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Rx Lupisit

S Strong **HbA1c** Control (1% Reduction)

A Assurance of **CV Safety** (Tecos Trial)

H **Hypoglycemia** risk is low

I Improved adherence with **OD Dose & pricing**

Rx Lupisit-M

Sitagliptin 50 mg + Metformin 500/1000 mg Tablets

S.A.H.I Start

Rx Lupisit-D 50/5 100/10

Sitagliptin 50/100 mg + Dapagliflozin 5/10 mg Tablets

S.A.H.I Defence

Rx Lupisit-DM

Sitagliptin 100 mg + Dapagliflozin 10 mg + Metformin 500/1000 mg Extended Release Tablets

S.A.H.I Control

For improved outcome in T2DM patien

The Asian Journal of
DIABETOLOGY
Vol. 24, No. 4, October-December 2024

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EDITORIAL

GUEST EDITORIAL

RETROSPECTIVE STUDY

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EDITORIAL

Sulfonylurea Stewardship

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Stewardship

The theme of stewardship is familiar to practitioners and students of health care. Antibiotic stewardship, steroid stewardship and insulin stewardship are some examples of the use of this framework in clinical medicine[1-3]. This concept has also been extrapolated to create a rubric known as glycemic guardianship[4].

Sulfonylureas in Service

As part of this ongoing campaign to improve diabetes care, we propose the term sulfonylurea stewardship. Sulfonylurea stewardship may be defined as a systematic approach to prescribe and monitor sulfonylurea therapy, in persons with type 2 diabetes, in a rational and responsible manner, balancing efficacy with safety and tolerability, so as to achieve optimal short-term as well as long-term outcomes. Their long record of service, prominent listing in World Health Organization's Lists of Essential Medicines[5], as well as treatment guidelines, and widespread usage across the globe, bear testimony to their usefulness.

Multifaceted Concept

Sulfonylurea stewardship may be practiced at a macro-, meso- and micro- level (Table 1). The various components of sulfonylurea stewardship, listed in Table 1, correlate with the teachings of 'good clinical sense', therapeutic parsimony', and 'first do no harm'[6,7]. Good clinical sense is defined as" the presence of sensory faculties, their usage and interpretation, by which one is able to practice good clinical medicine". Pragmatic clinical sense, based on evidence, and embellished by astute observation and experience, must be a part and parcel of all decision making. Therapeutic parsimony alludes to the adage to use minimal therapeutic interventions, in place of multiple ones, as long as equivalent therapeutic outcomes are achieved[7].

Table 1. Sulfonylurea Stewardship

Macro-Level

- Inclusion of modern sulfonylureas in lists of essential medicines
- Availability, accessibility and affordability of modern sulfonylureas, as monotherapy and in fixed dose combinations

Meso-Level

- Coverage of sulfonylurea usage in academic curricula and continuing medical education programmes.
- Continued research on modern sulfonylureas

Micro-Level

- Rational use of modern sulfonylureas in clinical practice
- Pre prescription evaluation
- Glucometric guardianship
- Adverse drug reaction monitoring
- Intensification or interchange of regimens as needed
- Dose titration as required

This promotes usage of fixed dose combinations, with lower frequency of administration, so as to reduce complexity of regimens. The teaching, 'First do not harm', reminds us to prioritize patient safety. These maxims fit under the umbrella of glycemic guardianship, i.e., activities carried out by all stakeholders to ensure optimal care of diabetes.

Responsibility

All these maxims can be addressed through sulfonylurea stewardship. The responsibility for this stewardship should be shouldered by all health care professionals and planners. Endocrinologists and diabetologists, however, must take the lead in advocating and propagating the importance of sulfonylurea stewardship, as a part of glycemic guardianship. Concerted, and continued focus on academic and clinical excellence, research, and advocacy is required to reap the benefits of modern sulfonylureas.

Safe And Smart Usage

There are voices which feel that sulfonylureas should be discontinued[8]. These should be engaged, through dialogue and discussion, to describe the heterogeneity of this drug class, and the benefits of modern sulfonylureas such a as glimepiride and gliclazide XR[9]. Contemporary evidence, as published in this issue of *Asian Journal of Diabetology*, should be shared with clinicians and other concerned stakeholders. This will improve confidence in the "safe and smart" sulfonylureas, enhance rational usage, and lead to better outcomes in diabetes care.

■■■■

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GUEST EDITORIAL

Modern Sulfonylureas, Modern Science

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Changing Times

Over the past century, diabetes has grown into a pandemic[1]. Newer facets of its causation, clinical presentation, complications and comorbidities are being unraveled. Simultaneously, newer means of treatment are being discovered. While these advances are more than welcome, this diachronicity comes with added responsibility.

The diabetes care professional needs to use newer, as well as conventional, therapies in a logical manner. Rational combinations should be used, keeping the etiopathogenesis of the disease, and the mechanism of action of drugs, in mind. The ever-increasing number of drug classes, drugs, and their preparations[2], however, make this easier said than done.

Consistency During Change

One class of drugs, which has served diabetes care consistently over more than half a century, is the unparalleled sulfonylureas. Along with metformin, a nearly 75-year-old classic, these drugs have offered efficacy in glucose control[3]. Used in type 2 diabetes, traditional sulfonylureas have been replaced by modern sulfonylureas, such as glimepiride and gliclazide MR. These drugs are listed in the World Health Organization's List of Essential Medicines, as well as in most national lists of essential drugs[4].

Classic Evidence

Modern sulfonylureas are an important option for second line management of diabetes, along with metformin and lifestyle modification. The "safe and smart" South Asian consensus, published a decade ago[5], remains a sempiternal publication in the field of sulfonylurea pharmacology. Trials such as ADVANCE, and Steno-2 have demonstrated the efficacy, safety and tolerability of gliclazide MR as part of a comprehensive management strategy[6,7]. ADVANCE ON and Steno-2 data have revealed the long-term benefits of such therapy in improving vascular health[8,9]. It must be noted that these trials were planned and executed much before the "wave" of regulator-mandated cardiovascular outcome trials (CVOTs) began. One such CVOT, the CAROLINA trial, was able to show that glimepiride was non-inferior to linagliptin in terms of cardiovascular outcomes[10]. Other CVOTs, which have demonstrated safety or benefit of drug classes such as dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1RA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i), have also been designed on a framework of standard of care, which includes sulfonylureas[11]. The sulfonylureas in fact, have been described as glucocidal, rather than glucostatic drugs (personal communication). This reflects their potency as glucose-lowering drugs.

Contemporary Data

Glimepiride is the most frequently prescribed glucose-lowering drug in India, after metformin. Therefore, the three real world evidence (RWE) trials that we feature in this issue of *Asian Journal of Diabetology* are of great relevance to our readers.

George J et al describe the patterns of usage of glimepiride + metformin fixed dose combination (FDC) based upon retrospective analysis of records of 6,250 persons living with diabetes, treated by 500 health care professionals across India. The FDC was able to achieve an HbA1c reduction of >1%, with minimal hypoglycemia. Other drugs, such as DPP4i, GLP1RA, SGLT2i, pioglitazone, alpha-glucosidase inhibitors, and insulin were used in combination with glimepiride + metformin FDC. The commonest of these were DPP4i, highlighting the versatility and safety of this class of drugs *(George J et al. p 31)*.

At times, however, DPP4i therapy may be inadequate. George J et al studied the effects of shifting from DPP4i to modern sulfonylureas + metformin combination. They reported a 1.11% reduction in HbA1c, along with a 41.77 mg% and 67.39 mg% improvement in fasting and postprandial glucose values. This study demonstrates the utility of modern sulfonylurea + metformin in managing type 2 diabetes characterized by DPP4i inadequacy. The analysis also documented the relative use of various DPP4i: 50% prescriptions were of vildagliptin, followed by 30.2% of sitagliptin *(George J et al. p 9)*.

Conclusion

These studies highlight the contemporary importance of modern sulfonylureas in the management of type 2 diabetes. Continued, and concerted, efforts at continuing medical education are required, however, in order to maximize the benefit of this class of drugs. The concept of sulfonylurea stewardship, as described in this issue *(page 9)*, should be popularized in a manner similar to that of antibiotic or steroid stewardship. Rational and responsible use of modern sulfonylureas will improve glycemic control, and enhance long-term outcomes in persons living with type 2 diabetes. We commend George J, Aushili M, and their teams of investigators, for having highlighted the role of glimepiride + metformin combination in the modern management of type 2 diabetes.

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RETROSPECTIVE STUDY

Retrospective Clinical Evidence on Switching to Modern Sulfonylurea/Metformin in Patients Uncontrolled on DPP4i-based Therapies

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ABSTRACT

Background: Many patients with type 2 diabetes mellitus (T2DM) struggle to control their glucose levels with dipeptidyl peptidase-4 inhibitor (DPP4i)-based therapy, highlighting the need to explore alternative treatments. This study aims to investigate the benefits of switching to a sulfonylurea/metformin combination in individuals with type 2 diabetes (T2D) who were previously on DPP4i. **Methods:** The study is a retrospective, multicenter, observational, case-based questionnaire survey conducted in T2DM patients who received DPP4i earlier but due to poor glycemic control switched to the combination in any strength. Statistical analysis was conducted using SPSS® Version 23.0 software. Continuous variables were analyzed using mean and standard deviations; categorical variables were analyzed using Fisher's exact and Chi-square tests. **Results:** The study analyzed data from 2,736 T2DM patients who were 18 years and above, having an average age of 38.46 ± 7.21 and average body mass index (BMI) of 27.79 ± 4.25 kg/m^2. The mean change in the glycated hemoglobin (HbA1c) values after treatment was found to be 1.11 ± 0.78, while the mean change in fasting plasma glucose (FPG) and postprandial glucose (PPG) was 41.77 ± 31.11 and 67.39 ± 51.57, respectively; 94.8% of patients had no hypoglycemic events and 96.2% did not gain weight after switching to glimepiride/metformin, additionally the HbA1c, FPG, and PPG levels were control well. HbA1c before treatment was 9.64 ± 1.79 and after treatment was 7.52 ± 1.97. Similarly, FPG was 175.14 ± 89.89 mg/dL before treatment, which reduced to 133.37 ± 43.59 mg/dL after treatment. PPG was found to be 251.38 ± 80.30 mg/dL before treatment and 183.98 ± 54.76 mg/dL after treatment. Vildagliptin (50%) was the most common DPP4i being prescribed, followed by sitagliptin (30.2%). The main reason of switching to glimepiride/metformin was to improve the HbA1c levels, followed by controlling the uncontrolled glycemic levels and further improving FPG and PPG levels. **Conclusion:** The study supports the effectiveness and safety of switching to modern sulfonylureas/metformin in T2DM patients who are inadequately controlled on DPP4i-based therapies.

Keywords: Type 2 diabetes mellitus, DPP4i, retrospective studies, sulfonylurea, glimepiride, metformin, glycemic control

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Introduction

Type 2 diabetes (T2D) is a progressive disease which often requires treatments to be added or switched in order to achieve glycated hemoglobin (HbA1c) targets. However, stringent glycemic targets in people over 65 years may increase the risk of hypoglycemia. People with multimorbidity may be less likely to receive multiple T2D therapies due to concerns about polypharmacy and drug interactions. T2D medication may be switched due to lack of efficacy or adverse drug events (ADEs)[1-4].

Dipeptidyl peptidase-4 inhibitors (DPP4i) have emerged as a novel class of oral antidiabetic agents, offering glucose-lowering effects by inhibiting the breakdown of incretin hormones. However, clinical reality sometimes presents challenges as some patients fail to achieve desired glycemic control despite DPP4i therapy[5].

Poor glycemic control increases the risk of cardiovascular disease, chronic kidney disease (CKD), and mortality. Studies have also shown that the use of dipeptidyl peptidase-4 (DPP-4) is contraindicated in people with CKD and might increase the risk of heart failure and acute pancreatitis[6,7].

Recent studies suggest that DPP4i are associated with an increased risk of developing bullous pemphigoid (BP) in patients with diabetes[8].

In many instances, discontinuation of DPP4i was found to be possible adverse events or tolerability issues related to adding insulin (58.9%), lack of efficacy/treatment goals not being met (55.4%) and cost of DPP4i in addition to insulin (48.5%)[9].

Modern antidiabetic strategies have evolved to incorporate a combination of medications to target multiple facets of glucose regulation, such as modern sulfonylureas (SUs) and metformin. Modern SUs are considered ideal options due to their high efficacy, relative cardiovascular safety, and low cost.

Hence, in the pursuit of refining diabetes management strategies, the transition from DPP4i-based treatments to contemporary modern SU/metformin combinations has emerged as a potential solution for patients encountering inadequate glycemic control.

This retrospective questionnaire based study examines the outcomes and implications of such a transition, shedding light on its effectiveness and relevance in optimizing the care of patients previously uncontrolled on DPP4i therapies.

Material and Methods

Study Design

This was a retrospective, multicenter, observational, case-based questionnaire survey. It was conducted with 225 health care professionals (HCPs) across different centers in India. The study protocol was designed according to the principles of the Declaration of Helsinki.

Study Population

The study included 2,736 patients of both sexes, aged above 18 years, diagnosed with T2DM and received DPP4i earlier but due to poor glycemic control switched to the combination in any strength. The average age of the participants was 38.46 ± 7.21 with an average body mass index (BMI) of 27.79 ± 4.25 kg/m^2. Participants were also found to be overweight and obese.

Data Collection

A case report format was developed to determine the effect of switching to modern SU/metformin in patients uncontrolled on DPP4i-based therapies. The questionnaire was sent to 225 HCPs across India via an online portal. Questions regarding demographic characteristics, such as age, sex, BMI, weight change, and economic class; duration of diabetes; antidiabetic drugs used (DPP4i) and (glimepiride/metformin); weight change; hypoglycemic episodes, reasons for switching to (glimepiride/metformin); adherence to lifestyle, were included in the questionnaire. An online portal was developed where the HCPs filled in the information. A descriptive analysis was performed with the data provided on the portal.

Statistical Analysis

All continuous variables are expressed as mean ± SD (standard deviation) or median with the interquartile range per the data distribution. Categorical variables are expressed as number and their respective percentage. Differences in binary and ordinal variables between two independent groups were analyzed by the exact Chi-square test. All the reported p-values are two-sided, and p-values <0.05 are considered to indicate statistical significance. All data entries and statistical analyses were performed by using SPSS@ Version 23.0 software.

Compliance with Ethics Guidelines

The study was approved by the ethical committees at all participating centers. All procedures adhered to the ethical standards established by the relevant institutional or national research committees. Since the

study used an anonymized database and was done retrospectively, patient consent was not needed.

Results

The study included, 2,736 T2DM patients who were 18 years and above with an average age of 38.46 ± 7.21. It showed significant control on the HbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG) levels after the switch. Hb1Ac before treatment was 9.64 ± 1.79 and after treatment was 7.52 ± 1.97. Similarly, FPG was 175.14 ± 89.89 mg/dL before treatment, which reduced to 133.37 ± 43.59 mg/dL after treatment. PPG was found to be 251.38 ± 80.30 mg/dL before treatment and 183.98 ± 54.76 mg/dL after treatment.

The participants had an average BMI of 27.79 ± 4.25 kg/m^2; 28.1% were obese and 49.2% of the participants were overweight as shown in Figure 1.

Demographic details showed that 61.5% of the participants belonged to the economically weaker section. About 45.5% were moderately active, while 26.4% were engaged in regular exercise and 13.2% were inactive as shown in Figure 2. Additionally 25.1% had a history of coronavirus disease 2019 (COVID-19) as illustrated in Figure 3. Further details showed that 94.8% of patients had no hypoglycemic events (Fig. 4) and 96.2% did not gain weight after switching to glimepiride/metformin (Fig. 5).

It was further observed that 36.4% physician had a view that the switching was having very good efficacy, followed by 28.2% physician having a view of excellent efficacy as is evident from Figure 6; 86.7% patients adhered to proper lifestyle changes as seen in Figure 7.

The survey also gave a clear picture of the DPP4i which was being prescribed the most along with metformin to the patient before switching to glimepiride/metformin. Vildagliptin (50%) was the most common DPP4i being prescripbed, followed by sitagliptin (30.2%), teneligliptin (16.0%), linagliptin (2.4%), saxagliptin (0.8%), evogliptin (0.3%) and alogliptin (0.1%) as is observed from Figure 8.

Further OD (once a day) dose was the most prevalent (64.5%) dose of DPP4i being prescribed by the physicians, followed by BD (twice a day) with 35.5% as seen on Figure 9.

The median dose of DPP4i used was found to be 50 with interquartile range (IQR) of 30. More specifically, the median dose of glimepiride used was 1 with IQR of (1.5) and the median dose of metformin used was 500 with IQR of 350. It was further observed

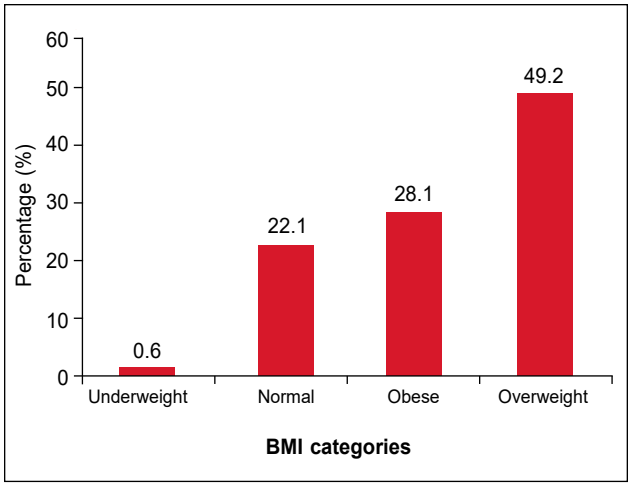

Figure 1. BMI category.

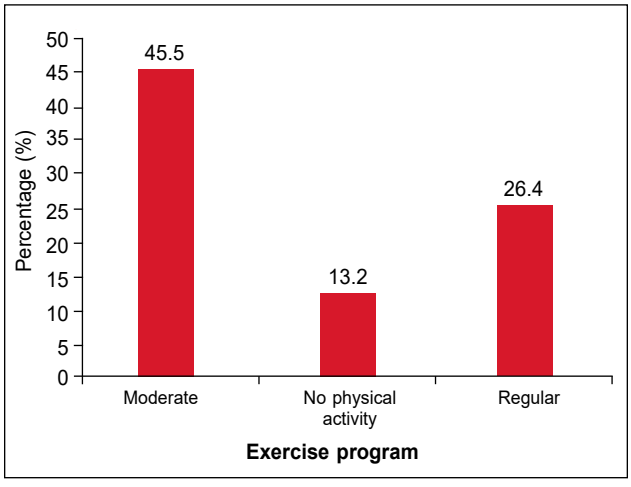

Figure 2. Frequency of exercising.

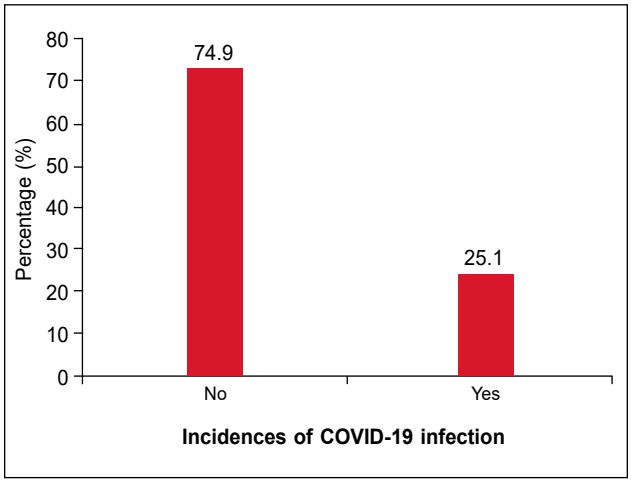

Figure 3. Incidences of COVID-19 infection.

that DPP4i being prescribed in patients as add-on to metformin was highest (69.2%), followed by first-line combination therapy with metformin (30.5%) as seen in

Figure 10. The most important reason for switching to glimepiride/metformin was found to improve HbA1c (71.7%), followed by aiming to control the uncontrolled

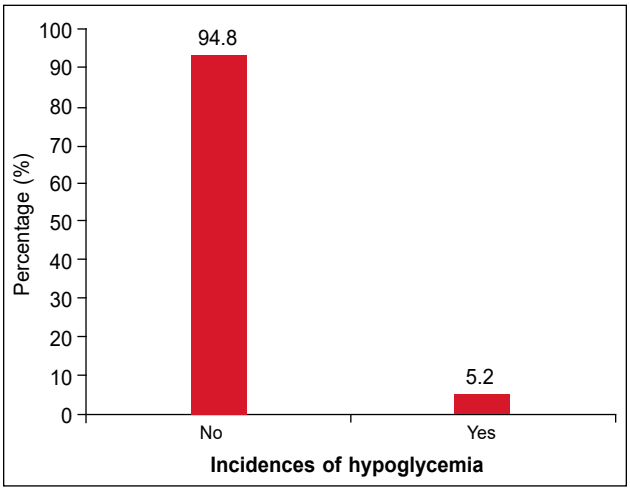

Figure 4. Incidences of hypogycemia.

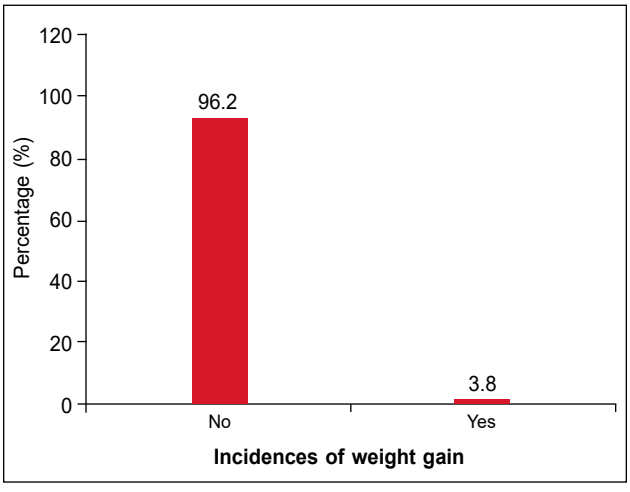

Figure 5. Incidences of weight gain.

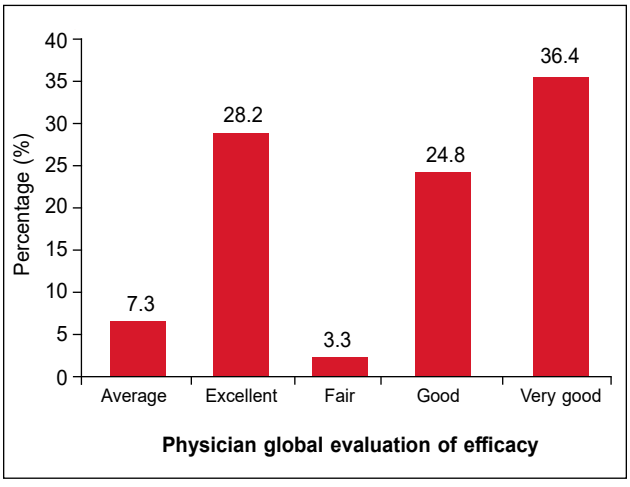

Figure 6. Physician global evaluation efficacy.

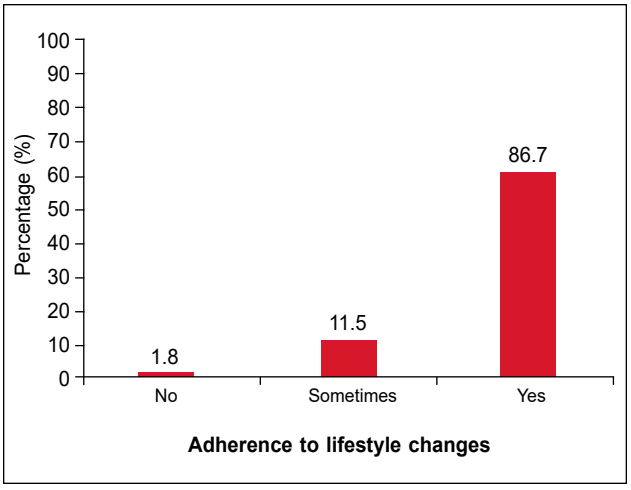

Figure 7. Patients adherence to lifestyle changes.

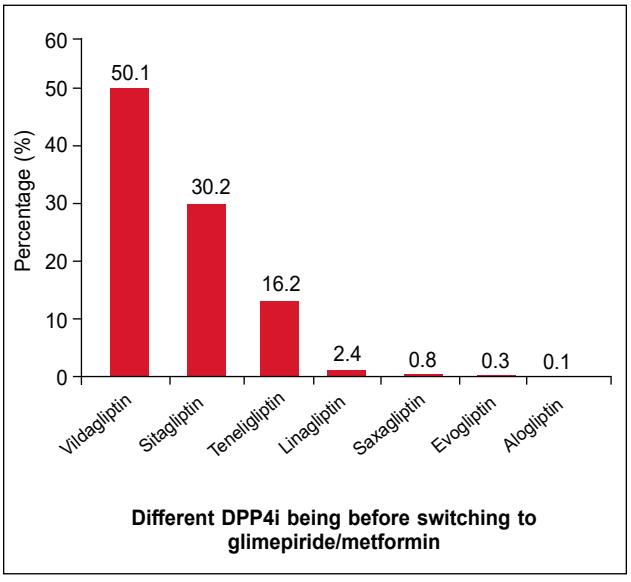

Figure 8. Frequency of different DPP4i being prescribed.

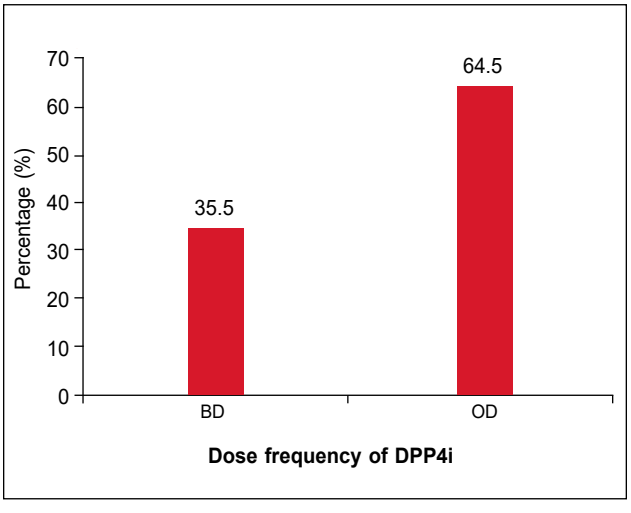

Figure 9. Dose frequency of DPP4i.

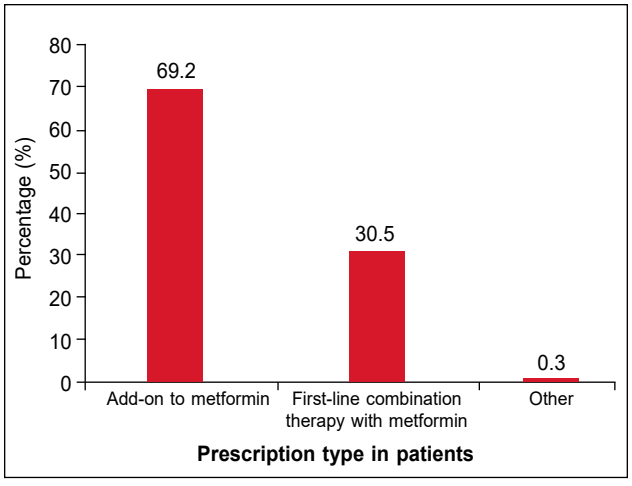

Figure 10. Prescription type in patients.

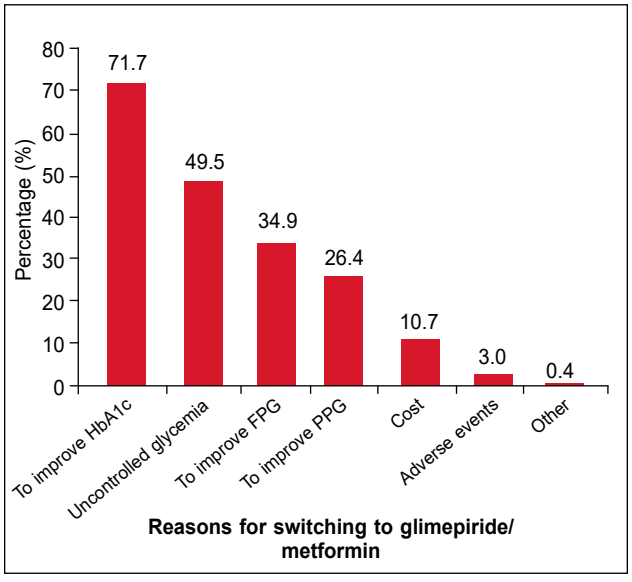

Figure 11. Reasons for switching to glimepiride/metformin.

glycemia accounting for 49.5% of patients, to improve FPG (34.9%), to improve PPG (26.4%), cost-effectiveness (10.7%), less adverse effects (3%), and other factors accounted for only 0.4% as is evident from Figure 11.

Discussion

Dipeptidyl-peptidase-4 inhibitors (DPP4i), in general, are recommended as second- and third-line therapy for T2DM and offer the option for improvement in both HbA1c and beta-cell survival, but a long-term clinical trial data are not yet available to assess the sustainability of glycemic control and protection of beta-cell mass[10].

Some reasons for switch from DPP4i to modern SUs might include modest glycemic lowering, relatively higher cost and reported incidences of pancreatic disease, arthritis, bullous pemphigoid (BP) some cases of heart failure[11]. Detailed effects of the drug combination on different parameters such as fasting blood glucose (FBG), PPG, HbA1c, and body weight are included. It further provides the clinical evidence on switching to modern SU/metformin in patients uncontrolled on DPP4i-based therapies.

The study included, 2,736 T2DM patients who were 18 years and above with an average age of 38.46 ± 7.21. It was observed that switching from DPP4i to modern SU/metformin combination was beneficial for patients who could not control their hyperglycemia even with DPP4i.

HbA1c reduced from 9.64 ± 1.79 before treatment to 7.52 ± 1.97 after treatment. Similarly, FPG which was 175.14 ± 89.89 mg/dL reduced to 133.37 ± 43.59 mg/dL after treatment. PPG lowered from 251.38 ± 80.30 mg/dL before treatment to 183.98 ± 54.76 mg/dL after treatment. Being overweight or obese significantly raises the risk of developing diabetes. Research indicates that approximately 86% of adults with T2D fall into the overweight or obese category[12,13].

A similar trend was also observed in the current study. About 28.1% were obese and 49.2% of the participants were overweight.

Studies have shown that the majority of the 463 million individuals who have diabetes globally reside in LMICs (low- and middle-income countries). Additionally, it was shown that less than 1 in 10 diabetics in LMICs are treated with complete, guideline-based care[14].

The Centers for Disease Control and Prevention (CDC) advises that engaging in physical activity not only helps regulate blood sugar levels but also reduces the risk of heart disease and nerve damage. They recommend 150 minutes of moderate-intensity physical activity per week[15].

In the present study, the demographic details showed that 61.5% of the participants belonged to the economically weaker section. About 45.5% were moderately active, while 26.4% were engaged in regular exercise and 13.2% were inactive as shown in Figure 2.

Research has established a mutual relationship between COVID-19 and diabetes mellitus. Diabetic individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) face an increased risk of hospitalization, severe pneumonia, and mortality compared to those without diabetes. The key characteristics of diabetes, namely insulin deficiency

and elevated blood glucose levels, are exacerbated by SARS-CoV-2's ability to target and harm the body's insulin-producing cells[16,17]. In the present study, it was seen that 25.1% of the participating population had a history of COVID-19 as illustrated in Figure 3.

DPP4i typically do not lead to weight gain and carry a low risk of hypoglycemia and other side effects. While they generally have a minimal impact on weight, some patients with lower baseline blood sugar levels have experienced slight weight reduction when using the DPP4i vildagliptin. This weight-neutral effect of vildagliptin may be attributed, at least in part, to its inherently low risk of hypoglycemia[18,19].

A similar observation was also seen in this study with 94.8% of patients reporting no hypoglycemic events (Fig. 4) and 96.2% did not gain weight after switching to glimepiride/metformin (Fig. 5).

The combination of glimepiride/metformin achieves good glycemic control and tolerability. In a recent study, Kumar also reported a similar finding that stated the efficacy and tolerability to be good to excellent (97.3% and 96.6%) in a vast majority of patients[20].

In another international prospective study, diabetic patients treated with glimepiride showed fewer hypoglycemic episodes compared to those treated with glibenclamide. Glimepiride's documented cardiovascular safety/neutrality and reduced hypoglycemia episodes make it an attractive alternative for the management of persons with long-standing diabetes[21,22].

Modern SUs (glimepiride/glibenclamide, etc.) offer superior glycemic efficacy, has better cardiovascular profile and are also available at a reasonable cost. Treatment with modern SUs is associated with a lower economic burden, and hence they are an effective alternative to other newer antidiabetic drugs[23,24].

It was further observed that 36.4% physician had a view that the switching was having very good efficacy, followed by 28.2% physician having a view of excellent efficacy as is evident from Figure 6. This is in line with a recent retrospective, nonrandomized, noncomparative, multicentric real-world study which showed that glimepiride and metformin combinations are frequently prescribed in diabetes with comorbidities like hypertension and dyslipidemia and complications for the best glycemic control[25].

Most of the global bodies and guidelines advise metformin and changes in the lifestyle for treating newly *diagnosed* T2DM, with variations mainly in the second- and third-line antidiabetic agents[26,27]. It was seen that 86.7% of the participating patients adhered to proper lifestyle changes as seen in Figure 7. The study also found that vildagliptin (50%) was the most common DPP4i being prescribed, along with metformin to the patient before switching to glimepiride/metformin. It was followed by sitagliptin (30.2%) as is observed from Figure 8 below.

Vildagliptin is a potent and selective inhibitor of DPP-4. It enhances glycemic control by increasing the responsiveness of both islet alpha-cells and beta-cells to glucose. When used in combination with metformin, pioglitazone, glimepiride, or insulin, vildagliptin leads to significant additional reductions in HbA1c levels in patients. Moreover, it has been found to reduce the occurrence of hypoglycemic episodes when added to insulin therapy. Preliminary findings suggest that the enhanced function of islet cells, which contributes to the effectiveness of vildagliptin in treating T2D, is also evident in individuals with impaired glucose tolerance. Vildagliptin treatment in such cases results in decreased fluctuations in blood sugar levels[28].

Besides being an antidiabetic drug vildagliptin also possesses a number of other pharmacological features, such as neuroprotective benefits *in vivo* and *in vitro* models[29].

Vildagliptin also causes a dosage-related reduction in HbA1c and FPG when added to a steady dose of metformin. Furthermore, metformin increases vildagliptin's ability to boost plasma levels of intact glucagon-like peptide-1 (GLP-1), which is one of the main ways that vildagliptin's therapeutic effects are mediated via GLP-1[30]. The above factors make vildagliptin a good candidate to top the list of DPP4i, which are generally prescribed along with glimepiride/metformin combination.

Vildagliptin and metformin were observed to significantly lower plasma glucose and HbA1c when taken once daily, suggesting that this regimen may be a more practical and affordable beginning point for treatment than a twice-daily regimen[31].

Hence, in the current study also OD (once a day) dose was the most prevalent (64.5%) dose of DPP4i being prescribed by the physicians, followed by BD (twice a day) with 35.5% as seen on Figure 9. The median dose of DPP4i used was found to be 50 with IQR of 30. More specifically, the median dose of glimepiride used was 1 with IQR of (1.5) and the median dose of metformin used was 500 with IQR of 350. Vildagliptin, when used as add-on therapy to metformin, improved Chinese patients' glycemic control and was well-

tolerated[32]. Further, a study found that individuals with T2DM who had poor glycemic control benefited from adding vildagliptin to their regimen of metformin and glimepiride[33]. A similar observation was seen in the present study.

DPP4i was being prescribed in patients as add-on to metformin was highest (69.2%), followed by first-line combination therapy with metformin (30.5%) as seen in Figure 10.

In the current study, a significant decrease in the FBG, PPG, and HbA1c was observed, which is in similar lines with the findings by Phung et al (2010), Hassan and Abd-Allah (2015), Kumar (2021), Shrivastava et al (2023)[20,34-36].

The most important reason for switching to glimepiride/metformin was found to improve HbA1c (71.7%), followed by aiming to control the uncontrolled glycemia accounting for 49.5% of patients, to improve FPG (34.9%), to improve PPG (26.4%), cost-effectiveness (10.7%), less adverse effects (3%), and other factors accounted for only 0.4% as is evident from Figure 11.

Numerous studies have demonstrated that incorporating glimepiride into the treatment regimen of T2D patients who were not achieving adequate glycemic control with metformin alone led to improved blood sugar management. Furthermore, the concurrent administration of glimepiride and metformin in a single medication form proved to be both effective and safe for individuals with T2D[37-39].

A study found that in T2D patients whose condition was not properly managed by low-dose metformin monotherapy, glimepiride/metformin fixed-dose combination treatment was more successful in glucose control than metformin uptitration and was well-tolerated[40].

This study also reported that only 5.2% of patients ($p < 0.001$) experienced hypoglycemia after switching to glimepiride/metformin combination. The combination of glimepiride/metformin achieves good glycemic control and tolerability. In a recent investigation, Prasanna Kumar et al similarly reported findings indicating that the majority of patients experienced a high level of effectiveness and tolerability, with rates reaching 97.3% and 96.6%, respectively[41].

In another worldwide prospective research it was found that diabetic individuals on glimepiride experienced fewer hypoglycemia episodes than those taking glibenclamide[42]. Glimepiride is a desirable choice for the management of people with long-term diabetes due to its shown cardiovascular safety/neutrality and decreased hypoglycemic episodes[43]. Modern SUs have better cardiovascular profiles, greater glycemic effectiveness, and are also reasonably priced. Modern SUs are an efficient alternative to other more recent antidiabetic medications since they are connected with a smaller financial burden during treatment[23]. According to a research by Barnett et al (2015), metformin plus SU, thiazolidinedione, or sodium glucose co-transporter 2 (SGLT2) inhibitor medication were typically well-tolerated and improved glycemic parameters when combined with a DPP4i[44].

Decisions regarding treatment are determined by considering factors such as the effectiveness of glycemic control, safety profiles, and the impact of the therapy on weight and the risk of hypoglycemia, existing comorbidities, and treatment costs. Switching to modern SU/metformin in patients uncontrolled on DPP4i-based therapies was an beneficial alternative for diabetes management.

Limitations

As the study was a multicenter observational survey it had limitations such as selection and response bias. Diverse patient populations across centers made the generalization difficult.

Conclusion

The retrospective clinical evidence has shed light on the clinical outcomes associated with transitioning patients from DPP4i-based therapies to modern SU/metformin combinations.

The study found that the transition to modern SU/metformin combinations in DPP4i-uncontrolled patients carries significant implications for diabetes management. It could play a crucial role in informing treatment paradigms. The transition provides an alternative treatment option in addressing inadequate glycemic control with DPP4i-based therapies and thus improves diabetes care, enhancing the quality of life for patients facing the challenges of diabetes management.

Major Findings

- Switching to modern SU/metformin showed significant improvement in the HbA1c values and FPG and PPG levels and were controlled well.
- Majority (94.8%) of patients had no hypoglycemic events and 96.2% did not gain weight after switching to SU/metformin.
- Vildagliptin (50%) was the most common DPP4i being prescribed, followed by sitagliptin (30.2%).

- The main reason of switching to SU/metformin was to improve the HbA1c levels, followed by controlling the uncontrolled glycemic levels and further improving FPG and PPG levels.
- Transitioning to SU and metformin combo is an effective choice for diabetes when DPP4i fall short.

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CONSENSUS STUDY

Expert Consensus on Effective Utilization of Patient-Centered Insulin Therapy in Nepal

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ABSTRACT

Diabetes presents a significant public health challenge in Nepal, compounded by its diverse topography and cultural beliefs. Despite a historical emphasis on patient-centered care, which fosters unity among physician, patient, drug, and caretaker, effective diabetes management is hindered by lack of awareness, cultural preferences for alternative therapies, and limited health care resources. Addressing these challenges requires a consensus to optimize insulin's historical significance, marking a century as the first antidiabetic agent. Although advancements have been made, a gap persists in understanding, awareness, and utilization of insulin among Nepalese physicians, necessitating tailored management approaches. A consensus meeting of leading experts and diverse advisors from Nepal highlights the need for collective guidelines to optimize insulin usage. Nepalese patients often exhibit reluctance towards insulin therapy, stemming from concerns about its complexity and efficacy. Blood glucose monitoring is vital for guiding insulin regimens, especially in critically ill patients, with the SECURE model offering a comprehensive management approach. Tailoring insulin regimens to individual lifestyles enhances treatment adherence and overall efficacy. A patient-centered approach is paramount in optimizing diabetes management in Nepal. Through collective agreement and guidelines, health care professionals can improve their knowledge and confidence in insulin therapy, leading to better patient outcomes and public health.

Keywords: Type 2 diabetes mellitus, insulin, patient-centered, Nepal

Introduction

Diabetes is recognized as a serious public health concern with a considerable impact on human life and health expenditures. Rapid economic development and urbanization have led to a rising burden of diabetes in many parts of the world. According to the 2021

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report by the International Diabetes Federation (IDF), a staggering 537 million adults globally were affected by diabetes, with 79.4% of cases concentrated in these lower-income countries, impacting individuals aged 20 to 79 years[1]. In Southeast Asia, the prevalence of diabetes was 8.8% in 2019, and it's expected to increase to 9.7% by 2030[2].

In Nepal, diabetes ranks as the third most common noncommunicable disease, with a prevalence ranging from 6.3% to 25.9%[3]. The country's diverse topography, spanning from the fertile Gangetic plains to the frozen Himalayan mountains, presents unique challenges in addressing diabetes. Due to this diversity, tailored approaches are required for different regions[4]. Additionally, the prevalence of type 2 diabetes mellitus (T2DM), prediabetes and impaired glucose tolerance stands at 10%, 19.4%, and 11% respectively[5].

Cases of type 1 diabetes mellitus (T1DM) in Nepal have increased significantly from 154.53 cases per 100,000 population in 1990 to 201.99 cases per 100,000 population in 2019[6]. The country's geographical diversity results in a wide range of climates, from scorching temperatures exceeding 45°C in the Tarai plains to alpine climates with temperatures below -30°C in the northern Himalayan region. Insulin emerges as the cornerstone of medical management for T1DM and is also utilized in individuals with uncontrolled T2DM, even when optimal oral antidiabetic drugs are being used. Customized strategies are necessary to navigate the challenges of diabetes across these varied regions and meet the specific needs of each area[4].

The concept of patient-centered care, as emphasized in recent diabetes guidelines, resonates deeply with ancient practices rooted in Indian history. While the term itself may be modern, the essence of patient-centered care can be traced back centuries. The famous Ayurvedic physician Atreya described the quadruple, which suggests that the patient is an integral part of the four equally important "angles" required for effective treatment. The other three angles mentioned by Atreya are the physician, the drug, and the attendant[7]. The quadruple concept of Atreya is culturally relevant to Nepal which emphasizes the necessity of unity among physician, patient, drug, and caretaker. Person-centered care prioritizes the individual with the disease, necessitating effective communication for cohesive teamwork. In Nepal, health care providers must ensure clear information for individuals with diabetes, empowering them in health care decisions. This approach improves outcomes and acknowledges unique circumstances. Beyond medical and nursing personnel, responsibility extends to family, policymakers, and civil society, forming a comprehensive strategy for managing diabetes[8,9]. Addressing the challenge of diabetes management in Nepal is undeniably complex due to a range of contributing factors.

Need for Consensus

The need for a consensus is to optimize the historical significance of insulin as the first antidiabetic agent available for 100 years. From its initial poorly defined extracts of animal pancreatic origin, insulin has evolved into pure and precisely controlled formulations designed to mimic physiological insulin release patterns. Despite these advancements, there remains a considerable grey area concerning the understanding, awareness, and utilization of insulin among practicing physicians in Nepal. Also, looking at the diverse lifestyles and landscapes of Nepal, there is a need for tailored approaches to the management of diabetes in different regions. To optimize diabetes management and ensure better patient outcomes, a collective agreement and guidelines on the appropriate use of insulin are imperative. This consensus will foster improved knowledge and confidence among health care professionals, leading to more effective and patient-centric insulin therapy in Nepal.

Methodology

A group of endocrinologists and diabetes specialists in Nepal held a focused board meeting to discuss the person-centered insulin approach for the management of diabetes mellitus. The meeting was moderated by leading endocrinologists from India and a panel of advisors across Nepal.

Role and Importance of Insulin in the Management of Diabetes Mellitus

The lack of awareness and understanding about diabetes within the community, along with a reluctance to adopt medication or advance treatment, pose significant hurdles. Additionally, preference for alternative therapies and limited health care resources exacerbate these challenges. The inadequate availability of diagnostic and laboratory facilities compounds these issues. Cultural beliefs surrounding treatment greatly influence patients' adherence to prescribed regimens, often deeply rooted in Nepalese society's sociocultural context. Limited exploration of specific sociocultural traditions and beliefs related to diabetes treatment further complicates matters[10]. Research reveals that Nepalese patients perceive antidiabetic medications as

potentially harmful and irreversible, impacting their willingness to initiate treatment and compromising adherence[11]. To effectively address patients' needs, a fundamental shift in the approach to diabetes management and attitudes toward insulin use is crucial. Reluctance to incorporate insulin therapy stems from perceived complexity, doubts about efficacy, and concerns regarding hypoglycemic episodes and weight gain[12].

Insulin therapy is vital for managing diabetes, particularly in T1DM, where lifelong replacement therapy is essential. Treatment options include multiple daily injections or continuous subcutaneous insulin infusion[13].

For newly diagnosed T2DM patients, initial treatment often involves dietary adjustments, exercise, and oral medications, but insulin may be necessary if blood sugar levels remain uncontrolled[14].

The American Association of Clinical Endocrinologists recommends considering insulin when A1c levels are >9% or when oral therapy fails. Insulin helps restore beta cells and can be used alone or with oral medications, especially for hospitalized or critically ill patients and those with end-stage liver disease or liver failure[15]. Insulin glargine is commonly prescribed and helps preserve beta-cell function when initiated early[16]. (Table 1 and 2).

Benefits of Early Initiation and Intensification

- Insulin is clearly the most effective way to control blood glucose.
- Better glycemic control to reduce the incidence and severity of long-term vascular outcomes.
- Early insulin supplementation may alter the progressive course of diabetes.
- Restores the function of beta cells and significantly reduces insulin resistance.
- Early initiation of insulin therapy improves beta-cell function and mass by inducing 'beta-cell rest'.

When to Initiate Insulin?

In managing diabetes, glycemic treatment should follow a stepwise approach, swiftly introducing successive interventions after treatment failure (A1c ≥10%). Initiation of insulin is recommended when A1c reaches ≥10% after 2-3 months of dual oral therapy, with once-daily basal insulin being the preferred regimen. Timely initiation and rapid titration of the insulin dose are crucial for successful therapy, and the risk of hypoglycemia is low in patients starting insulin therapy, making Neutral Protamine Hagedorn (NPH) insulin the most cost-effective option. If glycemic goals are still not achieved despite successful basal insulin titration (fasting plasma glucose ≤100 mg/dL) or if titration is

Table 1. Types of Insulin Available in Nepal

Long acting	Intermediate acting	Short acting	Rapid acting	Premixed insulin	
				Human insulin	Analogues
Insulin Glargine			Insulin Lispro	30/70 Regular/NPH	Insulin Degludec + Insulin Aspart
Insulin detemir			Insulin Glulisine	50/50 Regular/NPH	Insulin Aspart Biphasic
	Insulin (Human) NPH	Insulin (Human) Regular			30/70 Biphasic Aspart/Aspart protamine
Insulin Degludec			Insulin Aspart		50/50 Biphasic Aspart/Aspart protamine
					25/75 Biphasic Lispro/Lispro protamine
					50/50 Biphasic Lispro/Lispro protamine

NPH: Neutral protamine hagedorn

Table 2. List of Available Insulin Delivery Devices and Glucose Monitoring tools in Nepal

Insulin pen	Glucose monitoring tools
• Lupisulin pen	• POC assessment tools like one touch/Morepen's
• Basugine Pen	• On call plus
• Humalog pen	• Accu-Chek
• Levemir Flexpen	• VivaChek
• Ryzodeg pen	• Clever chek Sinocare
• Novomix pen	• Gluco One
• NovoRapid pen	
• Sanofi Allstar	

POC: Point-of-care

limited by hypoglycemia, treatment intensification is needed, involving the addition of prandial or biphasic insulin to the regimen[17]. (Fig 1)

Ethnic Differences in Nepalese Patients are Based on Diet and Lifestyle

The sociocultural traditions and beliefs of Nepal and the Nepalese population have not been extensively explored in relation to diabetes treatment[10].

Diet Pattern

In Nepal, the traditional eating patterns involve two main meals at around 9 am and 6 pm, accompanied by small snacks and tea in between. However, Nepal is witnessing dietary changes akin to the high-fat, high-sugar, and high-meat consumption patterns prevalent in Western countries. The consumption of refined grains, meat, and alcohol is linked to a higher prevalence of overweight, while fast food intake is associated with a higher prevalence of obesity in older adults (40 years and above)[18].

Contribution of FPG/PPG to HbA1c

Optimal glycemic control is paramount in diabetes management. Measurement of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) assesses glucose control. Although HbA1c is the gold standard, its cost limits accessibility in resource-constrained settings. In such cases, estimating postprandial and fasting glucose gains importance, especially in developing countries, to evaluate glycemic control[19].

In diabetes screening, dipstick kits are initially used for qualitative assessment of glucosuria, but their lack of quantitative precision necessitates confirmation through laboratory testing of urine glucose and HbA1c levels. These quantitative measures provide more accurate insights into glycemic control and guide health care providers in diagnosis, treatment, and monitoring strategies for diabetes management. Therefore, while dipstick kits serve as valuable initial indicators, reliance on laboratory reports ensures thorough evaluation and appropriate intervention in diabetes care[20].

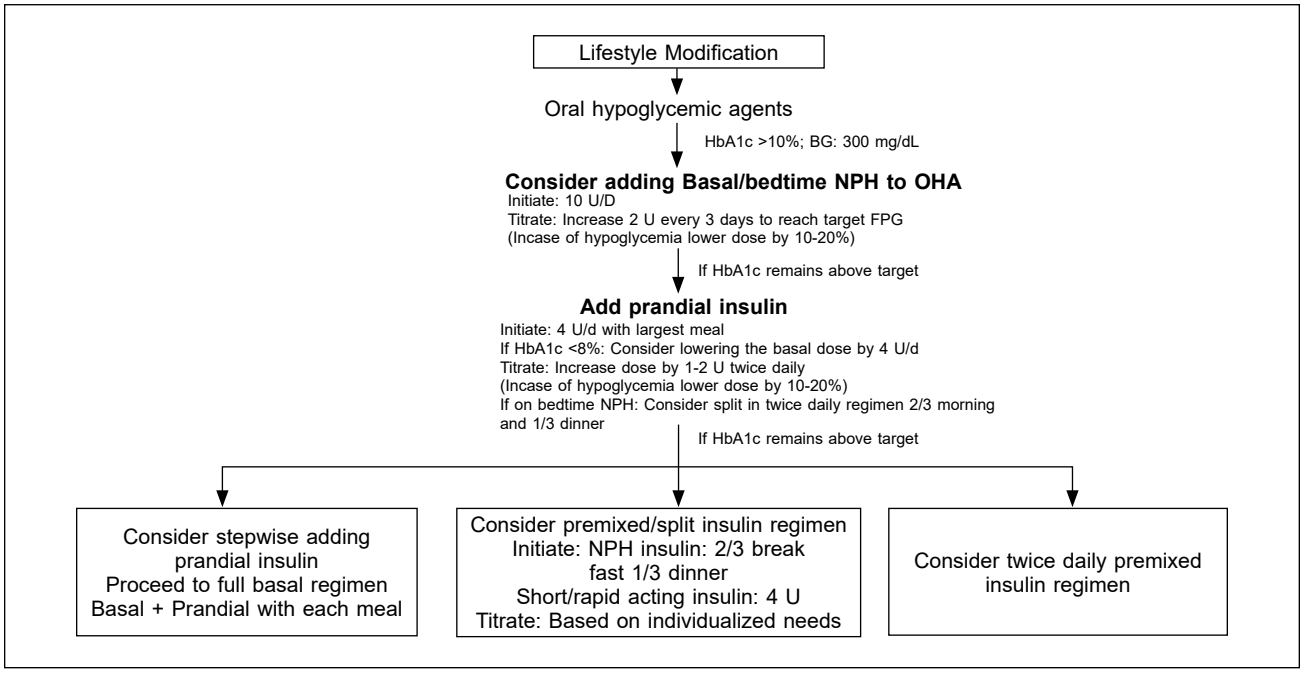

Figure 1. Approaches for initiating insulin.

Lifestyle Factors

Nepal's predominant agrarian nature entails a significant portion of its population engaging in labor-intensive occupations. The national living standard survey highlights this by revealing that approximately 80% of Nepal's populace resides in rural regions, where limited access to motor vehicle transportation infrastructure makes walking a prevalent mode of daily commuting[21].

Considering the diverse challenges posed by diabetes management and the extensive applications of insulin therapies, the following patient-centered recommendations have been formulated to guide health care professionals in navigating the complexities of treatment.

Expert Recommendations

Management of Diabetes has Moved from Glucocentrica to Patient Centric Approach

Panel Discussion: Insulin therapy plays a crucial role in maintaining glycemic control. According to experts, premixed insulins, favored for their balance of effectiveness and patient convenience, are particularly suitable for Asian patients with high-carbohydrate diets. Analog premixed variants offer faster onset and extended duration compared to conventional versions. Human insulin 70/30 and Lispro mix 25 provide flexibility and prolonged action. Insulin glargine stands out for its consistent 24-hour activity with a single injection, making it the most prescribed long-acting insulin analogue, offering patients safe, effective, and potentially cost-efficient treatment options.

Consensus 1: A person-centered approach should be used to optimize management of diabetes.

Evidence: Choosing pharmacologic agents for T2DM management should prioritize a person-centered approach, considering individual factors. For those with fasting hyperglycemia, bedtime basal insulin or premixed injections before dinner are options, while postprandial hyperglycemia may benefit from a breakfast dose. Consistent high glycemic levels may require a two- or three-dose premixed regimen influenced by dietary habits. High-carb meal consumers may respond better to high-mix formulations, while those prone to hypoglycemia may prefer low-mix formulations, especially analogues. Counseling individuals on premixed insulin should include advice to avoid vigorous physical activity within 2-3 hours of injection[22,23].

A systemic review indicated similar clinical efficacy and safety of Glargine compared to its reference products, making biosimilars viable alternatives for insulin therapy in both type 1 and type 2 diabetes patients[24,25]. Evidence suggests that increased use of biosimilar insulin may reduce costs for consumers, with a Canadian study projecting substantial potential savings compared to the originator. Furthermore, the introduction of biosimilar insulin was linked to reduced reimbursement, indicating increased market competition and lower insulin costs[26].

Choice of Insulin Based on Glycemic Parameters

Panel discussion: Basal insulin effectively controls FBG levels, while rapid-acting insulin is necessary for elevated PPG levels. As basal insulin aligns with FBG control, FBG levels can be an objective marker for insulin therapy determination[27]. A high FBG level suggests a basal insulin regimen, whereas relatively normal FBG levels, despite uncontrolled HbA1c, may prompt consideration of alternative treatments. However, relying solely on FBG has limitations as it doesn't assess postprandial hyperglycemia. When choosing between basal and basal-bolus insulin regimens, FBG, PPG, and HbA1c should be considered[28]. With its safer peak-less glycemic profile, insulin glargine is suitable for aggressive treatment regimens, potentially helping more patients achieve tight glycemic control as current guidelines recommend. (Table 3)

Consensus 2: Insulin therapy to be considered at any stage under specific circumstances. Periodic evaluation of clinical factors is crucial before initiating and titrating insulin to mitigate the risk of hypoglycemia.

Evidence: Basal insulin is more effective in managing fasting glycemia than prandial insulin, aligning with its fundamental pharmacology. Elevated FPG levels are recommended for prescribing basal insulin, whereas relatively normal FPG levels amidst uncontrolled HbA1c might suggest alternative approaches. High PPG levels indicate rapid-acting insulin requirement integrated into premixed, prandial, or basal-bolus regimens. Timing injections based on PPG peaks after meals can guide treatment. For instance, once-daily premixed insulin aligns with the meal, causing the highest PPG surge. Similar considerations apply to the bolus component of basal plus regimes. Basal-bolus protocols suit 'very high' HbA1c levels, while lower-dose regimens suffice for 'less high' HbA1c cases[29].

In a randomized controlled trial on T2DM patients, researchers compared once-daily and twice-daily intermediate-acting insulin (Neutral Protamine Hagedorn

Table 3. Choice of Insulin Based on Clinical Factors

Clinical factor	Basal	Premix	Intensive
Fasting hyperglycemia	++	+	++
Postprandial hyperglycemia	-	+	++
Both fasting and postprandial hyperglycemia	-	++	++
High HbA1c (>8.5%)	-	++	++
Low HbA1c (<8.5%)	+	++	-

HbA1c: Hemoglobin A1c

insulin) with or without oral drugs. Subjects with a ratio of ≥1.3 (observed in 60% of participants), indicative of fasting hyperglycemia dominance, exhibited similar responses across all four studied regimes. Those with a lower ratio (<1.3), suggestive of overall hyperglycemia, responded better to twice-daily insulin[30].

Strategies for Selection of Insulin in Nepalese Patients

SECURE Model

Panel discussion: The SECURE model highlights six critical factors for personalized glucose-lowering treatment and glycemic targets. Insulin analogs, like Lispro and glulisine, improve postprandial glucose control and reduce hypoglycemia risk in CKD patients. Dosing varies for different insulins based on estimated glomerular filtration rate (eGFR) stages, with glargine showing a lower hypoglycemia risk than NPH insulin. Detemir offers continuous coverage with twice-daily dosing, while newer glargine formulation minimizes hypoglycemia. Degludec insulin presents potential cognitive benefits with fewer hypoglycemic incidents. Overall, long-acting analogs detemir and glargine are preferred for better control and lower severe hypoglycemia, while human insulins suit those with cost constraints. Over the last decade, insulin glargine has become a standard of care in diabetes treatment in Nepal due to its well-established safety and efficacy profiles. (Table 4)

Consensus 3: SECURE model proposes a holistic and comprehensive approach to hyperglycemia management particularly in ill patients.

Evidence: Insulin analogs, such as lispro and glulisine, demonstrate reduced hypoglycemia risk and improved postprandial glucose control, which is particularly beneficial for chronic kidney disease (CKD) patients due to faster absorption[31]. Comparing prandial insulins, both lispro, and glulisine effectively suppressed postprandial hyperglycemia in comparison to regular insulin.

The dosing of aspart did not exhibit significant differences across various stages of eGFR (<60 mL/min, 60-80 mL/min, >90 mL/min). However, there was a notable decrease in lispro and human insulin doses among patients with eGFR <60 mL/min[32]. Insulin glargine demonstrates a reduced risk of nocturnal and overall hypoglycemia compared to NPH insulin, primarily attributed to the peak in action occurring 4-10 hours after NPH insulin administration. Nonetheless, NPH insulin remains a cost-effective choice for basal insulin[33].

Insulin detemir, at lower doses, requires twice-daily dosing for continuous coverage with no significant peak in action. The newer formulation of insulin glargine (300 units/mL) shows a lower hypoglycemia risk compared to the U-100 glargine (100 units/mL) formulation[34,35]. Human insulins offer advantages for individuals with cognitive impairment and are suitable for those pursuing less intensive A1c goals or facing insulin resistance and cost concerns. This is particularly relevant for type 1 diabetes patients who may not afford insulin analogs, including biosimilars[36].

Biopsychosocial Model

Panel discussion: Flexibility in insulin management, in line with the biopsychosocial model of health care, considers the individual's physical, psychological, and social aspects. Basal insulins, like glargine and degludec, offer simplicity and flexibility with one injection per day, allowing lifestyle freedom. Rapid-acting analogs provide greater flexibility with a shorter injection-meal gap.

Dual-action insulins, such as premixed insulins, offer some flexibility in injection timing but may have limitations in dose titration. Mastering basic skills enables the flexible use of premixed insulins despite their complexity. A number-based taxonomy approach encompasses traditional and newly developed insulin regimes, providing a comprehensive framework for classification. (Table 5)

Consensus 4: Tailoring insulin regimens to individual lifestyles optimizes diabetes management and enhances treatment adherence.

Evidence: Studies have shown that people with diabetes face various challenges in managing their condition and desire greater involvement in their care. Flexibility in insulin management responds to patient needs and convenience, consistent with the principles of person-centered care, which aims to tailor treatment plans to the individual's unique circumstances and preferences[37]. Basal insulin regimens are considered

Table 4. Choice of Insulin Based on the SECURE Model

SECURE Model	Choice of insulin	Benefits
Severity	Analogue insulin (Degludec + Aspart, Aspart)	Low-risk of hypoglycemia in CKD patients
		Better PPG control with faster absorption
	Rapid-acting (Lispro, Glulisine)	No change in PK parameters in CKD patients
	Basal insulin (Glargine)	Rapid HbA1c reduction, stable half-life, and longer duration of action in patients with renal failure
Expected prognosis	Basal insulin (Glargine, Detemir, Degludec)	Choice for obese patients with T2DM
Concomitant medication	Short-acting insulin (Regular human)	In patients with significant hyperglycemia or impaired health status after GC administration
	Rapid-acting insulin (Lispro, Glulisine, Aspart)	Hydrocortisone is usually administered twice or thrice daily, (multiple doses might be suitable to improve glycemic control)
Urgency of control	Basal bolus (Glargine, Detemir, Degludec)	It can be given to patients with type 1 diabetes or life-, organ-, or limb-threatening complications
Risk of hypoglycemia	Long-acting insulin (Detemir, Glargine)	In patients with more advanced cognitive dysfunction or dementia, it may be best to implement a regimen using a dose that will not cause hypoglycemia combined with conservative fixed mealtime doses that are given immediately after a patient has eaten an adequate meal.
Environmental factors	Long-acting insulin (Detemir, Glargine)	Both insulin detemir and glargine are cost-effective compared to NPH insulin for T2DM patients, especially when the benefit of reducing the hypoglycemia event rate is considered.

CKD: Chronic kidney disease; GC: Glucocorticoids; NPH: Neutral protamine hagedorn; PPG: Postprandial glucose; T2DM: Type 2 diabetes mellitus.

Table 5. Choice of Insulin Based on Psychosocial Factors

Psychosocial factor	Basal	Premix	Intensive
Inability to have regular meal	+	+	-
Inability to self-monitor/self-administration	+	+	-
Inability to remain in regular touch with the diabetes care team	+	+	-
Psychosocial factors	+	+	-
Poor family support and acceptance	+	+	-
Low personal acceptance of insulin	+	+	-

for their simplicity, minimal intrusion, and adaptability. They involve just one daily injection, don't necessitate strict meal adherence, and offer lifestyle flexibility[38]. While Neutral Protamine Hagedorn insulin is best taken with a snack, basal analogs can be administered without considering mealtimes. Human regular insulin should be given 30 minutes before a meal, whereas rapid-acting analogs like aspart, glulisine, and lispro offer a shorter injection-meal gap and can be injected 5 minutes before or after a meal without compromising effectiveness. Human premixed insulins require a 30-minute premeal injection, while premixed insulin analogs can be taken 5 minutes before or immediately after a meal[39]. Insulin coformulations, such as human insulin 30/70 and lispro mix 25, offer flexibility in adjusting administration timing[37,40].

Choice of Insulin in Special Condition

Panel discussion: In critically ill patients, continuous intravenous insulin is preferred, while noncritically ill patients with regular meals may receive basal and correction insulin doses. A basal plus bolus correction insulin regimen is recommended for noncritically ill patients with good nutritional intake. Sliding scale insulin is advised against in the inpatient hospital setting. Basal insulin is widely recommended for transitioning from intravenous to subcutaneous insulin therapy and maintaining glucose control. Once-daily glargine insulin offers practicality and simplicity, making it a convenient initiation strategy. Glargine insulin suits various treatment intensities, providing

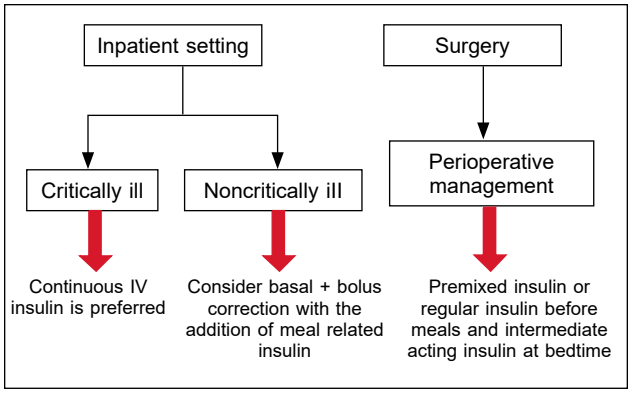

Figure 2. Choice of insulin in special condition.

regimen flexibility for patient convenience. Early insulin introduction in type 2 diabetes patients is encouraged. (Fig 2)

Consensus 5: In both critically ill and noncritically ill patients, when blood glucose levels reach 80 mg/dL, initiating insulin therapy is essential for addressing persistent hyperglycemia.

Evidence: For noncritically ill patients with good nutritional intake, a combination of basal, meal-related, and correction insulin doses is preferred. Subcutaneous rapid- or short-acting insulin can be administered before meals or every 4-6 hours to correct hyperglycemia in patients not on regular meals or receiving continuous enteral/parenteral nutrition, for noncritically ill patients with poor oral intake or those not taking anything by mouth, basal insulin or basal plus bolus correction insulin regimen is preferred over sliding scale insulin due to better glycemic control and reduced hospital complications. In the outpatient setting, premixed insulin is preferred, while in the inpatient setting, basal-bolus therapy is recommended. When transitioning patients with T1DM or T2DM to the outpatient setting, subcutaneous insulin should be started, with basal insulin initiated 2-4 hours before discontinuing IV insulin to facilitate a smooth transition[29]. For patients with T1DM and T2DM undergoing surgery, long-acting insulin (glargine) should be discontinued 2-3 days before the procedure. For glycemic control during the perioperative period, a combination of intermediate-acting insulin (NPH) with short—or rapid-acting insulin administered twice daily or regular insulin before meals, along with intermediate-acting insulin at bedtime[41,42].

Storage of Insulin Based on Geographical Conditions in Nepal

Panel discussion: Addressing the unique challenges of insulin storage in Nepal necessitates locally relevant and improvised solutions. Ideally, insulin should be stored in a refrigerator between 2 and 8°C and protected from light when unopened. In hot regions like Terai, mud pots with sand and water contraptions can keep insulin cool, while in cold areas, community storage rooms or insulated flasks are suitable. Patients are advised to wrap insulin in warm woolen cloth and store it in wooden or steel cupboards, considering frequent power cuts. Opened vials can be stored at room temperature (15-30°C) for 4 to 6 weeks or in a refrigerator (2-8°C) until expiry, but insulin should never be frozen. (Fig 3)

Limited access to medical services and dietary patterns poses challenges at higher altitudes. Extreme temperatures and difficulty in accessing and storing insulin are concerns. Various items like abdominal binders made from wool and yak, repurposed transceiver bags, homemade fleece bags, and foam pouches are used for storage and transport. Altitude may affect glycemic control, causing delayed carbohydrate absorption and potential postprandial hypoglycemia above 5000 meters. Adjustments to insulin dosages may be needed due to carbohydrate-rich diets. Glucometer readings may be slightly inaccurate at high altitudes, but their clinical significance is minimal.

Consensus 6: Proper storage of insulin is essential for Nepalese patients to ensure effective management of diabetes.

Evidence: In Nepal, where outdoor temperatures drop as low as -30°C and indoor temperatures vary between 4 to 20°C due to heating methods like burning iron stoves, maintaining appropriate storage conditions for insulin becomes a significant concern since access to health care facilities and supplies is limited. Extreme heat in living rooms and freezing temperatures in adjacent rooms make it challenging to find suitable storage locations. In warmer regions of Nepal like the Terai, where room temperatures often go above 25°C, insulin storage is a concern. Studies indicate that storing insulin (regular and biphasic) at 32°C and 37°C for 28 days leads to a 14-18% potency decrease. Moreover, it's advised not to refrigerate opened insulin cartridges installed in insulin pens[43,44].

Disposal Strategies for Insulin

Panel discussion: Proper disposal of needles and cartridges aligns with the National biomedical waste guidelines for responsible medical waste management, ensuring safe practices. Glucose monitoring sticks and similar solid waste items are disposed of in yellow non-chlorinated bags, offering flexibility while maintaining safety. Disposable insulin pens, especially after removing pen needles, should be appropriately disposed of to ensure individual safety and proper medical waste handling. Transportation of biomedical waste strictly follows guidelines, using

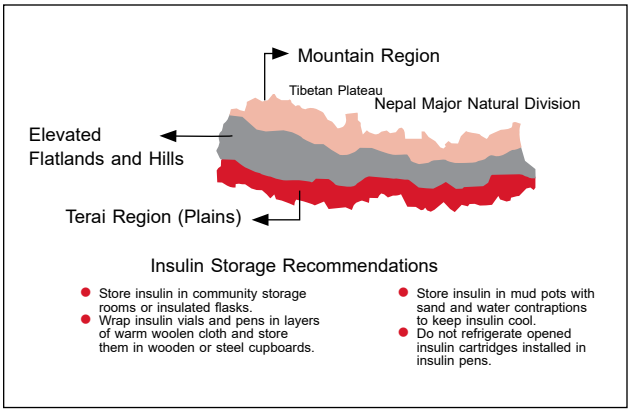

Figure 3. Insulin storage recommendations across different regions of Nepal.

authorized vehicles and safety protocols to minimize risks. To ensure timely and secure handling, storage of biomedical waste items, including those contaminated with blood and body fluids, should not exceed 48 hours without treatment.

Implementation of these measures ensures safe and effective insulin management, considering Nepal's environmental conditions and resources. Needles can be collected in narrow-mouth containers to prevent children from accessing them and discarded in biomedical waste centers. Patients should receive awareness regarding the disposal of single-use pens, cartridges, and needles from health care providers. Adopting vaccine vial monitor (VVM) technology is crucial for safeguarding insulin quality, as it changes color if a specific threshold is reached.

Consensus 7: Proper insulin disposal strategies are essential for Nepalese patients to safeguard public health and the environment.

Evidence: A survey in Nepal highlights concerning trends among diabetes patients, with many failing to adhere to proper insulin-related waste disposal practices. Approximately half of the surveyed participants reported disposing of used needles in bins, while others resorted to discarding them in isolated areas or burning them.

One patient even stored used needles in a plastic container inside their refrigerator for 3 months. These findings underscore the urgent need for enhanced awareness and education on safe insulin disposal methods in the Nepalese diabetes patient community[45].

Additionally, Nepalese patients often perceive insulin treatment as a last resort. Improper disposal practices for used needles were widespread, including handing them over to municipal waste disposal services or discarding them in isolated locations. Lack of awareness and regulatory requirements contribute to these practices[46].

Exposure to high temperatures can reduce insulin potency, with storage at 32-37°C causing a 14-18% potency loss. It's suggested that insulin manufacturers adopt cost-effective technology using VVM. It is a thermochromic label on vaccine vials that changes color to indicate temperature exposure beyond recommended levels, jeopardizing vaccine potency.

This technology, effective in the polio eradication program in India, can be scaled up, benefiting insulin storage and preserving its effectiveness, as recognized by the World Health Organization[47].

Diabetes Awareness and Prevention Strategies

Strategies beyond diabetes education are recommended to address insulin distress and improve self-management practices. Strengthening communication between physicians and patients, enhancing coping skills, and implementing motivational measures are suggested. These recommendations aim to enhance diabetes self-management, provide education and counseling, and offer emotional support to individuals with diabetes[48,49]. (Table 6 and 7)

Final Consensus Statements

- A person-centered approach should be used to optimize management of diabetes.
- Blood glucose monitoring is an integral part of insulin therapy, providing essential guidance for tailoring regimens.
- SECURE model proposes a holistic and comprehensive approach to hyperglycemia management particularly in ill patients.
- Tailoring insulin regimens to individual lifestyles optimizes diabetes management and enhances treatment adherence.
- In both critically ill and non-critically ill patients, when blood glucose levels reach 180 mg/dL, initiating insulin therapy is essential for addressing persistent hyperglycemia.
- Proper storage of insulin is essential for Nepalese patients to ensure effective management of diabetes.
- Proper insulin disposal strategies are essential for Nepalese patients to safeguard public health and the environment.

Table 6. Patient and Physician-oriented Strategies for Awareness and Prevention of Diabetes

Parameter	Physician-oriented	Patient-oriented
Awareness	Organize medical conferences or workshops to update physicians about the latest evidence-based guidelines and advancements in insulin therapy.	Conduct educational campaigns to increase awareness among patients about the importance of insulin therapy for diabetes management.
Adoption	Encourage physicians to proactively discuss and recommend insulin therapy to eligible patients, highlighting its advantages and addressing concerns.	Provide easily understandable information to patients about the benefits and necessity of insulin therapy, addressing misconceptions and fears.
Accessibility	Work with health care systems and policymakers to improve the availability of insulin in health care facilities and enhance distribution networks.	Advocate for improved accessibility of insulin, including availability in pharmacies, hospitals, and remote areas, to ensure patients can access it conveniently.
Affordability	Advocate physicians in identifying alternative insulin options or assistance programs for patients who face financial challenges.	Collaborate with insurance companies or government agencies to make insulin more affordable through subsidies, insurance coverage, or price reduction programs.
Acceptability	Offer continuing medical education programs to enhance insulin therapy and pen use understanding.	Demonstrate proper injection techniques and provide tools like pen injectors to make administration easier. Collect patient feedback to identify barriers and opportunities for improvement in insulin acceptability and adherence.

Table 7. Practical Guidance for Choice of Insulin

Parameter	Patient profile	Choice of insulin		
		Basal (Glargine, detemir, degludec, neutral protamine hagedorn (NPH) insulin)		**Prandial (Aspart, glulisine, lispro, regular insulin)**
Duration of diabetes/ uncontrolled hyperglycemia	Longer duration of diabetes and uncontrolled hyperglycemia	✔	±	✔
Symptoms of hyperglycemia	Persons with symptomatic diabetes (polyuria, polydipsia, polyphagia, weight loss, frequent infection)	✔	±	✔
Lifestyle and meal pattern*	High postprandial glucose levels due to the intake of high-carbohydrate meals in large quantity			✔
	Obese Patient with T2DM	✔		
Risk of hypoglycemia	CKD patient with T2DM	✔	±	✔
	Advanced cognitive dysfunction or dementia	✔		
Urgency of control	Diabetic patient with life-, organ-, or limb-threatening complication	✔		
Combination therapy	Inadequacy of multiple drugs that target postprandial glycemia, e.g., sulfonylureas and alpha-glucosidase inhibitors			✔
	Inadequacy of drugs that target both fasting and postprandial glycemia, e.g., DPP4i, GLP1RA and SGLT2i	✔	±	✔

	Inadequacy of basal insulin	✔ Add prandial insulin separately or as part of a dual-action insulin
	Inadequacy of once-daily premixed insulin	Twice daily or more frequent insulin administration
In patient setting	Critically ill	Continuous IV insulin is preferred
	Noncritically ill	Basal + Bolus correction with addition of meal related insulin
Surgery	Perioperative management	Premixed insulin before meals, intermediate acting insulin at bedtime

*Meal pattern (number of meals or snacks per day), relative quantity of meals, their composition (proportion of carbohydrates, glycemic index), and regularity

CKD: Chronic kidney disease; DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP1RA: Glucagon-like peptide-1 receptor agonist; IV: intravenous; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; T2DM: Type 2 diabetes mellitus.

Conclusion

Addressing the complex landscape of diabetes management in Nepal requires a multifaceted approach that acknowledges the country's diverse topography, cultural intricacies, and health care resource limitations. The consensus reached through collaborative efforts among health care professionals, guided by patient-centered principles, is crucial for optimizing insulin therapy and improving diabetes outcomes.

By recognizing the importance of effective communication, tailored treatment regimens, and proper utilization of insulin, health care providers can navigate the challenges posed by diabetes in Nepal more effectively. Moreover, the inclusion of diverse stakeholders, including patients, caregivers, policymakers, and civil society, is essential for implementing comprehensive strategies that address the unique needs of Nepalese communities.

Continued efforts to enhance awareness, promote evidence-based practices, and strengthen health care infrastructure will be pivotal in overcoming barriers to diabetes management in Nepal. Through collective agreement and concerted action, we can strive towards better patient outcomes, improved public health, and a more sustainable approach to diabetes care in Nepal and beyond.

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CLINICAL STUDY

Practice Patterns of Usage of Glimepiride and Metformin FDC Along with Other OADs: A New Age Approach to Diabetes Management in Indians

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ABSTRACT

Background: Diabetes is a progressive disease managed by different oral antidiabetic drugs (OADs) with or without glimepiride/metformin. As diabetes continues to be a significant health concern in India, novel therapeutic strategies are essential to effectively control the disease and improve patient outcomes. New drugs like sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) have intermediate efficacy. Understanding clinicians' prescription patterns is crucial for optimizing treatment strategies for better long-term type 2 diabetes mellitus (T2DM) control. **Methods**: This was a retrospective, multicenter, observational case-based questionnaire study on T2DM patients undergoing pharmacotherapy. It aimed to collect data on clinical utilization patterns of glimepiride and metformin FDC (fixed-dose combination) with other OADs and comorbidities. The study included responses from 500 health care professionals (HCPs) across India. Statistical analysis was performed using SPSS® Version 23.0 software. Independent *t*-test was used to compare the change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glycated hemoglobin (HbA1c) between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. P-value <0.05 was considered statistically significant. **Results**: The study analysis included responses from 500 HCPs. It showed that 6,250 patients received glimepiride/metformin FDC. The HbA1c was found to be 8.81% before treatment, which decreased to 7.75% after treatment. Among the 6,250 patients, 1,704 patients also recieved other OADs, where some patients recieved more thn one OADs. DPP4i was prescribed the most (1,064 patients followed by sodium-glucose cotransporter 2 inhibitors (SGLT2i) (573 patients), pioglitazone (229 patients), alpha-glucosidase inhibitor (AGI) (207 patients), insulin (178 patients), and lastly glucagon-like peptide 1 receptor agonist (GLP1RA) being prescribed in 35 patients along with the combination. Hypoglycemia was observed in very few patients (4.49%). Hypertension was the most prevalent (60.5%) comorbidity in the studied patient population. **Conclusion:** Use of glimepiride and metformin FDC along with other OADs offer optimized glycemic control, promote weight loss, and help to reduce complications in patients with T2DM.

Keywords: Type 2 diabetes mellitus, OADs, glimepiride, metformin, glycemic control, HbA1c

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Introduction

Diabetes has emerged as a global epidemic, affecting millions of people worldwide[1]. The incidence of diabetes has been increasing in South-East Asian countries for at least 20 years, according to the International Diabetes Federation (IDF) 10th edition, and current figures have surpassed all prior projections.

According to a recent study by Kumar et al the prevalence of diabetes was 10.5%, 8.8%, and 9.6%, respectively, in the globe, Southeast Asia, and India in 2021, and it will increase to 12.5%, 11.5%, and 10.9%, respectively, by 2045[2].

India, in particular, has witnessed a significant rise in the prevalence of diabetes over the past few decades, making it a major public health concern. Over 77 million people in India are dealing with diabetes. By 2045, researchers project that number will rise to 134 million[3].

Managing diabetes effectively requires a comprehensive approach, as shown in Figure 1.

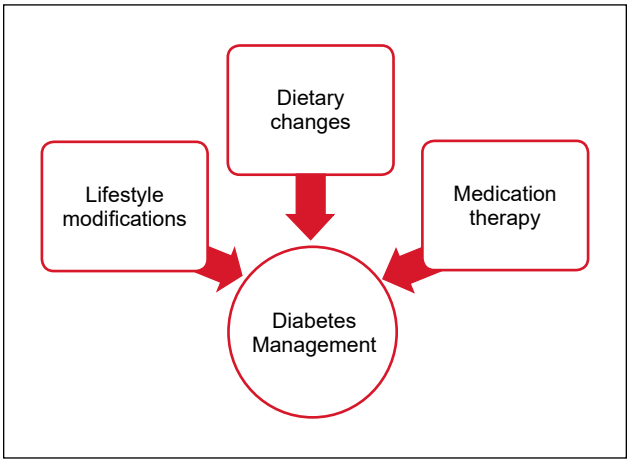

Figure 1. Diabetes management strategies[3].

Among the various treatment options available, oral antidiabetic drugs (OADs) play a crucial role in controlling blood glucose levels and preventing complications. Accordingly, metformin is the recommended first-line diabetes treatment option[4].

The use of modern sulfonylureas (SUs) like glimepiride in type 2 diabetes mellitus (T2DM) management has been advocated by a number of other international organizations, including the World Health Organization (WHO), South Asian Federation of Endocrine Societies (SAFES), IDF, and American Diabetes Association/ European Association[5-8]. The WHO advises using SUs in combination with the first-line therapy among patients who are unable to achieve treatment objectives with first-line oral hypoglycemic medications[9].

Additionally, the modern SUs have significant safety and efficacy profile. A study by Basit et al (2012) have shown that glimepiride is a safer and more affordable option for treating T2DM, as it lowers fasting blood sugar, post-meal glucose, and glycated hemoglobin (HbA1c) levels, without adversely affecting ischemic preconditioning[10]. The evidence of glimepiride's cardiovascular safety from the CAROLINA trial, compared to dipeptidyl peptidase-4 inhibitors (DPP4i), will provide cardiologists with greater confidence to use it in various conditions, including stable coronary artery disease, cerebrovascular disease, and peripheral arterial disease[11]. This article delves into analyzing the usage patterns of one of the most commonly prescribed OADs in India glimepiride and metformin along with other OADs.

Material and Methods

Study Design

The study was a retrospective, multicenter, observational case-based questionnaire survey on T2DM patients undergoing pharmacotherapy. It aimed to collect data on clinical utilization patterns of glimepiride/metformin FDC (fixed-dose combination) with other OADs, demographics, and comorbidities. Independent *t*-test was used to compare the change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. All the reported p-values were two-sided and p-values <0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS® Version 23.0 software.

Study Population

Patients of both sexes, aged above 18 years, diagnosed with T2DM who received glimepiride/metformin and patients with comorbidities who were prescribed medications. T2DM patients below the age of 18 years and who were on monotherapy for T2DM were excluded from the study.

Data Collection

A case report format (CRF) was developed to determine the pattern of use of different strengths of glimepiride/metformin FDCs with or without other oral hypoglycemic agents in diabetes patients. Vital parameters including body mass index (BMI), hypertension, and other comorbidities, T2DM duration, dosage regimens of different OADs and the laboratory glycemic investigations were also included.

A questionnaire was sent to 500 healthcare professionals in India via an online portal for a descriptive analysis.

Data was collected digitally from clinicians through digitized CRF, clinical characteristics, laboratory findings, and treatment regimens from electronic medical records or doctor's records. The data was independently supervised by two investigators and reviewed by different investigators.

Statistical Analysis

All continuous variables were expressed as mean ± standard deviation (SD) or median with the interquartile range per the data distribution. Categorical variables were expressed as numbers and their respective percentage. Independent *t*-test was used to compare the change in FPG, PPG, and HbA1c between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. All the reported p-values were two-sided and p-values <0.05 were considered to indicate statistical significance. All data entries and statistical analyses were performed by using SPSS® Version 23.0 software.

Compliance with Ethics Guidelines

The study was approved by the ethical committee. All procedures adhered to the ethical standards established by the relevant institutional or national research committees. Since the study used an anonymized database and was done retrospectively, patient consent was not needed.

Results

The study analysis included responses from 500 HCPs. It showed that 6,250 patients received glimepiride/metformin FDC. The ages of the patients were between 18 to 90 years and a mean BMI was 27.97 ± 4.29 who received glimepiride/metformin combination. The mean (±SD) duration for which patients were having diabetes was 7.54 ± 3.48 years. The HbA1c was found to be 8.81% before treatment, which decreased to 7.75% after treatment. Among the 6,250 patients, 1,704 patients also received other OADs, where some patients received more than one OADs. Figure 2 shows the trend of OADs in combination with Metformin + Glimepiride.

DPP4i was prescribed the most (1,064 patients) followed by sodium-glucose cotransporter-2 inhibitors (SGLT2i) (573 patients), pioglitazone (229 patients), alpha-glucosidase inhibitor (AGI) (207 patients), insulin (178 patients), and lastly glucagon-like peptide 1 receptor agonist (GLP1RA) being prescribed in 35 patients along with the combination as is depicted in Figure 2.

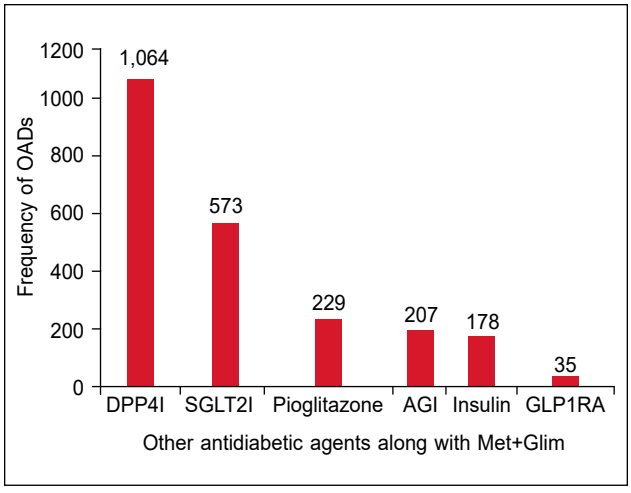

Figure 2. Trend of OADs being prescribed with glimepiride/metformin combination.

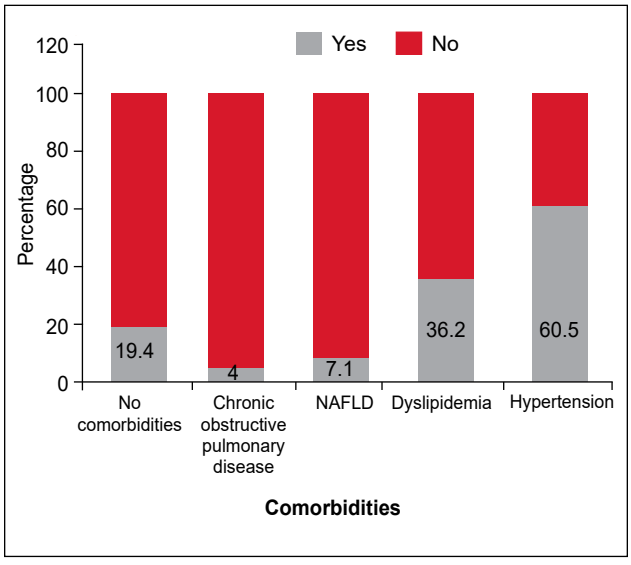

Figure 3. Comorbidities found in the participating diabetic patients.

NAFLD = Nonalcoholic fatty liver disease.

Hypoglycemia was observed in very few patients (4.49%). Hypertension was the most prevalent (60.5%) comorbidity in the studied patient population mostly aged between 18 to 90 years as is observed in Figure 3, followed by dyslipidemia (36.2%) among the patients included.

Discussion

Over half of the populations in India are at risk of having diabetes at some time in their life, which is making it a public health problem. An assessment in

the review article published in 2021 stated that people residing in the cities and metropolitan regions in India are more likely to get diabetes due to lifestyle changes which increases the person's BMI, a risk factor for diabetes. A significant surge is also being observed in rural parts of India[3].

Hence, selection of proper drugs to control the rise becomes essential. Presently, there are approximately 60 medications that have been authorized by the Food and Drug Administration (FDA) as therapeutic choices for the treatment of T2DM[11].

The selection of these drugs is typically affected by the numerous national and international recommendations created by various organizations in an effort to improve the management of diabetes mellitus[12-14].

For many T2DM patients, combination therapy is necessary to maintain blood glucose levels within the desired range and prevent complications from diabetes. Some OADs are advantageous for heart and renal health as well as weight loss[15,16].

Progressive beta-cell loss, a hallmark of T2DM, necessitates the sequential addition of various oral and injectable drugs to provide the best possible glycemic control. As the condition worsens, combination therapy becomes the need of the hour to establish appropriate glycemic control. Presence of comorbid conditions such as dyslipidemia, hypertension, and cardiovascular disease along with polypharmacy which comes with an increased load of pills and dose frequency, adds to the burden of medication[17,18].

In the present study, hypertension was the most prevalent (60.5%) comorbidity in the total studied patient population, followed by dyslipidemia and nonalcoholic fatty liver disease (NAFLD).

It was further seen that among 1,704 patients (some of whom also received more than one OADs along with Metformin + Glimepiride combination), 1217 (71.04%) were hypertensive, 720 (42.22%) had dyslipidemia, 1,164 (68.31%) had lifestyle related risk factors. Hence, the presence of these comorbidities might be one of the causes to add other OADs.

Also studies have shown that one method to improve drug adherence is to use additional OADs along with the existing combination therapy. Drug combinations have been associated with improved compliance and improved glycemic control[17].

The pattern observed in the present study showed that along with the glimepiride/metformin combination, DPP4i was prescribed the most (1,064 patients) followed by SGLT2i (573 patients), pioglitazone (229 patients), AGI (207 patients), insulin (178 patients), and lastly GLP1RA being prescribed in only 35 patients along with the combination as shown.

Dipeptidyl peptidase-4 (DPP-4) is a serine protease that cleaves and inactivates hormones, leading to decreased insulin secretion and disrupted visceral fat metabolism. It also plays a role in regulating postprandial glucose by degrading glucagon-like peptide 1 (GLP-1). DPP4i has been explored as a therapeutic target for the treatment and management of T2DM[19]. Research has demonstrated that DPP4i possess a favorable therapeutic profile, do not increase cardiovascular risk, and are safe and effective for most patients with T2DM[20].

A large retrospective real-world investigation shows that adding a DPP4i to the existing medication improves glucose control in normal diabetic outpatient clinical practice. While DPP4i and gliclazide both increase endogenous insulin secretion, DPP4i has a stronger physiological effect that is meal-dependent and may be better able to enhance beta and alpha cell activity, which would lead to improved glycemic control[21]. DPP4i were found to have no hypoglycemia risks, neutral effect with respect to weight change, atherosclerotic cardiovascular disease (ASCVD) and renal diseases. Also it was found to decrease postprandial triglycerides and blood pressure (BP), hence is beneficial for hypertensive diabetic patients. In the current study, most of the patients taking the combination were also hypertensive and were also given DPP4i. This is in accordance with the fact that DPP4i helps in lowering (BP) and with blood glucose level[22].

Metformin increases insulin sensitivity, while glimepiride increases - cell glucose sensitivity and promotes endogenous insulin production. A complementary mechanism of action between glimepiride and metformin results in a considerable decrease in glycemic indices (FPG, PPG, and HbA1c levels)[10,23].

In India, SUs are second-line medications for T2DM patients who are not obese and also reduce the risk of hypoglycemia. Hence, SUs are preferred in this population[24]. Glimepiride is also a desirable choice for the management of people with long-term diabetes due to its shown cardiovascular safety/neutrality and decreased hypoglycemic episodes[25]. Hence, addition of other OADs like DPP4i along with the glimepiride/metformin seems to be beneficial in T2DM patients having comorbidities such as hypertension, dyslipidemia, etc.

In T2DM patients, strict glycemic management lowers the related comorbidities and raises quality of life[26]. According to the United Kingdom Prospective Diabetes Study (UKPDS) trial, there is a 12% to 43% reduction in the risk of diabetes-related mortality and morbidity for every 1% drop in HbA1c[27,28].

Glimepiride increases cell sensitivity to glucose and promotes endogenous insulin production, whereas metformin increases sensitivity to insulin. Glycemic markers (FPG, PPG, and HbA1c levels) are significantly decreased when glimepiride and metformin are used in combination due to their complementary mechanisms of action.

When compared to older-generation SUs, glimepiride offers a number of benefits: weight-neutral effects, lack of cardiovascular risk, and fewer hypoglycemia episodes. It also has extrapancreatic effects, which are superior, enhanced insulin secretion[22]. Glimepiride + Metformin show synergistic effects by reducing hypoglycemia, weight gain, and cardiovascular risks, good glycemic control and improved safety profile[23,29-31].

Prasanna Kumar et al also reported similar observations in a trial which showed that the combination had a good to outstanding effectiveness and tolerability in the majority of patients (97.3% and 96.6%)[32].

Another prospective research found that diabetic individuals on glimepiride experienced fewer hypoglycemia episodes than those taking glibenclamide[33].

Glimepiride's documented cardiovascular safety/neutrality and reduced hypoglycemia episodes make it an attractive alternative for the management of persons with long-standing diabetes[25]. SUs are affordable and are also effective alternatives to other more recent antidiabetic drugs[31].

Combination drugs in diabetes treatment are cost-effective as they reduce the need for multiple medications, simplify dosing, and improve patient adherence, ultimately lowering overall health care costs. Hence, the combinations are preferred in developing countries like India[34]. This study showed that among 6,250 patients in the age between 18 to 90 years and a mean BMI of 27.97 ± 4.29 received glimepiride/metformin combination.

The mean (±SD) duration for which patients were having diabetes was 7.54 ± 3.48 years. The HbA1c was found to be 8.81 ± 1.25 before treatment, which decreased to 7.75 ± 3.62 after treatment. The mean FPG values before treatment was 190.46 ± 53.20 which reduced to 139.50 ± 39.51 mg/dL after treatment, while the mean PPG values before treatment was 274.62 ± 32.11, which decreased to 165.22 ± 45.63 mg/dL after treatment.

Among the 6,250 patients, 1,704 patients also received other OADs, 758 achieved HbA1c <7. Moreover, 228 patients achieved target FPG values, i.e., FPG values <100 and 95 achieved target PPG values, i.e., values <125.

In the current study, a significant decrease in the HbA1c, FPG, and PPG was observed, which is in similar lines with the findings by Hassan and Abd-Allah (2015), Surendra Kumar (2021), Shrivastava et al (2023)[23,30,35].

A variety of antidiabetic medications are now used as monotherapy or in combination for treating T2DM. Several studies have shown that in various Afro-Asian nations, including India, modern SUs alone or in combination with metformin are the OADs prescribed most often as they achieved better HbA1c, FPG, and PPG when used along with different OADs[36,37].

Conclusion

Prevalence of diabetes is increasing in India. Glimepiride/Metformin FDC can be used with various other OADs for better management of diabetes among patients with additional comorbidities. The study shows that DPP4i was the most common OAD being prescribed along with glimepiride/metformin combination.

This new age approach offers valuable insights into the multifaceted management of diabetes, highlighting the importance of individualized treatment strategies for Indian patients. The study would help HCPs to understand and optimize diabetes management in a better manner, which in turn would enable patients to lead healthier and more productive lives.

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Conflicts of Interest

Dr Aushili M, Dr Ashish Prasad, Dr Abhijit Pednekar are employees of USV Private Limited, Mumbai, Maharashtra, India.

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