
Economic class (n = 1,246)	
Upper Middle	529 (42.5)
Lower Middle	444 (35.6)
Higher Middle	180 (14.4)
Poor	54 (4.3)
Rich/elite	39 (3.1)
Smoking status (n = 172)	
Current	113 (65.7)
Former	59 (34.3)
Blood pressure (mmHg), mean (SD)	
SBP	135.3 (17.4)
DBP	85.3 (8.8)
Duration of T2DM (months), median (IQR)	36.0 (18.0-72.0)
HbA1c (%), mean (SD)	7.7 (0.8)
Blood glucose (mg/dL), mean (SD)	
FPG	157.8 (35.7)
PPG	236.4 (49.8)
Lipid parameter (mg/dL)	
Total cholesterol (n = 189)	198.0 (44.4)
LDL (n = 162)	132.3 (55.3)
HDL (n = 155)	45.1 (14.7)
Triglycerides (n = 144)	166.4 (76.2)
FH (n = 1073)	
FH of diabetes (First-degree relative)	671 (62.5)
FH of diabetes (Second-degree relative)	320 (29.8)
FH of obesity	227 (21.2)

Table 1. Demographic Characteristics

Parameters	Number of responses (n = 1,403)*
Complications	
Neuropathy	304 (21.7)
Retinopathy	192 (13.7)
CAD	155 (11.0)
Erectile dysfunction	46 (3.3)
PAD	42 (3.0)
TIA	28 (2.0)
Foot ulcer	24 (1.7)
Nephropathy	2 (0.1)
Other	10 (0.7)

Data shown as n (%), unless otherwise specified. *n = 1,403, unless otherwise specified.

BMI = Body mass index; CAD = Coronary artery disease; DBP = Diastolic blood pressure; FH = Family history; FPG = Fasting plasma glucose; HbA1c = Glycated hemoglobin; HDL = High-density lipoprotein; IQR = Interquartile range; LDL = Low-density lipoprotein; PAD = Peripheral artery disease; PPG = Postprandial plasma glucose; SBP = Systolic blood pressure; SD = Standard deviation; T2DM = Type 2 diabetes mellitus; TIA = Transient ischemic attack.

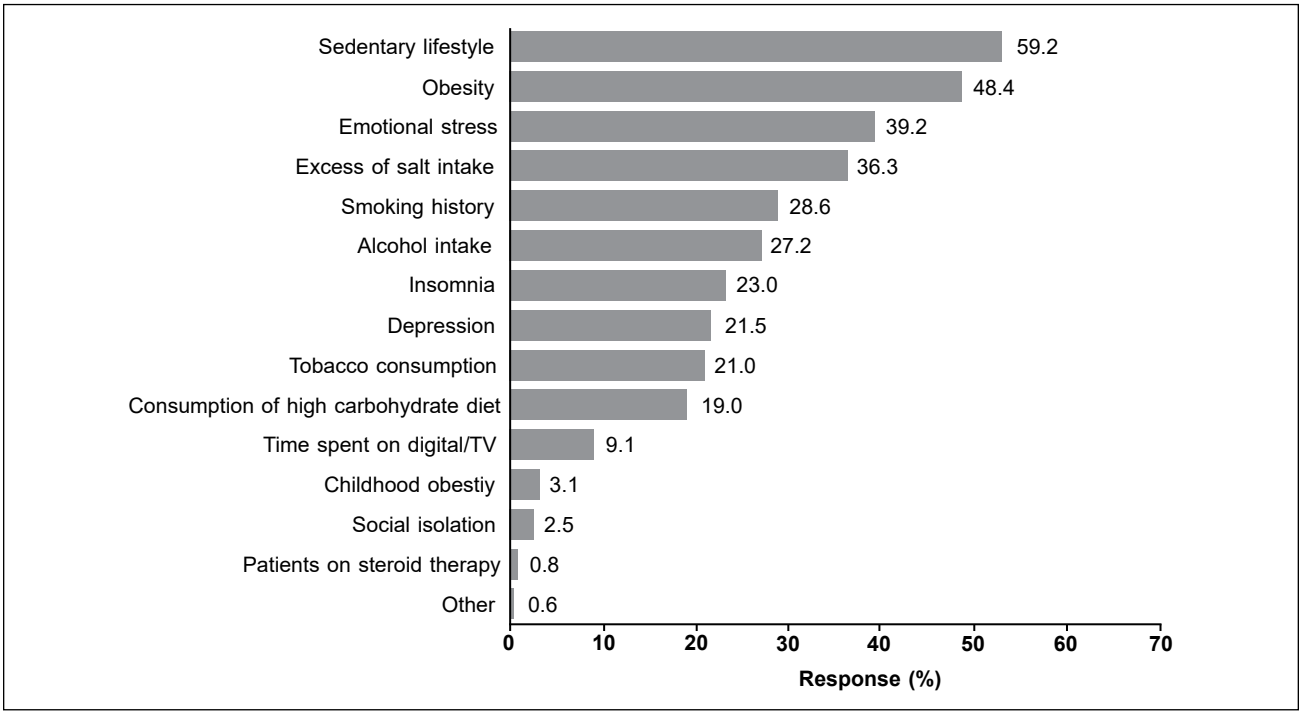

Figure 1. Risk factors related to T2DM.

*n = 1,402

observed in 9.5% of patients in the past 6 months (Table 2). A total of 34.7% (n = 487) patients received glimepiride and metformin FDC along with other antidiabetic medications. The majority of patients (n = 342) received dipeptidyl peptidase-4 (DPP-4) inhibitors along with glimepiride and metformin FDC. Insulin therapy was initiated in 54 (3.8%) patients along with glimepiride and metformin FDC (Table 3). The majority of the patients (54.1%) preferred digital platforms for accessing knowledge on diabetes (Table 4). The most common managing strategies other than antidiabetes treatment included 30 minutes of walk (66.7%), diabetes diet plan (65.3%) and weight loss program (50.0%) (Fig. 4). Full compliance with

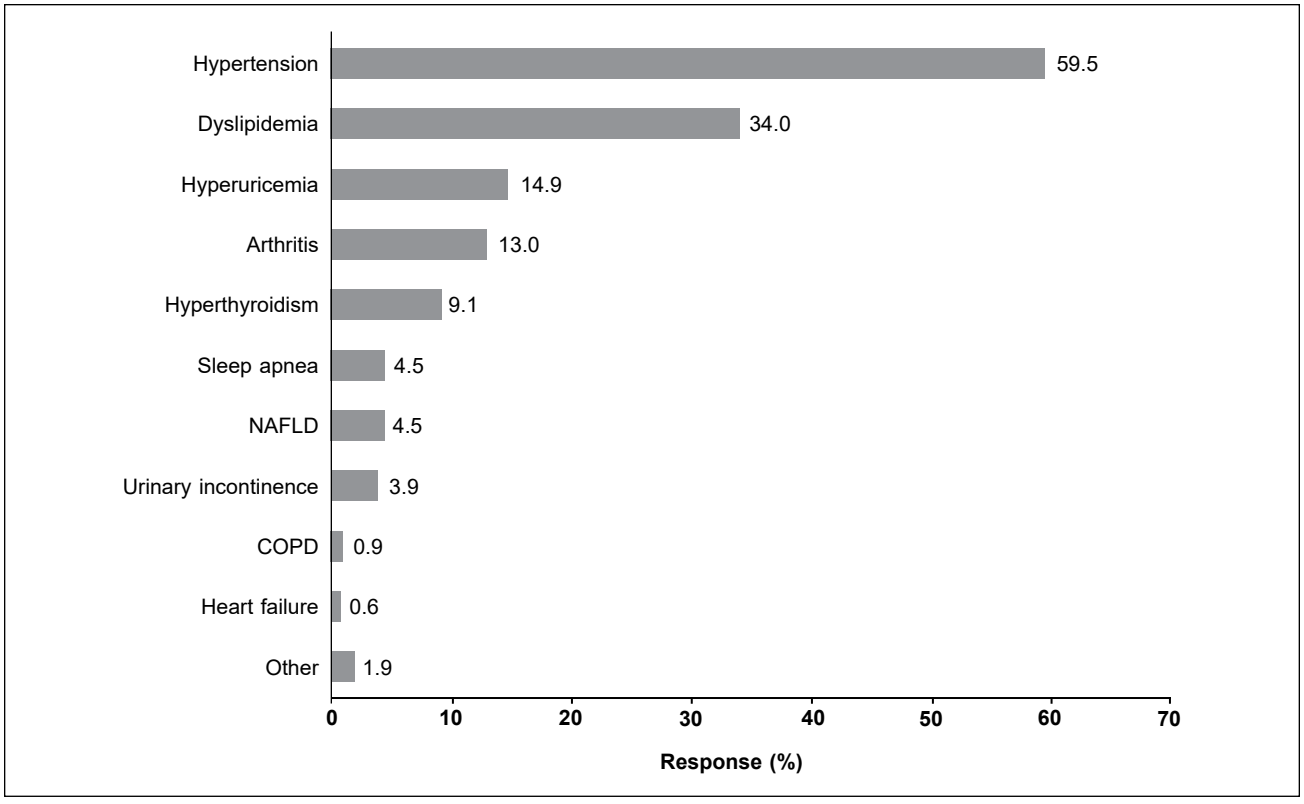

Figure 2. Comorbidities associated with T2DM.

*n = 645

COPD = Chronic obstructive pulmonary disease; NAFLD = Nonalcoholic fatty liver disease.

Table 2. Glimepiride and Metformin FDC Patterns and Post-treatment Parameters

Parameters	Number of responses (n = 1,403)*
Use of glimepiride and metformin FDC	
First-line therapy	1,217 (86.7)
Second-line therapy	186 (13.3)
Treatment pattern of drug dosage	
Glimepiride 0.5 mg + Metformin 500 mg	1,003 (71.5)
Glimepiride 0.5 mg + Metformin 1000 mg	400 (28.5)
Frequency of dose (n = 1,248)	
OD	733 (58.7)
BID	515 (41.3)
Duration of glimepiride and metformin FDC therapy (months), median (IQR) [n = 1110]	23.4 (12.0-38.0)
Up-titration or down-titration of glimepiride and metformin FDC (n = 231)	
Dosage up-titration	191 (82.7)
Dosage down-titration	40 (17.3)
Hypoglycemic event in the past 6 months	108 (7.7)
Weight gain	133 (9.5)

Data shown as n (%). *n = 1403, unless otherwise specified.

FDC = Fixed-dose combination; OD = Once daily; BID= Twice daily.

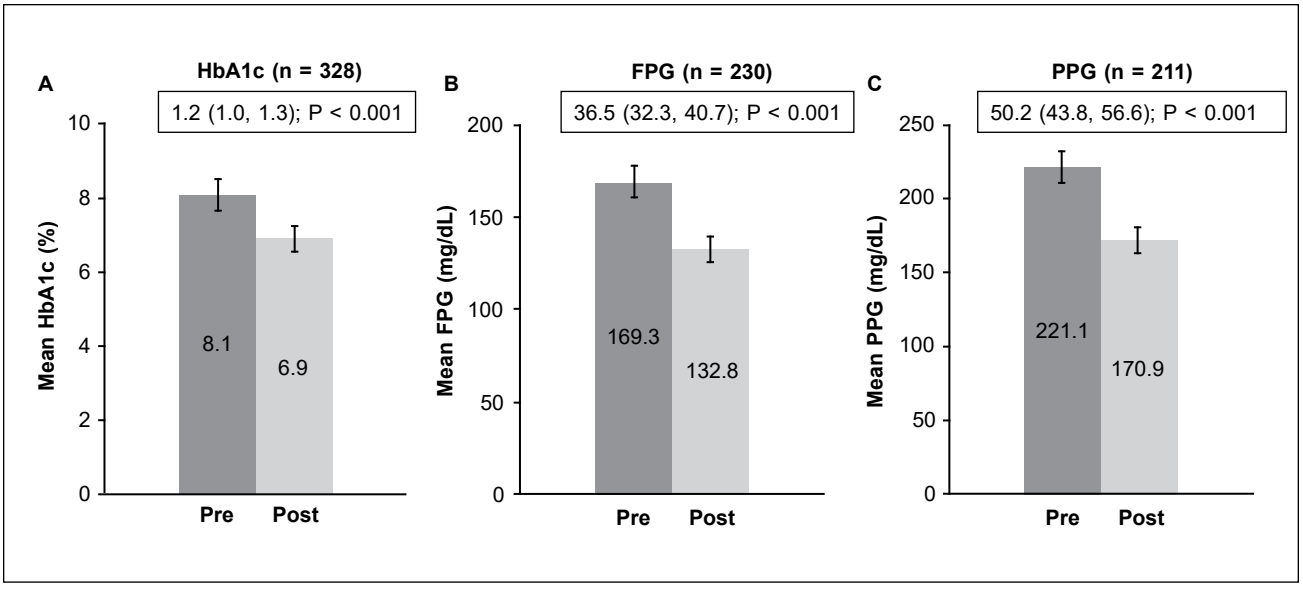

Figure 3. Change in glycemic parameters: A) mean HbA1c, B) mean FPG and C) mean PPG.

Table 3. Concomitant Antidiabetes Medications

Medications	Number of responses (n = 487)
Insulin therapy	54 (3.8)
DPP-4 inhibitors	342 (70.2)
SGLT2 inhibitors	100 (20.5)
Thiazolidinedione	78 (16.0)
AGIs	78 (16.0)
GLP-1 agonist	4 (0.8)

Data shown as n (%). *n = 1403, unless otherwise specified.
AGIs = Alpha-glucosidase inhibitors; DPP-4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide 1; SGLT2 = Sodium-glucose co-transporter 2.

medication was observed in 42.4% of the patients while 27.6% and 18.3% of patients forgot medication once a month and once a week, respectively (Table 4). Physician global evaluation of efficacy (88.7%) and tolerability (89.0%) showed that a majority of patients were on a good to excellent scale (Fig. 5).

Discussion

The use of a single antidiabetic agent in patients with long duration of diabetes fails to achieve the glycemic targets. Hence, many patients require combination therapy in the long run, to achieve optimal control.[7] Several guidelines recommended the use of early initiation of combination therapy in some patients to extend the time to treatment failure.[17,18] Newer generation sulfonylurea (glimepiride) is the most frequently used add-on drug when the HbA1c target is not achieved by metformin monotherapy.[10]

According to a clinical trial conducted in Korean patients with T2DM – that compared glimepiride, metformin and rosiglitazone monotherapy, the reduction in HbA1c was comparable among the three drugs. Furthermore, it was shown that a half-maximal dose is sufficient to achieve a glucose-lowering effect.[19] It seems advisable in patients with T2DM to use a combination of two drugs with different mechanisms of action than increasing the dose of monotherapy.[19] And therefore, glimepiride, a third-generation sulfonylurea is widely prescribed in Asian countries and also in many other countries as a primary drug or as add-on, when patients do not reach their target HbA1c levels on metformin monotherapy.

The present study retrospectively evaluated the approach of clinicians regarding the treatment pattern, the dosage used, efficacy and safety of a combination of low-dose glimepiride (0.5 mg) and metformin (500/1000 mg) in the management of T2DM continuum in the Indian settings.

The key observations of the present study were: i) sedentary lifestyle, obesity and emotional stress are possible modifiable risk factors associated with T2DM; ii) family history was found to be the most common association; iii) neuropathy and hypertension were the most common diabetes complication and comorbid condition, respectively, in the majority of patients; iv) low-dose (0.5 mg) glimepiride and metformin FDC was

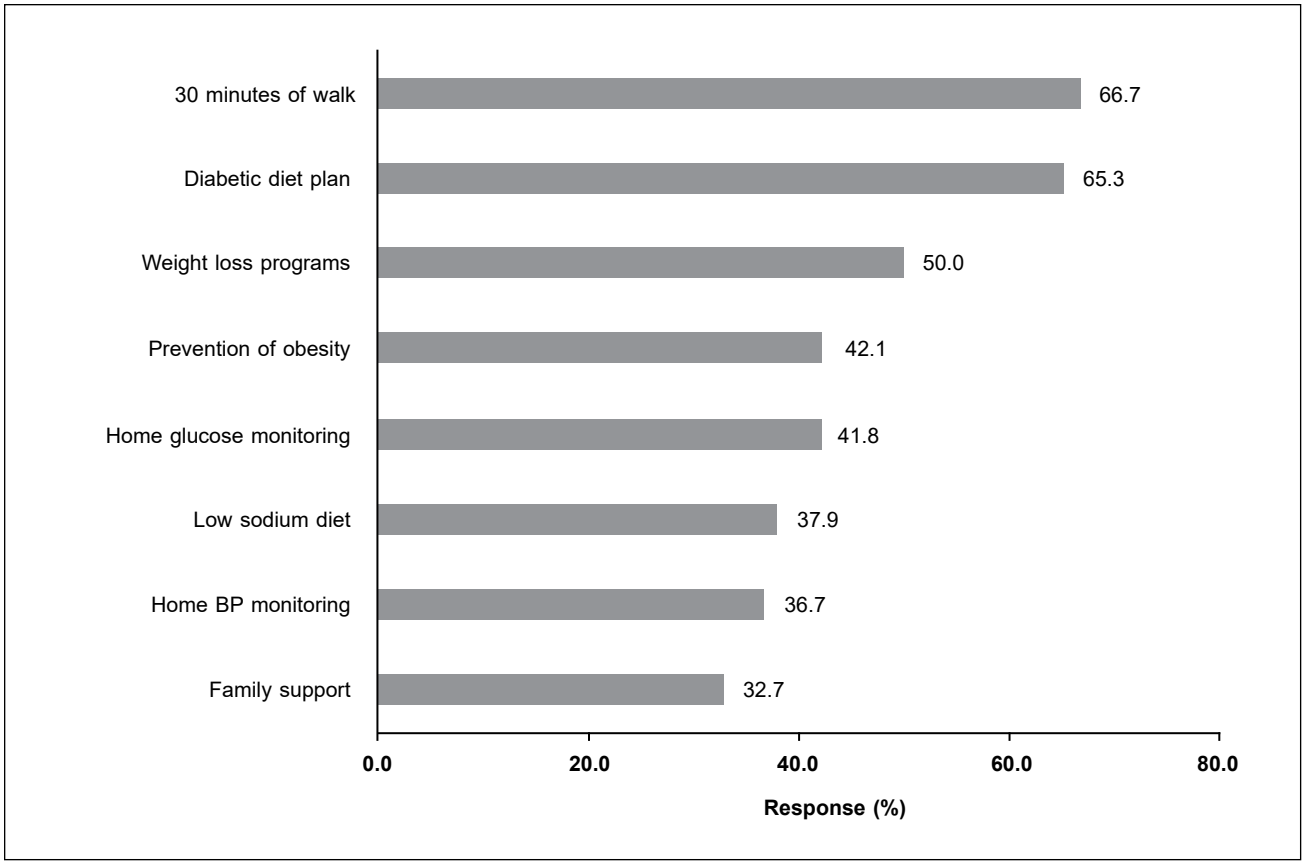

Figure 4. Other management strategies.

*n = 1,052

BP = Blood pressure.

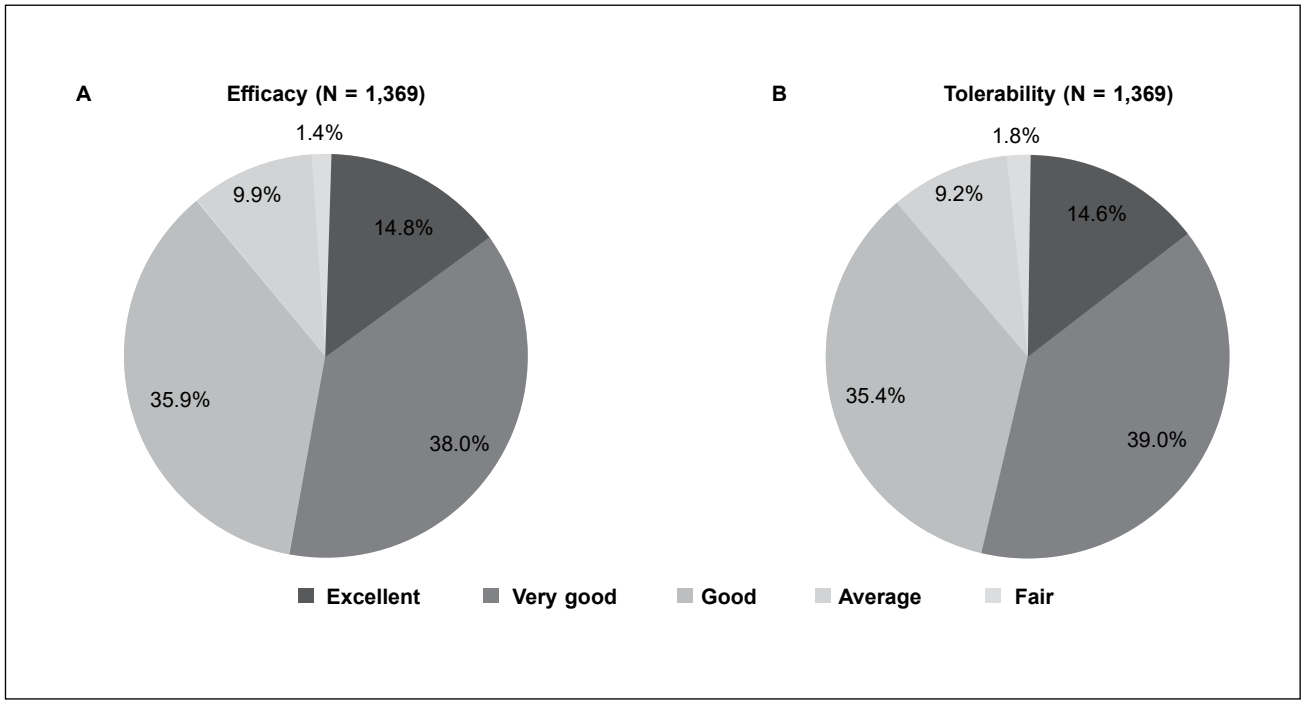

Figure 5. Physicians global evaluation of A) efficacy and B) tolerability.

Table 4. Observations Related to Patient Care

Parameters	Number of responses (N = 1,403)*
Diabetes knowledge sharing platform (n = 1,003)	
Digital	543 (54.1)
Telephonic	436 (43.5)
Other	24 (2.4)
Consultation	11 (45.8)
Leaflet	10 (41.7)
Family support	2 (8.3)
Literature	1 (4.1)
Patients having knowledge about T2DM	
Excellent	134 (9.6)
Very good	351 (25.0)
Good	557 (39.7)
Average	274 (19.5)
Fair	61 (4.3)
Exercise program (n = 1,273)	
Regular	732 (57.5)
Moderate	541 (42.5)
Adherence to medications (n = 1,171)	
Total compliance to medication	496 (42.4)
Forget medication once a month	323 (27.6)
Forget medication once a week	214 (18.3)
Partial compliance for medication	130 (11.1)
Forget medication once a year	114 (9.7)

Data shown as n (%). *n = 1403, unless otherwise specified.

prescribed as first-line therapy; v) the mean HbA1c, FPG and PPG levels decreased significantly after initiation of low-dose glimepiride and metformin FDC therapy demonstrating efficacy in terms of achieving glycemic target; vi) more than half of the patients achieved blood pressure and lipid levels within the normal range after treatment; vii) hypoglycemic events were reported in 7.7% of patients and weight gain was observed in 9.5% patients.

Considering the compliance and cost-effectiveness, the use of sulfonylurea and metformin FDC has recently increased.[8] FDCs have been shown to improve patient compliance by reducing pill burden[20] and is expected to provide better glycemic control with good durability and low risk of side effects. In the START study, the safety and efficacy of glimepiride (1 or 2 mg) and metformin (1000 mg) FDC once daily, compared with sitagliptin (50 mg) and metformin (500 mg) FDC twice daily, in patients with T2DM – who were either drug-naïve or uncontrolled on metformin. The mean HbA1c was significantly reduced from baseline in the glimepiride group compared to the sitagliptin group (0.42% vs. 0.30%; p = 0.001) at week-12. Moreover, FPG and PPG levels were significantly reduced in the glimepiride group.[11]

A multicentric, randomized study was conducted to compare the efficacy and safety of low-dose glimepiride and metformin (glimepiride 0.5 mg + metformin 500 mg) FDC in young adults (≤40 years) and those with early stage diabetes. The findings of this study showed a reduction in FPG (26%) and PPG levels (39%) post-glimepiride and metformin treatment with minimal hypoglycemic (8%) effects.[15] Unnikrishnan et al reported various strengths of glimepiride and metformin FDC therapy for the management of T2DM in India irrespective of age, duration of diabetes, body

mass index (BMI), diabetes complications and use of concomitant medications. Furthermore, authors alluded that low-dose glimepiride and metformin (glimepiride 0.5 mg + metformin 500 mg) FDC was not associated with hypoglycemic events.[8] In the present study, a low-dose combination of 0.5 mg glimepiride with 500 or 1000 mg metformin was effective in achieving glycemic target. This is in accordance with the study done by George J.[14]

Poor glycemic control and multiple cardiovascular risk factors can lead to the development of micro- and macrovascular complications in patients with T2DM.[7] A total of 59.5% of patients with T2DM were having hypertension as comorbidity and 21.7% had neuropathy.

These findings were supported by previous studies indicating glimepiride and metformin FDC therapy is the most preferred choice of treatment in patients with diabetes-related complications and comorbid conditions for blood-glucose control and to reduce cardiovascular event risk.[8,9,21] Early initiation of glimepiride and metformin FDC therapy may prevent progression of the disease as well as diabetes-related micro- and macrovascular complications and could provide legacy effect in the management of T2DM.[10]

A real-world analysis reported that glimepiride and metformin FDC was the preferred choice of treatment for T2DM patients with comorbidities and complications, for optimal blood glucose control.[8] Despite several classes of antidiabetic drugs available in the market, glimepiride and metformin FDC was the most frequently prescribed in patients with hypertension and diabetes.[9,22] In the current study, 86.7% of patients received glimepiride and metformin FDC as first-line therapy. This indicates that early initiation of low-dose glimepiride and metformin FDC therapy will achieve glycemic goals earlier.

The mean change in HbA1c levels was 1.2% at the end of the 6 months duration while FPG and PPG levels were significantly reduced by 36.5 mg/dL and 50.2 mg/dL post-treatment, respectively. Our results were in concurrence with the study conducted by George J, who evaluated the efficacy of low-dose (0.5 mg) glimepiride and metformin FDC therapy in 941 patients with an early-stage T2DM. A similar reduction in FPG (baseline: 151 mg/dL and after 3 months: 114 mg/dL), and PPG (baseline: 215 mg/dL, after 3 months: 158 mg/dL) levels were observed with no incidence of hypoglycemia and weight gain.[14]

Another study on low-dose glimepiride (0.5 mg) and metformin FDC conducted in patients with T2DM showed that this combination is more beneficial for young adults and patients with early-stage T2DM.[15] In young adult patients (<40 years), FPG and PPG levels were reduced by 25% and 43%, respectively. Similarly, in patients with early-stage T2DM, FPG and PPG levels were reduced by 26% and 39%, respectively.[15]

In the present study, hypoglycemic events were reported in 7.7% of patients while 9.5% of patients recorded weight gain. The rate of hypoglycemic occurrence and weight gain were comparable with existing literature.[11,23]

Glimepiride at a low-dose (0.5 mg) is a more effective treatment due to its peripheral insulin-sensitizing nature. The down-regulation of insulin receptors caused by this agent may prevent hyperinsulinemia and ß-cell function failure.[24] Overall results indicated good efficacy and tolerability in terms of achieving glycemic target and compliance to the treatment.

One of the key limitations of this study is the retrospective collection of data which limits the strength of the inference. Missing data of a few patients as a result of underreporting have compromised the analysis strength of the study outcomes. Large-scale, prospective, studies with longer follow-ups are necessary to validate these observations and will aid in further understanding of the clinical effectiveness and safety of glimepiride and metformin FDC in the management of T2DM.

Conclusion

A low dose of glimepiride (0.5 mg) and metformin (500/1000 mg) FDC therapy was found to be effective in achieving glycemic control through lowered HbA1c, FPG and PPG levels. The overall study indicated good tolerability with a low risk of hypoglycemia and weight gain. Thus, early initiation of low-dose (0.5 mg) glimepiride and metformin FDC is a promising approach in the management of T2DM.

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■■■■

REVIEW ARTICLE

Sodium-glucose Co-transporter 2 Inhibitors: A Novel Molecule for Health Care Practitioners in Diabetology, Cardiology and Nephrology

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ABSTRACT

Prevention and timely management of cardiovascular (CV) complications like myocardial infarction, heart failure (HF), stroke and renal complications, like chronic kidney disease (CKD) and end-stage renal disease, are important to improve the quality of life and survival in people with type 2 diabetes mellitus (T2DM). The multifaceted action of sodium-glucose co-transporter 2 inhibitors (SGLT2i) results in effective glycemic control with benefits on CV and renal risk factors, like body weight, blood pressure, uric acid and albuminuria. Robust CV and renal event reduction is reflected in the outcomes of large CV outcome trials, meta-analyses and real-world studies. Recent evidence has proven cardiac and renal benefits with SGLT2i in subjects with HF and CKD irrespective of their T2DM status. Until recently, SGLT2i was used as a glucose-lowering molecule with pleiotropic benefits, mainly by primary care practitioners and diabetologists. The potential for cardiac and renal protection in people with and without T2DM has shifted an interest in cardiologists and nephrologists to view it as a cardiac and renal molecule, respectively. Thus, the role of SGLT2i in the management of T2DM is undergoing a paradigm shift—straddling the interfaces of diabetology, cardiology, nephrology and primary care—moving away from being considered a pure antidiabetic molecule. We conducted a literature review of SGLT2i in management of T2DM along with their protective effects on CV and renal parameters in patients with or without baseline comorbidities.

Keywords: Cardiologist, diabetologist, nephrologist, primary care practitioners, SGLT2 inhibitors, type 2 diabetes mellitus

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Introduction

People with type 2 diabetes mellitus (T2DM) experience considerable micro- and macrovascular complications.[1] Cardiovascular disease (CVD), the main macrovascular complication (>30%) in subjects with T2DM, leads to subclinical or even overt heart failure (HF) (14.9%), with increased mortality (9.9%).[2] Additionally, silent coronary ischemia 10% to 20% in diabetics vs. 1% to 4% in nondiabetics[3] makes the T2DM population vulnerable

to an increased morbidity and mortality. The American Diabetes Association (ADA) recommends calculating the 10-year atherosclerotic cardiovascular disease (ASCVD) risk, besides including strong measures, like diet modification and tight control of blood pressure (BP) and lipid levels to reduce CVD.[4] Several large studies have documented that conventional therapies are unable to reduce the macrovascular complications.[5,6]

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have demonstrated an improvement in cardiovascular (CV) outcomes. SGLT2i have reduced the rate of hospitalization for heart failure (HHF) and CV death in patients with or without pre-existing HF or ASCVD.[7-9] Along with CVD protection, trials with SGLT2i have demonstrated renal protection. Diabetic kidney disease (DKD)—a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD)—occurs in ~40% of people with T2DM and is additionally associated with increased CVD.[10] SGLT2i have shown renal protection in multiple large cardiovascular outcome trials (CVOTs), which depict CV safety of this class of drugs with encouraging results on albuminuria and ESRD outcomes.[7,11-14] These renal benefits and recommendations are causing nephrologists to change their perception of SGLT2i in being just glucose-lowering drugs (GLDs). This review aims to provide an overview of SGLT2i dynamics in clinical practice from the perspective of diabetologists, cardiologists, nephrologists and primary care practitioners (PCPs).

Methodology

We searched for published literature on PubMed and Embase databases using the keywords – "type 2 diabetes mellitus", "sodium-glucose co-transporter 2 inhibitor", "SGLT2 inhibitor", "dapagliflozin", "canagliflozin", "empagliflozin", "efficacy" and "safety", etc. Instead of following systematic literature review methodology (using checklists and systematic screening), we focused on our specific area of priority. The data published up to November 2020 with language restriction in English were considered. Conference abstracts and available results from clinicaltrials.gov database were hand searched. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

Mechanism of Action

What makes it an molecule for diabetologists?

The unique insulin-independent action of SGLT2i contributes to minimal hypoglycemia and a low potential for beta-cell exhaustion.[15] The enhanced insulin sensitivity and innate insulin release from beta cells can reduce the need for external insulin injections and expenses associated with insulin therapy.[16] Randomized controlled trials have shown that SGLT2i therapy reduces insulin resistance[17] ($p < 0.001$) and improves insulin sensitivity[18] ($p = 0.0059$). SGLT2i may play a role even in advanced T2DM stages, characterized by irreparable decline in beta-cell function, because of their insulin independent mechanism.[19]

The ADA 2021 guidelines[4] recommend SGLT2i as the first-line treatment after metformin if there is a compelling indication to minimize hypoglycemia or weight gain, or to encourage weight loss. The European Society of Cardiology/European Association for the Study of Diabetes (ESC/EASD) guidelines place SGLT2i before metformin with a IA recommendation for empagliflozin, canagliflozin or dapagliflozin in subjects with T2DM and CVD or at very high or high CV risk to reduce CV events – with an recommendation for empagliflozin use in T2DM with CVD to reduce the risk of death.[20]

What makes it an molecule for cardiologists?

What attracts physicians and cardiologists is the positive impact of SGLT2i on CV comorbidities; efficacy in subjects with risk factors for CVD, alongside benefits in subjects with HF (with and without T2DM). Although the precise mechanism of CV benefits of SGLT2is is still under scrutiny, they are likely to be due to the hemodynamic and metabolic effects unrelated to their glucose-lowering efficacy.[21] Both ADA[4] and ACC/American Heart Association (AHA) guidelines[22] recommend the first-line addition of SGLT2i when ASCVD predominates, for reducing CV risk (secondary prevention), while the Food and Drug Administration (FDA) approval for dapagliflozin use in T2DM with multiple CV risk factors (along with those with established CVD [eCVD]) to reduce the risk of HHF suggests a primary preventive role in subjects with T2DM.[23]

Hemodynamic effects

High BP is a known CV risk factor; hence, lowering BP in T2DM population reduces CV events. The mechanism of BP reduction with SGLT2i occurs by osmotic diuresis and a lower sympathetic tone. The latter mechanism lowers BP, without causing a compensatory increase in heart rate.[24] Several studies have explored the adaptive ketogenesis theory, reduction in body weight and arterial stiffness to explain the BP-lowering benefit.[25,26]

SGLT2i also inhibit the heart Na^+-H^+ exchanger, thereby improving mitochondrial function, reducing cardiac remodeling and enhancing heart function.[27]

Metabolic effects

Metabolic benefits with SGLT2i in cardiac protection include a lower risk for hypoglycemia; adaptive ketogenesis; calorie restriction mimicry and improvement in body weight and lipid and uric acid levels. The lower incidence of hypoglycemia with SGLT2i is because of their insulin-independent mode of action, which also aids in reducing the CV risk.[28] Adaptive ketogenesis with increased ketones occurs with SGLT2i use because of the elevated glucagon levels. Ketones are an efficient fuel source for the ischemic heart, with added benefits of reducing free-radical injury, resulting in a better cardiac function.[29] Reduction in body weight and waist circumference has a positive impact on CV outcomes and insulin resistance.[30] A dose-dependant reduction in body weight of 1.6-2.5 kg was shown in a meta-analysis, while another study demonstrated that this weight reduction could be sustained at the 4-year follow-up.[31,32] The preferential loss of visceral and subcutaneous fats compared with lean tissue is a benefit.[33]

Elevated uric acid levels are a CV risk factor and mediate renal damage. The loss of uric acid in urine due to the inhibition of absorption in the renal proximal convoluted tubule by SGLT2i enables the reduction of CV risk and slows CKD progression.[11,34] Hematocrit improvement (2-4%) has been consistently seen with SGLT2i use, even in patients with CKD (except stage 4 CKD). This improvement is attributed to an enhanced erythropoietin levels. Elevated hematocrit levels may correct sympathetic hyperactivity in T2DM leading to a reduction in CV mortality and risk for HHF.[35] SGLT2is also favorably affect albuminuria, a CV risk factor, by restoring the tubuloglomerular feedback and reducing intraglomerular pressure.[36] An improvement in albuminuria translates into cardiac and renal protection.

Benefits in subjects with heart failure

People with T2DM are at a high risk for developing HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) and renal hypoxia leading to new-onset HF or HF progression.[20,37] SGLT2i action reduces sympathetic outflow to the heart, lowering cardiac wall stress, fibrosis and volume overload.[37] The HHF endpoint being the most sensitive to SGLT2i use in the completed CVOTs led to the theory that SGLT2i reduce CV events mainly by HF prevention rather than atherothrombosis inhibition.[38] SGLT2i can reduce morbidity and mortality in pure HF patients with or without comorbid diabetes. Ongoing SGLT2i trials in HF may confirm if it is a class effect. The CANOSSA trial in subjects with T2DM and HFpEF reported improved endothelial and diastolic functions with canagliflozin. HF markers like atrial natriuretic peptide ($p = 0.0001$), brain natriuretic peptide ($p < 0.0001$) and ejection fraction (EF) ($p = 0.005$) improved at 12 months compared with baseline.[39]

The EMPA-HEART trial[40] showed benefits on left ventricular remodeling in T2DM patients with eCVD. The improvement in left ventricular mass index (–2.6 vs. 0.01 g/m^2, $p = 0.01$) at 6 months mechanistically explained the HF benefits demonstrated in the EMPA-REG OUTCOME trial. The DAPA-HF[8] trial with dapagliflozin demonstrated a reduction in the composite of HHF or CV death or urgent HF visit (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.65-0.85; $p < 0.001$), HHF (HR: 0.70; 95% CI: 0.59-0.83), CV death (HR: 0.82; 95% CI: 0.69-0.98), and all-cause death (HR: 0.83; 95% CI: 0.71-0.97) in HFrEF patients with (42%) and without T2DM. DEFINE-HF results demonstrated a clinically meaningful improvement in the dual primary outcome of HF-related quality of life or natriuretic peptides (61.5%, dapagliflozin vs. 50.4%, placebo, adjusted odds ratio: 1.8, 95% CI: 1.03-3.06, $p = 0.039$), with similar results in subjects with or without T2DM.[41] The EMPEROR-Reduced trial reported a significant reduction in the composite of CV death and HHF (HR: 0.75; 95% CI: 0.65-0.86; $p < 0.001$) with consistent benefits in subjects with (49.8%) and without T2DM. These benefits with empagliflozin may broaden the target HF patient group to advanced New York Heart Association stages, as most participants (73%) had an EF <30%.[9]

The ADA 2021 guidelines already recommend SGLT2i as the first-line therapy in subjects with T2DM and comorbid HF.[4] The FDA approved dapagliflozin to reduce risk of HF in adults with T2DM and multiple CV risk factors or with eCVD.[42]

What makes it an molecule for nephrologists?

The renal benefits, evidenced by the reduction in albuminuria, slowdown in progression to ESRD and reduced need for renal replacement therapy (RRT), are mediated by several mechanisms.[7,11-13] Increased sodium access to the macula densa due to SGLT2 inhibition lowers the intraglomerular pressure, decreases albuminuria and possibly slows the decline of kidney function in people with diabetes.[42] Hypoxia in the milieu of proximal convoluted tubule is alleviated

as SGLT2is reduce oxygen consumption by the Na^+/K^+ pump in the epithelial cells.[35] Reduction in sympathetic outflow to the kidney by SGLT2i action reduces the renin-angiotensin-aldosterone system (RAAS) activity and corrects fluid overload. Adaptive ketogenesis by SGLT2i action improves renal function by ensuring a more efficient metabolic substrate like ketones.[43] EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials demonstrated improved renal outcomes, albeit as secondary endpoints with empagliflozin, canagliflozin and dapagliflozin.[7,11,12]

In the CREDENCE study involving T2DM subjects with albuminuric CKD, canagliflozin significantly reduced the composite of ESRD, a doubling of serum creatinine level or death from renal or CV causes by 30%.[13] DAPA-CKD results reported a significant impact (HR: 0.61; 95% CI: 0.51-0.72; p < 0.001) of dapagliflozin on the composite primary outcome of sustained decline in the estimated glomerular filtration rate (eGFR) of at least 50%, ESRD or death from renal or CV causes in subjects with CKD (n = 4,304) – with or without T2DM. This extension of benefit to pure CKD patients without T2DM (32.5%), and to patients with lower eGFR threshold (14.5% had eGFR <30 mL/min/1.73 m^2) confirmed renal protection in a broader group of patients. Moreover, a reduction was seen in the composite of sustained decline in eGFR of at least 50%, ESRD or death from renal causes (HR: 0.56; 95% CI: 0.450.68; p < 0.001), the composite of CV death or HHF (HR: 0.71; 95% CI: 0.55-0.92; p = 0.009), and mortality (HR: 0.69; 95% CI: 0.53-0.88; p = 0.004).[14]

Significant improvement in the urine albumin-creatinine ratio was seen with dapagliflozin vs. placebo in the DELIGHT trial[44] (−21.0%; 95% CI: −34.1, −5.2; p = 0.011) on follow-up at the end of 24 weeks while in the DERIVE trial,[45] a significant reduction at week-12 (−41.7%; 95% CI: −57.1, −21.0; p < 0.001) was maintained, but did not reach significance at week-24 (−14.0%; 95% CI: −42.3, 28.0; p = 0.454). Ertugliflozin revealed glycemic efficacy and an acceptable safety profile in 468 subjects with T2DM and stage 3 CKD over a 52-week period in the VERTIS-RENAL trial.[46]

However, the VERTIS-CV trial with ertugliflozin did not show a significant benefit for the renal composite endpoint (secondary endpoint) of death from renal causes, RRT or doubling of serum-creatinine level.[47] The ACC 2018 consensus pathway on novel therapies recommends the first-line addition of SGLT2i to metformin in T2DM and CKD subjects, with or without ASCVD, provided there is no ESRD.[21] The ADA 2021 guidelines[4] also recommend SGLT2i as a preferable option when CKD predominates. Canagliflozin received FDA approval for use in subjects with DKD (with albuminuria) to reduce the risk of ESRD, worsening of renal function, CV death and HHF.[48] Thus, the question remains – should SGLT2i form a targeted treatment option for DKD? SGLT2is with their multifaceted action at the level of the pancreas, heart and kidney, allow PCPs, diabetologists, cardiologists and nephrologists to provide multiorgan-targeted benefits for subjects with T2DM (Fig. 1).

Evidence with SGLT2i for Diabetologists, Cardiologists and Nephrologists

Evidence from randomized controlled trials

Table 1 summarizes the main CV and renal endpoints in the landmark CVOTs with SGLT2i. In EMPA-REG OUTCOME, the empagliflozin group demonstrated lower rates of 3-point major adverse cardiac events (MACE), death from CV causes, HHF and death from any cause.[49] EMPA-REG renal analysis demonstrated a reduction in the composite of incident or worsening nephropathy (HR: 0.61, 95% CI: 0.53-0.70), progression to macroalbuminuria (HR: 0.62, 95% CI: 0.54-0.72), serum-creatinine doubling (HR: 0.56, 95% CI: 0.39-0.79), and RRT initiation (HR: 0.45, 95% CI: 0.21-0.97).[11]

A recent post hoc analysis of EMPA-REG study observed consistent CV and renal benefits among all Kidney Disease Improving Global Outcomes (KDIGO) categories confirming benefits across the CKD spectrum.[50] In the CANVAS program, the canagliflozin group demonstrated lower rates of 3-point MACE, CV death, all-cause mortality and HHF with no heterogeneity of treatment effect across primary and secondary prevention groups and a significant reduction in albuminuria progression (HR: 0.73, 95% CI: 0.67-0.79).[49]

In the DECLARE-TIMI 58 trial of 17,160 patients, 10,186 patients did not have eCVD, but they had multiple risk factors for ASCVD. Dapagliflozin achieved the MACE criterion for noninferiority, with therapy results demonstrating lower risks for HHF (HR: 0.73, 95% CI: 0.61-0.88) and renal events (HR: 0.76, 95% CI: 0.67-0.87).[7] The CREDENCE trial with canagliflozin in subjects with T2DM and albuminuric CKD demonstrated a significant reduction in the primary outcome of composite of ESRD, serum creatinine doubling or death from renal or CV causes (HR: 0.70, 95% CI: 0.59-0.82, p < 0.00001), in addition to a reduction in the risk of CV death, myocardial infarction or stroke, and HHF.[13] It showed that the CV and renal benefits were observed

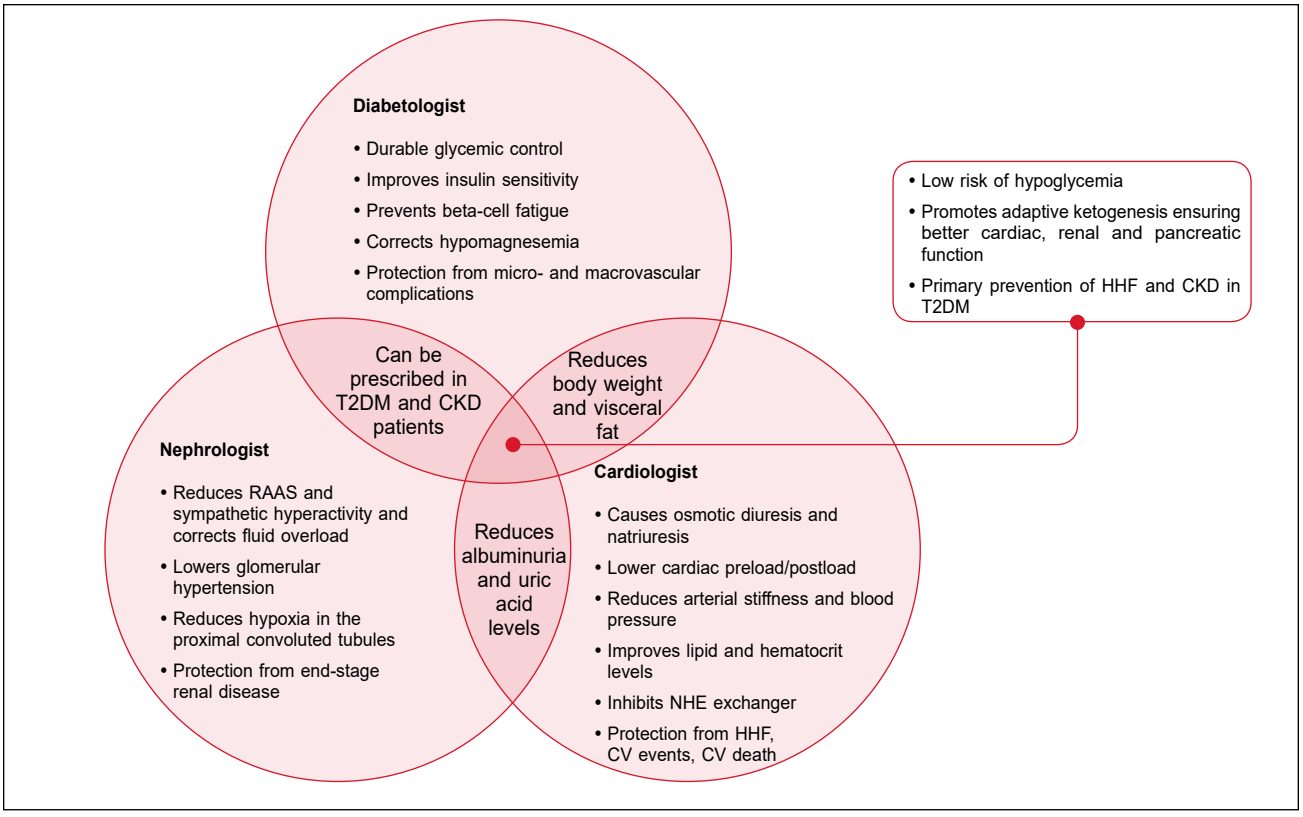

Figure 1. SGLT2i benefits for a diabetologist, cardiologist and nephrologist.

CKD = Chronic kidney disease; CV = Cardiovascular; HHF = Hospitalization for heart failure; NHE = Sodium-hydrogen exchanger; RAAS = Renin-angiotensin-aldosterone system; T2DM = Type 2 diabetes mellitus.

even at lower eGFR levels (30-45 mL/min/1.73 m^2), suggesting that SGLT2i can be used in more severe stages of CKD.

Evidence from systematic review and meta-analyses and post hoc analyses

A systemic review and meta-analyses (SRMA) of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials showed a significant reduction in MACE (HR: 0.86, 95% CI: 0.80-0.93, p = 0.0014) with SGLT2i in those with eCVD. Further, a 45% reduction in renal disease progression was also seen to be similar in subjects with and without ASCVD.[51]

Another SRMA confirmed SGLT2i benefits by demonstrating a significant reduction in CV outcomes (relative risk [RR]: 0.81, 95% CI: 0.70-0.94) and renal outcomes (composite renal outcome, HR: 0.71, 95% CI: 0.53-0.95) in subjects with T2DM and CKD, with a mitigation in the annual decline in eGFR slope (difference of 1.35 mL/min/1.73 m^2/year; 95% CI: 0.78-1.93).[52] Another SRMA reported consistency of SGLT2i effect across trials and different levels of eGFR (baseline eGFR 30-45 mL/min/1.73 m^2) and albuminuria with a reduction in the risk of dialysis, transplantation or death due to renal causes (RR: 0.67, 95% CI: 0.52-0.86, p = 0.0019), ESRD (HR: 0.65, 95% CI: 0.53-0.81, p < 0.0001) and acute kidney injury (HR: 0.75, 95% CI: 0.66-0.85, p < 0.0001).[53] A prespecified meta-analysis of the EMPEROR-Reduced and DAPA-HF trials reported significant reductions in the all-cause death (HR: 0.87; 95% CI: 0.77-0.98; p = 0.018), CV death (HR: 0.86; 95% CI: 0.76-0.98; p = 0.027), and composite renal outcome (HR: 0.62; in patients with HFrEF, with benefits consistent across subgroups, such as age, sex, diabetes and baseline eGFR.[54]

Real-world evidence

In CVD-REAL[55] (n = 3,09,056), the use of SGLT2i (n = 1,54,528) versus other GLDs demonstrated a lower risk for HHF (HR: 0.61, 95% CI: 0.51-0.73, p < 0.001), death (HR: 0.49, 95% CI: 0.41-0.57, p < 0.001); and HHF or death (HR: 0.54, 95% CI: 0.48-0.60, p < 0.001) without a country-wise difference. An analysis of the CVD-REAL study (n = 1,53,078) reported that SGLT2i use was associated with a lower risk of mortality in patients with (HR: 0.56, 95% CI: 0.44-0.70) and without

Table 1. Summary of Cardiovascular and Renal Benefits with SGLT2i

	EMPA-REG OUTCOME (n = 7,020, T2DM)	CANVAS (n = 10,142, T2DM)	DECLARE-TIMI 58 (n = 17,160, T2DM)	CREDENCE (n = 4,401, T2DM with albuminuric CKD)
Patients with established CVD (n, %)	7,020 (100%)	6,656 (66%)	6,974 (40.6%)	2,220 (50.4%)
Follow-up (years)	3.1	2.4	4.2	2.62
SGLT2i	Empagliflozin 10 or 25 mg vs. placebo daily	Canagliflozin 100 or 300 mg vs. placebo daily	Dapagliflozin 10 mg vs. placebo daily	Canagliflozin 100 mg vs. placebo daily
Primary endpoint: Composite of CV death, MI or stroke	HR: 0.86 (0.74-0.99), p < 0.001 for NI, p = 0.04 for superiority	HR: 0.86 (0.75-0.97) NI, p < 0.001 Superiority, p = 0.02	HR: 0.93 (0.84-1.03) NI, p < 0.001 Superiority, p = 0.17	HR: 0.80 (0.67-0.95), p = 0.01
CV death	HR: 0.62 (0.49-0.77), p < 0.001	HR: 0.87 (0.72-1.06), p = NS	HR: 0.98 (0.82-1.17), p = NS	HR: 0.78 (0.61-1.00), p = 0.05
HHF	HR: 0.65 (0.50-0.85), p = 0.002	HR: 0.67 (0.52-0.87), p = NS	HR:0.73 (0.61-0.88), p = 0.005	HHF: 0.61 (0.47-0.80), p < 0.001
All-cause mortality	HR: 0.68 (0.57-0.82), p < 0.001	HR: 0.87 (0.74-1.01), p = NS	HR: 0.93 (0.82-1.04), p= NS	HR: 0.83 (0.68-1.02), p = NS
Worsening nephropathy*	HR: 0.61 (0.53-0.70) p < 0.001	HR: 0.60 (0.47-0.77)	HR: 0.76 (0.67-0.87)	HR: 0.66 (0.53-0.81), p < 0.001

*Worsening nephropathy was defined as doubling of serum creatinine level and an eGFR of ≤45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy or death due to renal events in EMPA-REG OUTCOME; 40% reduction in eGFR, renal-replacement therapy or death from renal causes in CANVAS; sustained decrease of ≥40% in eGFR to <60 mL/min/1.73 m^2, new end-stage renal disease or death from renal or CV causes in DECLARE-TIMI 58; end-stage kidney disease, doubling of serum creatinine or renal death in CREDENCE.

CKD = Chronic kidney disease; CV = Cardiovascular; CVD = Cardiovascular disease; eGFR = Estimated glomerular filtration rate; HHF = Hospitalization for heart failure; HR = hazard ratio; MI = Myocardial infarction; NI = Noninferiority; NS = Nonsignificant; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus.

(HR: 0.56, 95% CI: 0.50-0.63) CVD. Furthermore, HF (HR: 0.72, 95% CI: 0.63-0.82 and HR: 0.61, 95% CI: 0.48-0.78, with and without CVD, respectively) and the composite of HF or death (HR: 0.63, 95% CI: 0.57-0.70 and HR: 0.56, 95% CI: 0.50-0.62, with and without CVD, respectively) were lowered significantly.[56]

Preliminary results of the EMPRISE study demonstrated a 50% risk reduction with empagliflozin in HF discharge diagnosis in the primary position (HHF-specific) (HR: 0.50, 95% CI: 0.28-0.91) and 49% in HF discharge diagnosis in any position (HHF-broad) (HR: 0.51, 95% CI: 0.390.68) compared with sitagliptin. The results were consistent for both doses of empagliflozin (10 and 25 mg) and irrespective of the baseline CVD status.[57]

The CVD-REAL 3 study showed a lower risk of eGFR decline (difference in slope 1.53 mL/min/1.73 m^2, 95% CI: 1.34-1.72, p < 0.0001) and renal outcomes (HR: 0.49, 95% CI: 0.35-0.67, p < 0.0001) in the group receiving SGLT2i.[58]

Emerging evidence in chronic heart failure with HFrEF and HFpEF

Table 2 shows emerging evidence with multiple phase 2/3 and 4 trials evaluating SGLT2i in subjects with pure HF (HFrEF and HFpEF), without comorbid T2DM, on parameters like cardiac biomarkers, exercise capacity, quality of life, echocardiographic features, HF symptoms, worsening HF and CV death. These study results may elevate the importance of SGLT2i in the clinical practice of a cardiologist.

Emerging evidence with SGLT2i for coexistent T2DM and HF

Several trials currently investigating the benefits of SGLT2i in subjects with the dual burden of T2DM and HF are described in Table 3. These trials will assess the mechanisms and effects of SGLT2i on exercise capacity, systolic and diastolic cardiac function, and HF biomarkers when T2DM and HF coexist, and their results may augment the importance of SGLT2i in the practice of diabetologists and cardiologists.

Table 2. Phase 2/3/4 Trials Evaluating SGLT2i in HF

Trial (NCT Number)	Study population	Expected outcomes	Study status
Phase 2 trial evaluating SGLT2i in HF			
EMPIRE-HF (NCT03198585)	190 participants Stable, symptomatic HFrEF (LVEF ≤40%)	Evaluate empagliflozin 10 mg on cardiac biomarkers, cardiac function at rest, at stress and during exercise, renal function, metabolism, daily activity and health-related QoL	Completed: January 2020*
Phase 3 trials evaluating SGLT2i in HFrEF			
EMPERIAL-Reduced (NCT03448419)	312 participants Chronic HFrEF LVEF ≤40%	Evaluate empagliflozin 10 mg vs. placebo on exercise capacity using 6MWT	Completed: October 2019
DETERMINE-Reduced (NCT03877237)	313 participants HF (NYHA class II-IV) with reduced ejection fraction defined as LVEF ≤40%	Evaluate dapagliflozin 10 mg on exercise capacity in patients with HFrEF (LVEF ≤40%)	Completed: March 2020*
Phase 3 trials evaluating SGLT2i in HFpEF			
EMPERIAL-Preserved (NCT03448406)	315 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate empagliflozin 10 mg vs. placebo on exercise ability using 6MWT	Completed: October 2019*
DETERMINE-Preserved (NCT03877224)	504 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate dapagliflozin 10 mg on exercise capacity using 6MWT	Completed: July 2020*
EMPEROR-Preserved (NCT03057951)	5,988 participants Chronic HFpEF (NYHA class II-IV) LVEF >40%	Evaluate efficacy and safety of empagliflozin 10 mg vs. placebo on top of guideline-directed medical therapy	April 2021
DELIVER (NCT03619213)	6,100 participants HFpEF (NYHA class II-IV) with LVEF >40%	Evaluate dapagliflozin 10 mg on reducing CV death or worsening HF	November 2021
Phase 4 trials evaluating SGLT2i in HF			
EMBRACE-HF (NCT03030222)	60 participants NYHA class II-IV HFpEF (LVEF >40%) or HFrEF (LVEF ≤40%) ischemic or nonischemic etiology who already have a CardioMEMs device	Evaluate empagliflozin 10 mg on hemodynamic parameters (pulmonary artery diastolic pressures)	October 2020 (not recruiting)
PRESERVED-HF (NCT03030235)	320 participants Dyspnea (NYHA class II-IV) without evidence of a noncardiac or ischemic explanation for dyspnea LVEF ≥45%	Evaluate dapagliflozin 10 mg on HF-specific biomarkers (NTproBNP and BNP), symptoms, health status and QoL	February 2021

*Results not published

BNP = Brain natriuretic peptide; CV = Cardiovascular; HF = Heart failure; HFpEF = Heart failure with preserved ejection fraction; HFrEF = Heart failure with reduced ejection fraction; LVEF = Left ventricular ejection fraction; NTproBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; QoL = Quality of life; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus; 6MWT = 6-minute walk test.

Table 3. Emerging Evidence with SGLT2i in HF with T2DM and CKD With and Without T2DM

Trial (NCT number)	Sample size	Study objective and population	Study status
In subjects with T2DM and HF			
Treatment of DM in HFrEF (NCT02920918)	36	Evaluate canagliflozin 100 mg vs. sitagliptin 100 mg on exercise capacity, cardiac function and cardiac biomarkers in HFrEF (EF ≤40%)	Completed*: September 2018
RECEDE-CHF (NCT03226457)	23	Compare empagliflozin 25 mg, to placebo in patients with T2DM and chronic HF (NYHA II/III) with left ventricular systolic dysfunction and who are already on a loop diuretic	Completed: January 2019
ELSI (NCT03128528)	84	Evaluate empagliflozin 10 mg vs. placebo on reduction of tissue sodium content in patients with chronic HFrEF (<40%) and HFmEF (40-49%) with T2DM	Completed: April 2020
IDDIA (NCT02751398)	60	Evaluate dapagliflozin on diastolic dysfunction in T2DM patients with ≥ grade 1 diastolic function at resting echocardiography	Completed: June 2020
SOLOIST-WHF (NCT03521934)	1,222	Evaluate sotagliflozin on clinical outcomes in hemodynamically stable patients with T2DM post-WHF (EF <40%).	Terminated prematurely: June 2020
ERADICATE-HF** (NCT03416270)	36	Evaluate mechanism by which ertugliflozin 15 mg modifies cardiorenal interactions that regulate fluid volume and neurohormonal activation in T2DM and HF (EF ≥20%).	Completion: March 2021
EXCEED (UMIN000027095)	100 (target)	Evaluate ipragliflozin on cardiac function in patients with chronic HF (NYHA I-III) and T2DM vs. non-SGLT2i antidiabetic drugs	Completion: Date not available
In subjects with CKD (with and without T2DM)			
SCORED (NCT03315143)	10,584	Evaluate sotagliflozin, on time to: a) first MACE or b) CV death or HHF. Patients eligible if T2DM and eGFR ≥25 and ≤60 mL/min/1.73 m^2	Terminated prematurely: July 2020
RACELINES (NCT03433248)	66	Evaluate empagliflozin 10 mg and linagliptin 5 mg monotherapy or combination vs. gliclazide 30 mg on changes in GFR Patients eligible if T2DM and eGFR ≥45 and on treatment with RAAS blockers	Completion: December 2021
EMPA-KIDNEY (NCT03594110)	6,000	Evaluate empagliflozin, on composite of time to first occurrence of kidney disease or CV death Patients eligible if CKD and eGFR ≥20 to <45 or ≥45 to <90 with UACR ≥200 mg/g	Completion: October 2022

*Results not published; **Not yet recruiting

CKD = Chronic kidney disease; CV = Cardiovascular; DM = Diabetes mellitus; EF = Ejection fraction; eGFR = Estimated glomerular filtration rate; ESRD = End-stage renal disease; HF = Heart failure; HHF = Hospitalization for heart failure; HFmEF = Heart failure with mid-range ejection fraction; HFrEF = Heart failure with reduced ejection fraction; MACE = Major adverse cardiovascular events; NYHA = New York Heart Association; RAAS = Renin-angiotensin-aldosterone system; SGLT2i = Sodium-glucose co-transporter 2 inhibitor; T2DM = Type 2 diabetes mellitus; UACR = Urine albumin-to-creatinine ratio; WHF = Worsening heart failure.

Emerging evidence with SGLT2i in CKD (with and without T2DM)

Trials currently investigating SGLT2i in subjects with CKD (with and without T2DM) are described in Table 3. These trials will assess the renal physiology, biomarkers and renal and CV endpoints at different CKD stages. The EMPA-KIDNEY trial[59] like the DAPA-CKD trial[14] specifically plans to evaluate renal outcomes in CKD subjects without T2DM. Results from these trials may cause a paradigm shift in the practice of nephrologists.

Role of PCPs for SGLT2i Use

PCPs form the first touch point of care for T2DM in many countries; 90% of people with T2DM were treated by PCPs in the United States.[60] In the United Kingdom, only 20% of people with T2DM see a specialist, implying 80% are seen by PCPs.[61] T2DM management in primary care is complex with multiple challenges including clinician and patient inertia in ensuring treatment compliance and implementing therapeutic advances.[62]

A Canadian survey highlighted the importance of PCPs in individualizing treatment decisions when initiating SGLT2i therapy.[63] While the PCP role is important in the everyday management, expert evaluation for diabetes-related complications, CV risk and renal status by diabetologists/endocrinologists, cardiologists and nephrologists, is essential to optimize treatment decisions and improve clinical outcomes.[64]

Conclusion

PCPs, diabetologists and endocrinologists play a prime role as the first contact for most subjects with T2DM and rely on novel therapies like SGLT2i for effective glycemic control and microvascular and macrovascular risk reduction. Cardiologists and nephrologists can play an equally prime role by routinely screening their patients for T2DM, and optimally managing CV and renal risk factors by assimilating SGLT2i use in their clinical practice. SGLT2i offer a meeting point for PCPs, diabetologists, cardiologists and nephrologists by delivering benefits as antidiabetic, cardiac and renal molecules.

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REVIEW ARTICLE

Will Oral Semaglutide be a Game-Changer in the Management of Type 2 Diabetes in Indian Context?

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ABSTRACT

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) have important beneficial effects on glycemic control and body weight along with their pleiotropic effects on various systems of the body. However, until now these agents were administered via an injection posing a challenge to patient convenience. Oral semaglutide is a first in class oral GLP-1RA co-formulated with an absorption enhancer for the treatment of type 2 diabetes mellitus (T2DM). The clinical efficacy and safety of oral semaglutide has been extensively evaluated in the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) program of clinical trials. This review shall elaborate on the unique diabetes situation in India and why the oral GLP-1RA (semaglutide) will be a game-changer in the Indian setting.

Keywords: Semaglutide, type 2 diabetes, GLP-1RAs, glucose-lowering drugs

Background

Type 2 diabetes mellitus (T2DM) accounts for almost 90% of all diabetes cases worldwide. The prevalence of diabetes around the world is likely to reach up to 592 million by the year 2035.[1] The genetic component among South Asians makes them up to four times more susceptible to T2DM compared to other ethnic groups.[2] The concept of an "Asian Indian Phenotype" was advanced by Mohan et al,[3] as the presence of insulin resistance along with abdominal obesity, higher C-reactive protein (CRP) and lower levels of adiponectin. Asian Indians have a lean-fat body composition with higher levels of central obesity (waist circumference, waist-to-hip ratio and visceral fat).

They also have more body fat for a given body mass index (BMI) compared to other ethnic groups.[4] Thus, the lean-fat Indian is at a larger risk of diabetes, which results from genetic predisposition along with other factors like lifestyle changes, rapid urbanization and changing dietary patterns.

The baseline data of Indian type 2 diabetic patients in an observational study showed high prevalence of micro- and macrovascular complications due to poor glycemic control (mean glycated hemoglobin [HbA1c] = 9.2 ± 1.4).[5] The relation between glycemic status and incidence of complications highlights the importance of optimum glycemic control in T2DM. The glycemic control, however, continues to deteriorate as the disease progresses.[6]

Obesity which is often described as 'Diabesity' in obese type 2 diabetics is a major risk factor leading to hypertension, hyperlipidemia, atherosclerotic cardiovascular disease (ASCVD), and its complications, and also to many types of cancers.[7] The prevalence of diabesity is reaching epidemic proportions around the globe with no clear guidelines for its optimum management.[8] In Indian adults aged 20 to 69 years, the prevalence of overweight will more than double while the prevalence of obesity will triple by 2040.[9]

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The management of patients with T2DM has become individualized with different therapies available and owing to the presence of specific patient factors that influence the appropriate choice of medication. In 2018, the American Diabetes Association (ADA) presented a decision algorithm, which included the assessment of key patient characteristics including comorbidities like ASCVD, chronic kidney disease (CKD) or heart failure (HF). The presence of these comorbidities should allow preferential use of certain classes of glucose-lowering drugs as second-line therapy.[10]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established class of glucose-lowering drugs that have a pleiotropic action on the pathophysiological defects of T2D – leading to effective glycemic control, loss of weight, minimal risk of hypoglycemia and a consistent safety profile.[11]GLP-1RAs have similar mechanisms of action but they vary in structure, pharmacokinetics and efficacy (their ability to reduce HbA1c, body weight and cardiorenal protection).[12,13]

The previous success in clinical trials of exenatide and liraglutide renewed interest in the GLP-1 therapy area. The daily injection regime was inconvenient for some patients and hence, better patient convenience was needed for patient adherence and satisfaction.[14] The fear of injections and difficulty in administration along with the perception of injectable therapy was a major barrier to the use of GLP-1RA therapy.[11]

Semaglutide is a GLP-1RA with 94% structural homology to endogenous GLP-1, and it has three important structural differences that prolong its half-life but do not compromise receptor binding. The efficacy and safety of subcutaneous semaglutide is already demonstrated in numerous clinical studies. The efficacy of oral semaglutide was expected to correspond with subcutaneous semaglutide and was proved with the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) studies.[15] Oral semaglutide is co-formulated with SNAC {Sodium N-[8-(2-hydroxybenzoyl)amino] caprylate} which is an absorption enhancer and promotes semaglutide absorption across the gastric mucosa.

This review will specifically elaborate on why oral semaglutide will be ideal for Indian diabetic patients in the light of evidence from studies on oral and injectable semaglutide.

Diabetes and Prediabetes

The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study was a national study designed to estimate the prevalence of diabetes and prediabetes in the Indian population. It was the largest ever study conducted to capture the diabetes scenario in India.

The evidence of prevalence were reported from 15 states, which represented 50.7% of the adult population of the country. The main factors identified to be driving the epidemic of diabetes in India were obesity, age and a family history of T2DM. Prediabetes prevalence in India was high and exceeded diabetes in many states implying a huge risk of progression to overt diabetes.[16] This finding is very important in the Indian context as it has been shown in several studies that Asian Indians progress faster through the prediabetes stage when compared with other ethnic groups.[17]

Beta-cell dysfunction was prominent even with mild dysglycemia in the Asian Indian population (impaired glucose tolerance [IGT] or impaired fasting glucose [IGF] or both). This finding is important as it highlights the need for primary prevention strategies focussing on preservation of beta-cell function and reduction in cell decline.[18]

Increase in beta-cell function and insulin biosynthesis was shown with semaglutide along with improved proinsulin to insulin ratios when compared with other antidiabetic agents including sulfonylureas, which increase insulin secretion with no effect on the biosynthesis of insulin. Also, reduction in insulin resistance was greater with semaglutide vs. placebo, sitagliptin or exenatide extended-release (ER).[19]

Glycemic efficacy of oral semaglutide

Oral semaglutide was effective in reducing HbA1c across the PIONEER trials. In the PIONEER 1 trial, oral semaglutide monotherapy significantly reduced baseline HbA1c compared with placebo after 26 weeks of treatment in patients with early T2DM.

In patients with established T2DM who were receiving background oral antidiabetic medications (PIONEER 2-4), 14 mg of oral semaglutide was more effective than empagliflozin 25 mg, sitagliptin 100 mg and similar to liraglutide 1.8 mg at week-26. Flexible dose adjustment of oral semaglutide was more effective than sitagliptin 100 mg for reducing HbA1c at 52 weeks in the PIONEER 7 trial.

In advanced T2DM patients receiving insulin, oral semaglutide significantly reduced HbA1c as compared to placebo at weeks-26 and week-52. In patients with moderate renal impairment (PIONEER 5), oral semaglutide 14 mg was significantly more effective

than placebo at reducing HbA1c at week-26. In high cardiovascular (CV) risk patients (PIONEER 6), oral semaglutide reduced HbA1c by a mean of −1.0% vs. −0.3% in the placebo group.

Proportion of patients who achieved ADA recommended target of HbA1c <7.0% was persistently greater with 7 and 14 mg of oral semaglutide as compared with placebo and active comparators. Fasting plasma glucose was also generally reduced in patients on oral semaglutide, compared to the placebo and active comparator groups.[20]

Obesity

Obesity in India has been rampantly increasing in prevalence and the recent trends indicate a rate any where between 13% to 50% among the urban population and 8% to 38.2% in rural population of obesity. Obesity among Asian Indians has distinctive features like greater truncal, intra-abdominal, subcutaneous and total adipose tissue when compared with Caucasians.[21] Several comorbid conditions are associated with obesity like hypertension, hyperglycemia, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), etc. This constellation of conditions is broadly defined as metabolic syndrome.[22]

NAFLD is an important component of metabolic syndrome which can progress to fibrosis and even cirrhosis in the presence of portal inflammation (nonalcoholic steatohepatitis [NASH]).[23] Approximately one-fourth of the urban Indian population has NAFLD and according to a case-control study, Asian Indians in North India with NAFLD have increased adipose tissue, fasting hyperinsulinemia, IGT and metabolic syndrome.[24] The improvement in NAFLD/NASH with GLP-1RAs is thought to be through an indirect mechanism – through which these drugs aid in reducing inflammation.[25]

Dyslipidemia is described as an increased level of total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol and hypertriglyceridemia (present alone or in concurrence).[26] In Asian Indians with insulin resistance, the plasma adipose tissue metabolites, fatty acids and leptin are higher along with lower adiponectin levels.[27] In a study conducted with oral semaglutide to assess its effects on postprandial glucose and lipid metabolism, it was found that fasting LDL and total cholesterol concentrations were lower with oral semaglutide compared with placebo.

Treatment with oral semaglutide also resulted in lower fasting and postprandial triglycerides than with placebo. In the PIONEER 6 trial, improvements in elevated total cholesterol, LDL and triglycerides, reduced HDL were seen with oral semaglutide. The trial met its primary objective of proving CV safety of oral semaglutide.[28]

Body weight reduction with oral semaglutide

In the PIONEER clinical trial program, greater number of patients achieved a weight loss of ≥5% across clinical trials with oral semaglutide 7 and 14 mg (13-44%) versus placebo (3-15%) and active comparators (10-36%) at week-26, which was sustained at the end of the trial. Other body size measures like BMI and waist circumference were also reduced with oral semaglutide compared with placebo and active comparators.[20]

Atherosclerotic Cardiovascular Disease

According to the Global Burden of Disease study, 24.8% of all deaths in India are associated with cardiovascular disease (CVD). Ischemic heart disease and stroke are responsible for 21.1% of all deaths in India.[29] T2DM and the associated microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (coronary artery disease, peripheral arterial disease and stroke) complications contribute substantially to the morbidity and mortality of the disease. The core pathophysiological mechanism leading to arterial lumen narrowing is atherosclerosis. Recent studies have indicated the central role played by endothelium and inflammation in atherosclerosis.[30]

In animal studies, semaglutide reduced the size of the aortic atherosclerotic plaque lesion independent of its effect on diabetes, body weight, and lipids.[25] It is important to note that the findings from the cardiovascular outcomes trial (CVOT) with semaglutide showing effects – consistent with reduction in atherosclerotic burden, suggest that the findings seen in animal studies may translate to humans.[14]

The largest cause of diabetes associated morbidity and mortality is CVD. The international diabetology and cardiology guidelines have been updated to put forth a combined approach for the management of T2DM and CVD. The GLP-1RAs or sodium-glucose co-transporter 2 inhibitors (SGLT2i), which have a demonstrated CV benefit are recommended as first- or second-line agents in this regard.

The CAPTURE study found that almost one out of three adults with T2DM had established CVD. Most of the burden was contributed by ASCVD with coronary artery disease, carotid artery disease and stroke with

maximum contribution. The management of most participants was not according to recent guidelines on diabetes and cardiac disease. There was an unmet need of reducing risk through interventions based on current evidence.[31]

Cardiovascular safety of oral semaglutide

The PIONEER 6 trial was a CVOT designed to establish the CV safety of oral semaglutide; it was not powered for proof of superiority and CV benefit. The investigators concluded the noninferiority of oral semaglutide safety profile to placebo, on a background of standard care. The CVOT of oral semaglutide to prove superiority in major adverse CV event (MACE) reduction is ongoing as A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL). Pooled analysis, which combined data from CVOTs of oral and injectable semaglutide showed that the once-daily oral and once-weekly injectable showed very similar effects on glycemic and body weight control. Post-hoc analyses suggest a potential for improved CV outcomes with semaglutide irrespective of the route of administration.[32]

Hypoglycemia

There is a huge corpus of evidence available suggesting that intensive glycemic control with a goal of euglycemia should be instituted as early as possible in diabetic patients. The Diabetes Control and Complications Trial (DCCT) and Stockholm Diabetes Intervention Study (SDIS) showed reduction in the incidence of microvascular complications with intensive glycemic control in type 1 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study found that tighter glycemic control can delay the onset and progression of micro- and macrovascular complications in T2DM patients.[33-37]

However, due to the risk of hypoglycemia, strict glycemic control is not achieved in majority of patients in real life clinical settings, and this was also a major finding in the above studies. In the DCCT, there was a threefold increase in severe hypoglycemia with intensive therapy as compared with conventional therapy–during the study. In the UKPDS, major hypoglycemic episode in a year was significantly higher in the intensive treatment group.[33,35]

The risk of hypoglycemia is increased with insulin excess (exogenous insulin or agents causing release of insulin), and faulty glucose regulation. Progressive beta-cell failure in T2DM increase the characteristics and severity of hypoglycemic episodes.[37]

Hypoglycemia is a significant barrier to patient adherence to medications leading to suboptimal glycemic control along with the risk of development of complications. Recurrent hypoglycemia worsens the quality of life and can also prove fatal.[38]

In a cross-sectional study conducted in an Indian hospital, to find out proportion of T2DM patients reporting at least one or other symptom of hypoglycemia, almost 96% of subjects reported one or the other symptoms of hypoglycemia. Severe hypoglycemia episodes were reported by 19% patients and 8% patients required admission due to hypoglycemia. This study showed the reported prevalence of hypoglycemia among T2DM patients and the urgent need for intervention.[39]

GLP-1RAs have an inherently low propensity to cause hypoglycemia, which was also consistent with oral semaglutide. The PIONEER 4 study was associated with very low proportions of patients experiencing severe or blood-glucose confirmed hypoglycemia (1% and 2% patients, compared with 2% in placebo group). In the PIONEER 8 study, the number of such events was higher in patients having a background of insulin therapy, but the addition of oral semaglutide to insulin did not increase the proportion of patients with hypoglycemia compared to placebo. Most events occurred in patients receiving basal-bolus background therapy with insulin.[40]

Conclusion

Oral semaglutide is a revolutionary new drug in the management of T2DM which overcomes the injectable barrier associated with GLP-1RA therapy. It is administered as a co-formulation with an absorption enhancer called SNAC. Oral semaglutide has glycemic control and weight reduction benefits–consistent with the GLP-1RA class. India is fast becoming the type 2 diabetes capital of the world with associated conditions like obesity and ASCVD complicating the picture. The pleiotropic benefits of GLP-1RAs are well known and are consistent with oral semaglutide. All guidelines relating diabetes and cardiology have evolved and now recommend a cardiovasculocentric approach to T2DM as opposed to earlier more glucocentric approach.

With oral semaglutide, we have robust data on the clinical efficacy and safety of oral semaglutide, as well as the added advantage of once-daily oral administration, improving patient convenience. The beneficial effects with oral semaglutide like superior

glycemic control, weight loss, CV safety and minimal risk of hypoglycemia make it a game-changer for T2DM management in India.

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Imeglimin: Finding a Place in Modern Diabetes Pharmacotherapeutics

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A B S T R A C T

Type 2 diabetes mellitus (T2DM) is a multifactorial disease. Newer facets of its causation, clinical course, complications and therapy are being unraveled regularly. This editorial describes imeglimin, a first-of-class oxidative phosphorylation inhibitor, that has been approved for T2DM in Japan and India.

Keywords: Gluconeogenesis, imeglimin, oxidative phosphorylation inhibitor, mitochondria, pharmacotherapeutics, type 2 diabetes mellitus

Introduction

Newer facets of the pathophysiology of diabetes are being recognized by researchers. This has opened up novel possibilities and avenues for the treatment of this syndrome. Oxidative phosphorylation is a key biochemical reaction, which occurs in our cells, and ensures energy homeostasis. Modification of the pathways of oxidative phosphorylation is a promising therapeutic target for diabetes, and imeglimin, a novel drug, utilizes this mechanism. The clinical trial program of imeglimin has shown favorable results. This editorial analyzes this new molecule as a potential treatment of diabetes.

Table 1. Mechanism of Action of Imeglimin

Biochemical
• Inhibition of oxidative phosphorylation
• Modulation of mitochondrial function and structure
Physiological
• Increase in insulin sensitivity (muscle uptake of glucose)
• Reduction of hepatic gluconeogenesis
• Increase in insulin secretion
Downstream
• Reduction in formation of reactive oxygen species (antioxidant effect)

Mechanism of Action

Imeglimin has a dual mechanism of action. It acts simultaneously to increase insulin sensitivity as well as insulin secretion. Both these mechanisms are mediated through separate biochemical pathways (Table 1).[1]

Insulin secretagogue

Imeglimin enhances insulin secretion of nicotinamide phosphoribosyltransferase (NAMPT). NAMPT is the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis. If expressed properly, it increases intracellular NAD^+ concentration, which in turn optimizes the efficiency of the mitochondrial electron transport chain, and increases mitochondrial adenosine triphosphate (ATP) content in the beta cells. This inhibits ATP-sensitive potassium (K_{ATP}) channel activity, encourages calcium influx into the beta cells, and promotes insulin secretion. A NAD^+ metabolic known as cyclic ADP-ribose (cADPR) also increases glucose-stimulated release from the beta cells.[1]

Insulin sensitization

Imeglimin also optimizes mitochondrial function in hepatocytes. It inhibits complex I activity, restores complex III activity and suppresses formation of

reactive oxygen species (ROS). In the muscle, it improves uptake of glucose by increasing the expression of a transcriptional coactivator termed as peroxisome proliferator-activated receptor-γ coactivator 1α (PgC1α).[1]

Imeglimin vs. Metformin

Imeglimin differs from metformin in that it is a competitive inhibitor of complex I activity and balances complex III: I function. Its insulinotropic effect also sets it apart from metformin. There is no risk of lactic acidosis with imeglimin. Metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPDH) and causes pyruvic acid to be converted to lactic acid, which may accumulate to toxic levels. However, imeglimin is not an mGPDH inhibitor and therefore this safety concern does not arise with its use.[2]

Place in Taxonomy

Imeglimin is the first of its class of oxidative phosphorylation inhibitors. It is thought to act by increasing the mitochondrial bioenergetic efficiency of cells in the pancreas, liver and skeletal muscle. Imeglimin does not find mention in contemporary classifications of glucose-lowering therapy,[3,4] though it is listed in a classification of obesity-lowering drugs.[5] However, it can be comfortably placed along with other insulin secretagogues as well as insulin sensitizers. Imeglimin does not lead to hepatic AMP kinase activation in murine models.[6]

Clinical Trial Program

A robust clinical trial program has been conducted using imeglimin as monotherapy as well as in combination with other glucose-lowering drugs in Caucasian and Japanese participants. A recent meta-analysis of 8 studies involving 1,555 participants with type 2 diabetes mellitus (T2DM) reported a statistically significant reduction in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) as compared to the control group.[7] The Trials of Imeglimin for Efficacy and Safety (TIMES) 1 study compared imeglimin monotherapy with placebo in 213 Japanese participants over 24 weeks. It demonstrated a 0.87% reduction in HbA1c with a safety profile similar to that of placebo.[8] The open-label TIMES 2 study, assessed imeglimin in 714 participants, both as monotherapy and in combination with other glucose-lowering drugs (acarbose [n = 64], metformin [n = 64], dipeptidyl peptidase-4 inhibitors [n = 63], glinide [n = 64] glucagon-like peptide-1 receptor agonist [n = 70], sodium-glucose co-transporter 2 inhibitor [n = 63], sulfonylurea [n = 127] and glitazone [n = 65]). This Japanese study lasted 52 weeks, and showed an HbA1c reduction of 0.92%. Most adverse events were mild or moderate in nature.[9]

TIMES 3 was a 16-week long study with a 36-week open-label extension period conducted in 215 Japanese participants. It assessed the safety and efficacy of imeglimin in combination with insulin. An HbA1c reduction of 0.60% and 0.64% was noted at 16 and 52 weeks, respectively, with a satisfactory safety profile. Imeglimin use did not increase the risk of hypoglycemia.[10]

Safety

Imeglimin has shown a good safety and tolerability profile in both animal models and clinical studies. Angiomatous hyperplasia leading to development of hemangioma and possibly hemangiosarcoma has been observed in the small intestine of rats, but this appears less relevant to humans considering the relative dose used.[1] In clinical trials, no major safety or tolerability issue has been flagged. Imeglimin is well-absorbed orally, and is excreted through the kidney. The drug is safe for use even in severe renal insufficiency, albeit in reduced doses, though it has not been studied in severe hepatic impairment.

Place in Treatment Algorithms

The drug should be a welcome addition to our existing choice of glucose-lowering drugs. A rational approach incorporating both nonpharmacological and pharmacological modes of treatment is the way to successful diabetes management. Table 2 lists the

Table 2. Potential Indications for Imeglimin

Initiation
- If other drugs are contraindicated or considered to have averse risk-benefit ratio, e.g.;
  - Elderly
  - Renal insufficiency
- Isolated fasting hyperglycemia

Interchange
- If other drugs are not well-tolerated, e.g.;
  - Gastrointestinal effects
  - Risk of acidosis
  - Weight gain
  - Hypoglycemia

Intensification
- If other drugs are insufficient in achieving euglycemia

Table 3. Posology of Imeglimin

- Available as 500 mg tablets
- Dose 1000 mg twice a day post-meal
- Indication: type 2 diabetes
- Contraindications:
  - Pregnancy, lactation, preconception
  - Childhood
  - Intensive muscle exercise
  - Excessive alcohol intake
  - Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 [for full dosage]
  - Significant hepatic dysfunction
  - Pituitary or adrenal dysfunction
- Dose 500 mg if eGFR 15-45 mL/min/1.73 m^2
- Dose 500 mg OD if eGFR <15 mL/min/1.73 m^2
- No clinically significant drug-drug or drug-food interactions

potential position for imeglimin in T2DM, and suggests some specific indications for its use. Table 3 highlights the important posological considerations, caveats and contraindications which must be kept in mind while prescribing the drug.

We take this opportunity to reiterate, however, that no drug, singly or in combination can address the wide spectrum of pathophysiological abnormalities that lead to and are associated with type 2 diabetes. We also iterate that a balanced lifestyle and mind style including focus on diet, exercise, stress and sleep management are integral to diabetes care.

Summary

Imeglimin is now approved in India. The basic and clinical pharmacology of the molecule is encouraging and we hope that it will prove its mettle in the fight against diabetes.

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Lighter Side of Medicine

HUMOR

But where were you yesterday?

Tom had this problem of getting up late in the morning and was always late for work. His boss was mad at him and threatened to fire him if he didn't do something about it. So, Tom went to his doctor who gave him a pill and told him to take it before he went to bed. Tom slept well, and in fact, beat the alarm in the morning. He had a leisurely breakfast and drove cheerfully to work. "Boss", he said, "The pill actually worked!" "That's all fine" said the boss, "But where were you yesterday?

New Teeth

Our local minister had all of his remaining teeth pulled and new dentures made a few weeks ago.

The first Sunday, his sermon lasted 10 minutes. The second Sunday, he preached only 20 minutes. But, on the third Sunday, he preached for an hour and a half.

I asked him about this. He then told me "well, John, that first Sunday, my gums were so sore it hurt to talk. The second Sunday, my dentures were still hurting a lot. Now the third Sunday, I accidentally grabbed my wife's dentures AND I COULDN'T STOP TALKING!"

My Grades

A high-school student came home one night rather depressed.

"What's the matter, Son?" asked his mother.

"Aw, gee," said the boy, "It's my grades. They're all wet."

"What do you mean 'all wet?'"

"You know," he replied, "…below C-level."

Bank name

Mother decided that 10-year-old Cathy should get something 'practical' for her birthday. "Suppose we open a savings account for you?" mother suggested. Cathy was delighted. "It's your account, darling," mother said as they arrived at the bank, "so you fill out the application."

Cathy was doing fine until she came to the space for 'Name of your former bank.' After a slight hesitation, she put down 'Piggy.'

Doc says, "Joe, I got some bad news for you. You've got 6 months to live."

Joe says, "Six months? Doc, I can't pay your bill in 6 months, I can't do it!"

Doc says, "OK, I give you a year..."

Patient: "Doctor, I get heartburn every time I eat birthday cake."

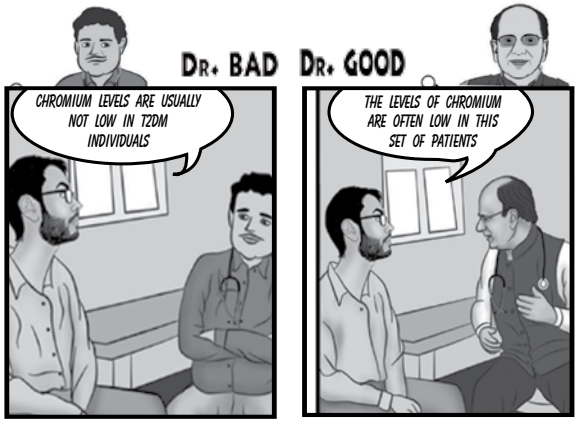
Doctor: "Next time, take off the candles."

When an employment application asks who is to be notified in case of emergency, I always write, "A very good doctor".

My therapist told me that a great way to let go of your anger is to write letters to people you hate and then burn them. I did that and I feel much better but I'm wondering... do I keep the letters?

Dr. Good and Dr. Bad

SITUATION: A 45-year-old type 2 diabetic male had lower plasma chromium levels.



LESSON: According to a case-control study, an inverse association has been demonstrated between plasma chromium levels, T2DM and prediabetes.

Nutrients. 2017;9(3):294.

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