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COMPARISON OF GLICLAZIDE OR GLICLAZIDE PLUS METFORMIN COMBINATION ON GLYCAEMIC CONTROL IN PATIENTS WITH T2DM IN INDIA

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KEYWORDS :

Introduction

The diabetes burden has increased with time worldwide and India having the second largest numbers in the world, after China.[1] Presently, India has 77 million people with diabetes; these numbers are based on the nationwide Indian Council of Medical Research—India Diabetes (ICMR—INDIAB) study.[2] Further, India has a high prevalence of prediabetes and undiagnosed diabetes.[2,3] In spite of the advances in diabetes therapies and technologies, a substantial proportion of people with diabetes struggle to achieve better glycemic outcomes.[4,5] The complex manifestation of diabetes demands tailored treatment support for those living with diabetes. The key complications that patients experience in diabetes management include (1) optimizing the use of existing therapies to ensure the adequate glycemic, blood pressure, and lipid control; (2) educating regarding diabetes self-management; (3) improving treatment adherence; (4) clearing the impediments to delayed diagnosis and the early initiation of insulin when indicated; and (5) improving the healthcare delivery to people with chronic conditions.[6,7]

Glycemic control is poorly maintained with monotherapy; around 10% of patients per year require the addition of another antidiabetic drug. One of the reason for this is that the disease itself is progressive and the therapeutic attempts to achieve as well as maintain glycemic control often fail in the long term. Hence, a need to combine drugs with different and complementary mechanisms of action frequently arises in daily clinical practice.[8]

Numerous guidelines such as the American Diabetes Association 2019 guidelines[9], IDF clinical practice recommendations for managing Type 2 Diabetes Mellitus (T2DM) in primary care 2017[10], and Research Society for the Study of Diabetes in India—Endocrine Society of India clinical practice recommendations for the management of T2DM 2020[11] recommend oral antihyperglycemic drugs (OADs) such as sulfonylureas to be used as monotherapy (if metformin is not tolerated) or as combination therapy. Furthermore, a network meta-analysis reported the new sulfonylureas glimepiride and gliclazide to be associated with a lower risk of all-cause (risk ratio [RR] 0.65; 95% confidence interval [CI] 0.53, 0.79) and cardiovascular-related mortality (RR 0.60; 95% CI 0.45, 0.84) than other sulfonylureas[12]. Another network meta-analysis reported gliclazide to be the only OAD that significantly reduced left ventricular mass (an important factor leading to cardiovascular disease) versus placebo (standardized mean difference [SMD] − 1.09, 95% CI − 1.62, − 0.57)[13].

Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes

A study was conducted to assess in a systematic review and meta-analysis of randomized controlled trials the safety and efficacy of gliclazide compared to other oral glucose-lowering agents. It revealed that the number of severe hypoglycemic episodes was extremely low, and gliclazide appears at least equally effective compared to other glucose lowering agents. [14]

There were 19 trials that were included; 3,083 patients treated with gliclazide, and 3,155 patients treated with other oral blood glucose lowering drugs. Gliclazide was slightly more effective (−0.13% (95%CI: −0.25, −0.02, I2 55%)) compared to other glucose lowering agents except metformin. [14]

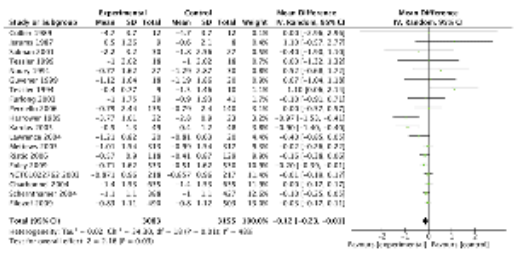

Figure 1 : Forest plot of the main effect outcome. The main effect outcome HbA1c; gliclazide versus other glucose lowering agents. Metf = metformin, SU is sulphonylurea, Pio is pioglitazone.

Metformin plus Gliclazide Combination Therapy

Metformin, a biguanide oral anti-hyperglycaemic agent that improves insulin sensitivity, reduces basal liver glucose production, and increases insulin-stimulated uptake and utilisation of glucose by peripheral tissues in patients with type 2 diabetes.[15] A meta-analysis consisting of 35 trials in type 2 diabetes indicated that metformin monotherapy lowered HbA1c by an average of 1.12% (12 mmol/mol) versus placebo in individuals previously being treated by lifestyle modification alone, by 0.95% (11 mmol/mol) versus placebo when added as a combination therapy to another oral anti-diabetic drug (OAD) and by 0.6% (6 mmol/mol) versus placebo when added to insulin therapy. Gastrointestinal events (including diarrhoea, nausea, vomiting, flatulence and abdominal pain) are the most common adverse events reported with metformin, but are generally mild to moderate and temporary. [16]

Gliclazide, a second-generation sulfonylurea oral anti-hyperglycaemic agent improves defective insulin secretion. [17] The immediate release (IR) formulation of gliclazide requires twice-daily dosing, but a modified-release (MR) version has been developed that is therapeutically equivalent to gliclazide IR, but allows for once-daily dosing. [18]

There are many trials that have assessed the efficacy and safety of combination therapy with gliclazide and metformin in individuals with type 2 diabetes insufficiently controlled with metformin, or other OAD monotherapy; with combination OAD therapy or with lifestyle modification alone as summarised in Table 1. [19]

Efficacy [19]

The metformin and gliclazide combination is effective in improving

glycaemic control in patients with type 2 diabetes insufficiently controlled by first-line monotherapy.

As summarized in table 1, the combination of gliclazide to metformin monotherapy was associated with reductions in HbA1c of between 0.27% and 1.7% (equivalent to 3.3 to 18.6 mmol/mol). Reported HbA1c reductions with gliclazide were comparable with those observed with nateglinide, pioglitazone, and rosiglitazone. FPG reductions ranging between the equivalent of 12.43 to 67.08 mg/dL were seen following the addition of gliclazide to metformin monotherapy. In the more limited number of trials that reported post-prandial glucose (PPG) results, reductions were in the range of 40.0 to 96.03 mg/dL. Following the addition of gliclazide to metformin monotherapy, between 37% and 47% of participants across trials achieved HbA1c ≤7% (equivalent to 53 mmol/mol). HbA1c reductions of ≥0.5% (5.5 mmol/mol) were reported in 49.2% of participants at 24 weeks, and in 24.2% of participants at 52 weeks (6-month extension) after the initiation of gliclazide and metformin combination therapy.

Reference	Population	Study design	Treatment	Main efficacy outcomes			Main safety outcomes
				Outcome	Baseline	Follow-up	
Pareek et al.	T2D (n=115) uncontrolled with oral monotherapy	12-week, prospective, open-label, multicentre study	GLI (80 to 320 mg OD) MET (500 to 2000 mg OD)	HbA1c, % ΔHbA1c≥0.5 %, % HbA1c <7%, % FPG, mg/dL PPG, mg/dL	8.51 ± 0.77 N/R N/R 178.34 ± 37.64 261.68 ± 66.77	Δ –1.16 ± 1.02* 84.35 37.39 Δ –67.08 ± 36.18* Δ –96.03 ± 64.03*	AEs: 22/124 (17.7%); 20 mild, 2 moderate 16 AEs possible hypos
Ristic et al.	T2D (n=247) uncontrolled with MET monotherapy (≥1000 mg)	24-week, double-blind, double-dummy, parallel group, randomised, multicentre study	GLI (80 to 240 mg OD) (n=118)	HbA1c, % (SE) ΔHbA1c≥0.5 %, % HbA1c <7%, % FPG, mmol/L (SE)	7.57 ± 0.57 N/R EC HbA1c 6.8–9% 8.65 ± 1.49	Δ −0.57* (0.08) 49.2 46.6 Δ −0.82* (0.18)	Drug-related AEs: 7.1% Confirmed hypo: 22.2% Weight: +<0.5 kg (n=126)
			NAT (60 to 180 mg TID) (n=129)	HbA1c, % ΔHbA1c≥0.5 %, % HbA1c <7%, % FPG, mmol/L	7.66 ± 0.59 N/R EC HbA1c 6.8–9% 8.49 ± 1.49	Δ −0.41 ± 0.08* 48.8 34.9 Δ −0.63 ± 0.17*	Drug-related AEs: 6.9% Confirmed hypo: 21.5% Weight: +<0.5 kg (n=130)
Ristic et al.	T2D (n=213) uncontrolled with MET monotherapy (>1000 mg)	52-week, (6-month trial and 6-month extension) double-blind, double-dummy, multicentre study	GLI (80 to 240 mg OD) (n=101)	HbA1c, % ΔHbA1c≥1.0 %, % HbA1c <7%, % FPG, mmol/L (SE)	7.55 ± 0.57 N/R EC HbA1c 6.8–9% 8.51 ± 1.44	Δ −0.27 LS 24.2 47.5 Δ –0.69 (0.23)LS	Confirmed hypo: 14.9% Weight: +0.91 kg
			NAT 60 to 180 mg TID (n=112)	HbA1c, % ΔHbA1c≥1.0 %, % HbA1c≤7%, % FPG, mmol/L (SE)	7.65±0.60 N/R EC HbA1c 6.8–9% 8.98 ± 1.52	Δ −0.14 20.0 40.0 Δ –0.20 (0.22)	Confirmed hypo: 15.2% Weight: +0.42 kg (NS vs GLI group)
Vilar et al.	T2D (n=250), monotherapy or combination therapy	Retrospective study	GLI (60 to 90 mg/d) + MET (850 to 1000 mg BID) (n=65)	HbA1c, % HbA1c <7%, % FPG, mg/dL PPG, mg/dL	9.3±0.6 EC HbA1c >7% 195.1 ± 10.7 205.2 ± 19.4	Δ –1.7±0.2 41.5 –58.2±5.3% –50.6±4.2%	Symptomatic hypo: 7.7% Weight: +2.2 kg
			ROSI (4 mg BID) + MET (850 to 1000 BID (n=30)	HbA1c, % HbA1c <7%, % FPG, mg/dL PPG, mg/dL	9.2 ± 0.8 EC HbA1c >7% 192.9 ± 7.7 204.1 ± 20.5		Symptomatic hypo: 3.3% Weight: +2.1 kg
			GLI (60 to 90 mg/d) + ROSI (4 mg BID) (n=30)	HbA1c, % HbA1c <7%, % FPG, mg/dL PPG, mg/dL	9.2 ± 0.5 EC HbA1c >7% 193.8 ± 8.8 206.5 ± 19.6	Δ –1.6 ± 0.3 40 –55.4 ± 7.8% –48.2 ± 6.6%	Symptomatic hypo: 10.0% Weight: +5.5 kg**
Betteridge and Verges	T2D (n=630) uncontrolled with MET monotherapy	2-year, randomised, double-blind, double-dummy trials	GLI (80 to 320 mg/d) + MET (n=313)	HbA1c, %	N/R	Δ –0.77	N/R
			PIO (15 to 45 mg/d) + MET (n=317)	HbA1c, %	N/R	Δ –0.89	N/R
Hamann et al.	T2D (n=596) uncontrolled with MET monotherapy	52-week, randomised, double-blind, parallel-group study	GLI (80 to 320 mg/d) or GLIB (5 to 15 mg/d) + MET (2000 mg/d)	HbA1c, % FPG, mmol/L	8.0 ± 1.0 10.2 ± 2.9	Δ –0.86 ± 0.06 Δ –2.25 ± 0.16	AEs: 58% ≥ 1 hypo event: 30%** Confirmed hypo: 7.0% Weight: +1.6 kg
			ROSI (4 to 8 mg/d) + MET 2000 mg/d (n=294)	HbA1c, % FPG, mmol/L	8.0 ± 0.9 10.5 ± 2.8	Δ –0.78 ± 0.06 Δ –2.29 ± 0.16	AEs: 56% ≥ 1 hypo event: 6% Confirmed hypo: <1.0% Weight: 2.7 kg#
Matthews et al.	T2D (n=630) uncontrolled with MET monotherapy	52-week, randomised, double-blind, parallel-group, double-dummy study	GLI (80 to 320 mg/d) + MET (500–3000 mg/d) (n=313)	HbA1c, % FPG, mmol/L	8.53 ± 0.89 11.3 ± 2.6	Δ –1.01 Δ –1.6	AEs: 58.1% Hypo event: 11.2% Weight: +1.4 kg
			PIO (15 to 45 mg OD) + MET (500–3000 mg/d)	HbA1c, % FPG, mmol/L	8.71 ± 1.00 11.8 ± 3.1	Δ –0.99 Δ –2.1	AEs: 55.5% Hypo event: 1.3% Weight:
Onuchin et al.	Uncontrolled T2D in women aged >55 years	1-year, open-label prospective study	Group 1: MET (2500 to 5000 mg/d)	HbA1c, %	10.4 ± 1.6	7.1 ± 0.6	Safety: N/R
			Group 2: MET (1500 to 2500 mg/d) + GLI (30 to 90) mg/d)	HbA1c, %	10.6 ± 1.8	6.7 ± 0.5	N/R
Galeone et al.	Uncontrolled T2D with maximum dose of GLI (240 mg/d, n=57)	3-month, prospective, uncontrolled study	GLI (120 mg/d divided into 3 daily doses) + MET (1500 mg/d divided into 3 daily doses)	HbA1c, % FPG, g/L PPG (lunch), g/L PPG (dinner), g/L	9.9 ± 1.1 1.94 ± 0.30 2.29 ± 0.41 2.08 ± 0.19	8.4 ± 1.0¶ 1.48 ± 0.30¶ 1.74 ± 0.27¶ 1.68 ± 0.16	No severe hypos or lactic acidosis Weight: No significant change
Lee et al.	Uncontrolled T2D (drug-naïve) (n=116)	24-week, prospective, nonrandomised, open-label study	Group 1: GLI (30 to 60 mg), or GLIM (2.5 to 4.0 mg) + MET (1000 mg/d)	HbA1c, median %, (range) HbA1c≤7%, % FPG, median mg/dL (range) PPG, median mg/dL (range)	8.9 (8.2 to 10.3) EC HbA1c >7% 166.5 (139.0 to 195.0) 226.5 (192.5 to 312.0)	6.4* (6.0 to 6.7) 89.3 103.5* (89.0 to 112.0) 157.0* (124.0 to 219.5)	No major hypos
			Group 2: PIO (15 m/d) + MET (1000–1700 mg/d) (n=30)	HbA1c,median %, (range) HbA1c≤7%, % FPG, median mg/dL (range) PPG, median mg/dL (range)	9.0 (8.4 to 11.2) EC HbA1c >7% 174.0 (145.0 to 223.0) 238.0 (195.5 to 324.0)	6.6* (6.1 to 6.9) 81.5 111.0* (101.5 to 120.0) 157.0* (133.5 to 196.5)	No major hypos
			(Group 3, n=38) SITA (100 mg/d) + MET (1000-1700 mg/d)	HbA1c,median %, (range) HbA1c ≤ 7%, % FPG,median mg/dL (range) PPG, median mg/dL (range)	9.3 (7.8 to 10.4) EC HbA1c >7% 173.0 (135.0 to 204.0) 251.0 (196.0 to 306.0)	6.3* (6.0 to 6.7) 84.8 105.0* (100.0 to 124.0) 148.0* (115.0 to 172.0)	No major hypos

Schernthaner et al.	T2D (n=845) treated with diet or MET or α-GLUi monotherapy	27-week, randomised, double-blind, parallel-group	GLI MR (30 to 120 mg/d) + MET, or α-GLUi (pre-study dose; n=405)	HbA1c, % HbA1c≤7%, % FPG, mmol/L	8.4±1.1 EC HbA1c 6.9–11.5% 10.2 ± 2.6	Δ −1.1±1.1* ~50 Δ–1.4	Confirmed hypo: 3.7%‡ Other AEs: 40.9% Weight: +0.5 kg
			GLIM (1 to 6 mg/d) + MET, or α-GLUi (pre-study dose; n=440)	HbA1c, % HbA1c <7%, % FPG, mmol/L	8.2 ± 1.0 EC HbA1c 6.9–11.5% 10.1 ± 2.6	Δ −1.0 ± 1.1* ~50 Δ–1.3	Confirmed hypo: 8.9% Other AEs: 40.1% Weight: +0.6 kg
Filozof et al.	Uncontrolled T2D with MET (n=1007)	52-week, randomised, double-blind, active-controlled, multicentre	GLI (80 to 320 mg/d) + MET (1500 mg/d) (n=494)	HbA1c, % (SE) HbA1c≤7%, % FPG, mmol/L	8.5 ± 1.0 EC HbA1c 7.5–11% 10.6 ± 2.8	Δ –0.85 (0.06) 31.9 Δ 1.52 (0.14)	AEs: 61.3% Hypos: 11 events Withdrawal due to AE: 4.7% Weight: +1.36 kg
			VILDA (50 mg BID) + MET (1500 mg/d (n=513)	HbA1c, % HbA1c <7%, % FPG, mmol/L	8.5 ± 1.0 EC HbA1c 7.5–11% 10.8 ± 2.8	Δ –0.81 ± 0.06 29.6 Δ 1.31 ± 0.14	AEs: 61.8% Hypos: 6 events Withdrawal due to AE: 6.7% Weight: +0.08 kg**

Table 1: Summary of major studies involving metformin and gliclazide combination therapy in patients with type 2 diabetes †p<0.05; ‡p<0.05 vs comparator; ¶p<0.01; #p=0.002 vs comparator; *p<0.001 vs baseline; **p<0.001 vs comparator groups.

AEs: Adverse Events; BID: Twice Daily; EC: Entry Criteria; FPG: Fasting-Plasma Glucose; GLI: Gliclazide; GLIB: Glibenclamide; GLIM: Glimepiride; HbA1c: Glycated Haemoglobin; Hypo: Hypoglycaemia; LS: Least Square; MET: Metformin; N/A: Not Applicable; NAT: Nateglinide; N/R: Not Reported; NS: Not Significant; OD: Once Daily; PIO: Pioglitazone; PPG: Post-Prandial Glucose; ROSI: Rosiglitazone; SITA: Sitagliptin; TID: Three-Times Daily; T2D: Type 2 Diabetes; VILDA: Vildagliptin; α-GLUi: α-Glucosidase Inhibitor; Δ: Change All data are means ± SD unless otherwise stated Adopted from Gottwald-Hostalek U, Schlachter J, Geloneze B (2016) [19]

Safety and Tolerability

Both metformin and gliclazide have been licensed for many years and have proven to have favourable tolerability and safety in monotherapy and in free combination. [19]

Gliclazide is usually well tolerated by most patients, with mild gastrointestinal, skin and central nervous system effects being the most commonly reported adverse events. The majority of adverse events seen with gliclazide and metformin were mild-to-moderate in severity and withdrawals due to adverse events were uncommon. [19]

Effect of Gliclazide or Gliclazide plus Metformin Combination on Glycemic Control in Patients with T2DM in India

Electronic medical record data of adult Indian patients who were diagnosed with T2DM who were newly initiated on or had been prescribed gliclazide or gliclazide + metformin combination for<30 days as monotherapy or as add-on therapy to other antihyperglycemic agents and had HbA1c≥6.5% were retrospectively analysed. The study revealed that Gliclazide or gliclazide + metformin given as mono- or add-on therapy during routine clinical practice effectively reduced HbA1c in Indian patients with T2DM. [20]

The patients included (n=498) were categorized into gliclazide only (n=66), gliclazide in combination with metformin only (n=179), gliclazide add-on (n=169), and gliclazide + metformin add-on (n=84) groups. Mean (95% confidence interval [CI]) change in HbA1c among patients with baseline HbA1c>7% was − 0.8% (− 1.26, − 0.34) in gliclazide only group; − 1.6% (− 1.89, − 1.31; p□ <□ 0.001) in gliclazide□+□metformin group; − 1.2% (− 1.50, − 0.90; p□<□0.001) in add-on gliclazide group; and − 1.4% (− 1.75, − 1.05; p□<□0.001) in add-on gliclazide□+□metformin group. [20]

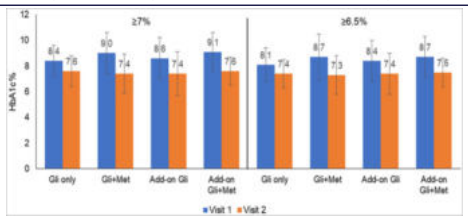

Figure 2 : Effect of gliclazide or gliclazide□ +□ metformin on HbA1c%. The figure shows the HbA1c% levels after at least 90 days of treatment. The data are divided into patients with HbA1c□ ≥□ 7% and□ ≥□ 6.5% at baseline. Mean□ ±□ SD values are represented. Gli gliclazide, HbA1c glycated hemoglobin, Met metformin, SD standard deviation

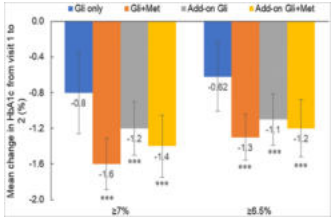

Figure 3 : Gliclazide- or gliclazide□ +□ metformin-induced mean change in HbA1c%. The figure shows the mean (95% CI) change in HbA1c% levels from visit 1 to visit 2 after at least 90 days of treatment. Visit 2 readings were statistically compared against Visit 1 readings. The data are divided into patients with HbA1c□≥□7% and□≥□6.5% at baseline. ***p□ <□ 0.001. CI confidence interval, Gli gliclazide, HbA1c glycated hemoglobin, Met metformin.

A fixed-dose combination may improve patient adherence to anti-diabetic therapy

Polypharmacy can cause an additional burden on patients, potentially reducing treatment adherence, which could adversely impact clinical outcomes as well as it can be inconvenient and may cause confusion, with patients mixing up the timing of doses. [19]

Due the issues issue of polypharmacy in people with type 2 diabetes, single tablet, fixed-dose combinations of two OADs can reduce treatment complexity, and can significantly improve adherence over separate dual combination therapy. For example, a meta-analysis examining fixed-dose combination drugs and free-drug regimens in diseases such as tuberculosis (2 studies), hypertension (4 studies), HIV (1 study) and diabetes (2 studies) identified a 26% decrease in non-adherence with fixed-dose combinations vs free drugs (RR: 0.74; 95% CI: 0.69 to 0.80; p<0.0001). In a study of patients receiving anti-diabetic monotherapy, free-combination therapy or fixed-dose combination therapy that included metformin (N=6502), adherence rates were significantly lower (54%; 95% CI: 0.52 to 0.55) in patients switched to free-combination therapy compared to those receiving fixed-dose combination therapy (77%; 95% CI: 0.72 to 0.82). Likewise, adherence was also significantly improved in patients who switched from free- to fixed-dose combination therapy (71% vs 87%; p<0.001). Altogether, these data suggest that fixed-dose combinations such as metformin plus gliclazide can help alleviate the key issue of polypharmacy in people with type 2 diabetes and improve treatment adherence. [19]

Summary

The studies indicate that a combined, single-tablet metformin and gliclazide treatment option for patients with type 2 diabetes would be a safe and effective treatment. For few patients with type 2 diabetes, the management of symptoms and maintenance of glycaemic control necessitates several therapeutic interventions. Given the problems of the burden of polypharmacy, reducing the number of tablets a patient needs to take, would provide the benefits of improved glycaemic control, while improving patient adherence to their therapeutic regimens. Hence, considering the benefits of a fixed-dose combination of metformin and gliclazide is an attractive prospect for improving clinical outcomes for such patients.

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