ORIGINAL ARTICLE

Sustained Glycemic Control and Improved Well-being on Early Induction of Triple Drug Therapy in Newly Diagnosed Type 2 Diabetes Mellitus Patients with HbA1c ≥9%: A Prospective, Cross-sectional, and Observational Study

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Abstract

Introduction: To study outcomes of the triple-drug therapy in newly diagnosed type 2 diabetes mellitus (T2DM) [glycated hemoglobin (HbA1c) ≥9%] with respect to change in HbA1c, low-density lipoprotein (LDL) levels, weight, waist circumference, variation in drug dosages, hypoglycemic events, patient response of well-being, and corresponding result satisfaction.

Materials and methods: It was a prospective, observational study conducted from 1st June 2018 to 31st May 2019 at Indira Gandhi Medical College and Hospital, Shimla, a tertiary care hospital in Himachal Pradesh. During the initial 3 months, patients were treated with triple-drug [oral hypoglycemic agents (OHAs)] therapy and then switched over to dual or single therapy (OHAs) depending on the HbA1c levels and were followed up for 1 year.

Observations: A total of 137 participants completed the study period. At baseline, the mean values of fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), HbA1c, and LDL were 218.4 ± 36 mg/dL, 343.94 ± 60 mg/dL, 10.5 ± 1.42%, and 120.34 ± 30.99 mg/dL, respectively. At the end of 12 weeks, the mean values of FPG, PPPG, HbA1c, and LDL were reduced to 123 ± 16 mg/dL, 164 ± 30 mg/dL, 8.14 ± 0.97%, and 109.04 ± 28.28 mg/dL, respectively. The differences were highly significant statistically when compared with the baseline observations. At the end of the study (52 weeks), the mean values of FPG, PPPG, HbA1c, and LDL were 96 ± 10 mg/dL, 146 ± 16 mg/dL, 6.14 ± 0.43%, and 90.55 ± 28.14 mg/dL. Reductions in values were statistically significant when compared with both the baseline and 12-week values.

Conclusion: Early induction of combination therapy with glimepiride, metformin, and pioglitazone results in more desirable outcomes in terms of greater reduction in HbA1c level and lower incidence of hypoglycemia as compared to the conventional add-on therapy.

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Introduction

Diabetes mellitus is a metabolic syndrome characterized by an increase in blood glucose level (hyperglycemia).[1] Abrupt increase in blood glucose level and deficiency of insulin may result in many hyperglycemia-related symptoms, metabolic decompensation, and hospitalization. Chronic hyperglycemia is responsible for diabetes-related microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications like cardiovascular events and stroke.[1] Prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly, and presently 287 million people are affected with it globally. It is projected that 592 million people will be affected with T2DM by 2035. India has emerged as a center for T2DM in the Southeast Asia region, having >69 million people affected with diabetes, which is expected to affect nearly 101 million people by 2035.[1,2] A population-based study, conducted by "The National Urban Diabetes Society" (NUDS) in a few metropolitan cities of India, revealed that the age-standardized prevalence of T2DM was 12.1%. Further, it was reported that the prevalence was higher in the southern part of India (13.5% in Chennai, 12.4% in Bengaluru, and 16.6% in Hyderabad) than in eastern India (Kolkata, 11.7%), northern India (New Delhi, 11.6%), and western India (Mumbai, 9.3%).[3] The management of T2DM with regard to targeted glycated hemoglobin (HbA1c) and internationally recommended clinical guidelines for individualized approach is relatively difficult.[4]

Recent treatment guidelines given by the American Diabetes Association (ADA) (2019)[5] and the European Association for the Study of Diabetes recommend an individualized approach in selecting the appropriate drug for the treatment of T2DM. This includes consideration of efficacy of the drug and other patient factors such as: (1) important comorbidities such as atherosclerotic cardiovascular disease, chronic kidney disease, and heart failure; (2) hypoglycemia events; (3) body weight; (4) various side effects; (5) economy; and (6) patient's choice. The various treatment guidelines have considered metformin as the first-line pharmacological measure in the treatment of T2DM unless contraindicated. If desired glycemia is not achieved, dual therapy with metformin and sulfonylureas has been advocated by many international guidelines.[4] Even the triple-drug therapy has been instituted recently, which provided a significantly better and clinically relevant reduction in HbA1c when compared to dual therapy. Significant reduction in HbA1c, optimum body weight, and reduced incidence of hypoglycemia were major outcomes in the triple therapy.[4]

The ADA showed that triple-drug combinations had better outcomes in HbA1c, glucose metabolism, lipid levels, hypoglycemic events, body weight, and urine albumin as compared to dual therapy.[6] In contrast to the currently recommended sequential add-on therapy, we planned to assess the efficacy and safety of a triple-drug combination of metformin, glimepiride, and pioglitazone, initiated at earlier stages during the management of newly diagnosed T2DM patients.

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Aims and Objectives

To study the outcomes of triple-drug therapy in newly diagnosed T2DM (HbA1c ≥9%) with respect to change in HbA1c, low-density lipoprotein (LDL) levels, weight, waist circumference, variation in drug dosages, hypoglycemic events, patient response of well-being, and corresponding result satisfaction.

Materials and Methods

Patient Population

About 137 newly diagnosed T2DM patients who attended the outpatient department of the tertiary care hospital in the Department of Medicine at Indira Gandhi Medical College and Hospital, Shimla, were enrolled. The patients were enrolled according to the following inclusion criteria—aged between 20 and 80 years, patients willing to give informed consent, HbA1c ≥9%, and no treatment with insulin or oral agents for the recent 6 months. Patients were excluded if they had T1DM, secondary diabetes (chronic pancreatitis, drugs, Cushing's disease, pituitary, and thyroid disorders), presented with acute illness [acute fever, urinary tract infection (UTI), diabetic ketoacidosis (DKA), severe hypertension (HTN), congestive heart failure, short-term marked hyperglycemia, rigorous exercises], were younger than 20 years, had contraindications to metformin, sulfonylurea, and thiazolidinediones, or were pregnant or lactating women. Criteria delineated by the WHO were used for the diagnosis of T2DM, that is, a random plasma glucose concentration ≥200 mg/dL with symptoms of hyperglycemia, fasting plasma glucose (FPG) ≥126 mg/dL, or 2-hour postprandial plasma glucose (PPPG) ≥200 mg/dL during an oral glucose tolerance test with 75 gm oral glucose. This study was approved by the Institutional Ethics Committee. All patients were put on triple drug therapy, that is, metformin (1,000 mg) BD, sulfonylurea glimepiride (2 mg) OD, and thiazolidinediones (pioglitazone 15 mg) OD. Modification of treatment was done based on the glycemic levels of the patient during follow-up.

Study Design

It was a prospective and observational study.

Study Duration

It was conducted from 1st June 2018 to 31st May 2019.

Data Collection

After enrollment, a detailed history was recorded, followed by a general physical and systemic examination of the study participants. The various anthropometric variables, such as weight, height, waist, and body mass index (BMI), were recorded for all the study participants. FPG, PPPG, HbA1c, and blood pressure were recorded for every subject. Routine blood investigations, such as complete hemogram, liver function tests, kidney function tests, and lipid profile, were conducted. Where indicated, specific tests, such as chest X-ray and thyroid function tests, were performed. Contact details of the patients were noted, and all the participants were advised to report for follow-up at 3-month intervals. During their enrollment in the study, patients were warned about the symptoms of hypoglycemia. They were also educated about the use of corrective measures in case of hypoglycemia. Patients and their attendants were advised to contact the treating physician in case of severe symptoms of hypoglycemia. The study participants were followed up at 3, 6, 9, and 12 months. FPG, PPPG, HbA1c, weight, and waist were recorded at every visit. Symptoms of minor as well as major hypoglycemia, if any, were noted. Any episode of hospitalization and subjective feelings of well-being were also recorded.

Statistical Analysis

The categorical variables were analyzed using descriptive statistics and frequency percentages. The mean value and standard deviations were measured for quantitative data. In our study, we used Pearson's Chi-squared test and one-way ANOVA or paired *t*-test for analyzing qualitative data. A *p*-value < 0.05 was considered statistically significant. We used the statistical software IBM SPSS Statistics for Windows, version 21.0.

Results

Out of 137 participants in our study, the number of males was 77 (56.2%) and females were 60 (43.8%). Among all patients, 92 (67.2%) patients belonged to rural areas, and 45 (32.8%) belonged to urban areas. Among male patients, 27 (93.1%) were farmers, 21 (95.5%) were employees, and 29 (87.9%) belonged to different occupations. In the female patient group, 2 (6.9%) were farmers, 1 (4.5%) was an employee, 53 (88.3%) were housewives, and 4 (12.1%) belonged to other occupations. Out of 137 patients, 20 (20.4%) were smokers and 36 (26.3%) were alcoholics, whereas 58 (42.3%) patients had a positive family history of T2DM, of which the mother was predominantly affected. Further, 21 (15.3%) patients presented with HTN, and it was also observed that 6 (4.4%) of them had findings of diabetic retinopathy (grade 1/2) as well. In this study, the most common presenting complaint was osmotic features, which were seen in 83 (60.6%) patients, followed by complaints of easy fatigability/lethargy, which were seen in 21 (15.3%) patients; 16 (11.6%) patients presented for routine checkup; 7 (5.1%) patients were planned for surgery; 5 (3.7%) patients presented with vulvovaginitis; and 5 (3.7%) patients presented with skin lesions (Fig. 1). At baseline, the mean FPG was found to be 218 ± 36.9 mg/dL; among males, it was 218.40 ± 36.93 mg/dL, and among females, it was 209.22 ± 47.66 mg/dL. The mean PPPG was 343.94 ± 60.84 mg/dL, which was 343.93 ± 60.85 mg/dL among males and 342.12 ± 69.05 mg/dL among females. The mean HbA1c at baseline was recorded as 10.51% (±1.42), which was 9.47% (±1.56) in males and 11.55% (±1.28) in females. At baseline, the mean LDL level of all patients was 120.34 ± 30.99 mg/dL; it was 123.47 (±34.65) mg/dL in males and 116.33 (±25.26) mg/dL in female patients. The mean weight and mean waist circumference of all the patients enrolled were 68.50 (±8.01) kg and 91.04 (±8.85) cm, respectively (Table 1).

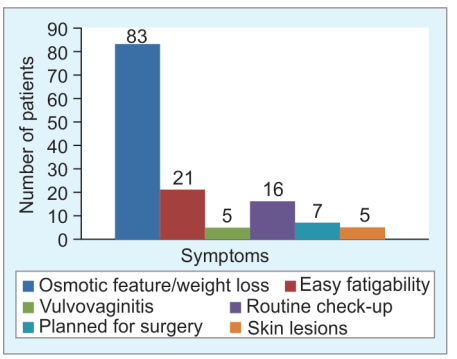

Fig. 1: Presenting symptoms (*n* = 137)

Table 1: Demographic profile and baseline clinical parameters (*n* = 137)

Variables	*Male*	*Female*	*Total*
Age (years)	49.48 (±8.26)	50.23 (±7.98)	49.81 (±8.12)
Weight (kg)	70.86 (±7.33)	65.47 (±7.88)	68.5 (±8.01)
Waist (cm)	90.62 (±6.95)	91.57 (±10.84)	91.04 (±8.85)
BMI (kg/m^2)	25.05 (±2.59)	24.20 (±2.75)	25.05 (±2.59)
FPG (mg/dL)	218.40 (±36.93)	209.22 (±47.66)	218.4 (±36.93)
PPPG (mg/dL)	343.94 (±60.85)	342.12 (±69.05)	343.94 (±60.84)
HbA1c (%)	9.47 (±1.56)	11.55 (±1.28)	10.51 (±1.42)
LDL (mg/dL)	123.47 (±34.65)	116.33 (±25.26)	120.34 (±30.90)

All patients were put on triple-drug therapy as per the protocol.

First Follow-up Visit at 3 Months

At the end of 3 months, FPG levels of study participants ranged from 84 to 195 mg/dL, with a mean of 123 ± 16 mg/dL. The PPPG levels ranged from 116 to 257 mg/dL, with a mean of 164 ± 30 mg/dL, and HbA1c ranged from 5.4 to 12.1%, with a mean HbA1c of 8.14 ± 0.97%. The LDL level ranged from 45 to 221 mg/dL, with a mean of 109.04 ± 28.28 mg/dL (Table 2). The reduction in the mean FPG, PPPG, HbA1c, and LDL levels was highly significant at 3 months of follow-up ($p < 0.001$) (Fig. 2). There was no noticeable change in weight and waist circumference at 3 months when compared with baseline. Out of 137, 109 (79.6%) patients were put on a triple-drug combination with reduced-dose glimepiride (1 mg) OD + metformin (1,000 mg) BD + pioglitazone (15 mg) OD, whereas 21 (15.3%) were kept on the same original drug combination. Further, four (2.9%) were prescribed dual-drug therapy of pioglitazone (15 mg) OD + metformin (1,000 mg) BD or glimepiride (1 mg) OD + metformin (1,000 mg) BD, and the remaining three (2.2%) were prescribed single therapy, metformin (1,000 mg) BD (Table 3). Only three minor events of hypoglycemia were recorded, for which patients had taken self-remedy in the form of sugar at home, and no major adverse events were documented.

Follow-up Results at 12 Months

At 12 months, it was found that FPG ranged from 81 to 146 mg/dL with a mean of 96 ± 10 mg/dL, PPPG ranged from 118 to 167 mg/dL with a mean of 146 ± 16 mg/dL, and the HbA1c ranged from 5.2 to 8.5% with a mean of 6.14 ± 0.43%. The LDL level ranged from 38 to 201 mg/dL with a mean of 90.55 ± 28.14 mg/dL (Table 2). Decreased mean values in all three parameters (FPG, PPPG, and HbA1c) were significant at 12 months when compared with baseline levels (Fig. 2). There was an average 860 gm increase in the body weight of study participants from 68.5 to 69.36 kg and an average 0.62 cm increase in waist circumference of the participants from 91.04 to 91.66 cm when compared with baseline. Based on clinical response, all patients were assessed for continuation or modification of further treatment. At the end of the study, 94 (68.6%) patients who had HbA1c <7–6% were prescribed dual drug therapy of glimepiride (1 mg) OD + metformin (1,000 mg) BD or pioglitazone (15 mg) OD + metformin (1,000 mg) BD. About 40 (29.2%) patients who had HbA1c <6% (better glycemic index) were prescribed single therapy of metformin (1,000 mg) BD. However, three (2.2%) patients were kept on triple drug therapy with reduced doses, such as glimepiride (1 mg) OD + metformin (1,000 mg) BD + pioglitazone (15 mg) OD; these patients had HbA1c ≥7 and <9% (Table 3). Among all study participants, there were 9.48 episodes/patient of hypoglycemia. However, all the hypoglycemia events were minor. Out of 137 patients, 117 (85.4%) were satisfied with their treatment, and there was improvement in their quality of life with the ongoing treatment. The patients were relieved from osmotic symptoms, and they felt more energetic; together, it was considered the "feel-good phenomenon." Thus, at the end of 12 months, the majority of patients were on dual-drug or single-drug regimens, while only a few needed triple-drug regimens.

Discussion

There are many options available for triple drug combinations in newly diagnosed T2DM (HbA1c ≥9%). Large numbers of patients with a high glycemic index (HbA1c ≥9%) are usually put on a combination of metformin, sulfonylurea, and insulin. However, due to the high cost of insulin, fear of injections, and increased risk of hypoglycemic events, compliance with such treatments is low. Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) and glucagon-like peptide-1 (GLP-1) agonists can be added as the third drug with the dual combination of metformin and sulfonylureas, as these two different classes of drugs tend to have good HbA1c, cardiovascular, and renal outcomes. Unfortunately, due to their high costs, they also present affordability issues in our clinical setup. Thus, in our study, we used a combination of metformin, sulfonylureas, and thiazolidinedione, which resulted in significant reductions in HbA1c and LDL levels (bad cholesterol) without significant gains in weight and waist circumference. The added advantage of these three drugs in combination is that each drug targets a different pathophysiology of T2DM simultaneously, complementing each other's mechanism of action, which results in a greater reduction in HbA1c and a decreased incidence of micro/macrovascular adverse events. In

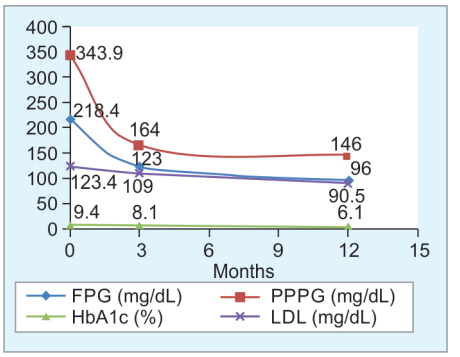

Fig. 2: Progressive decline in level of clinical parameters from baseline to end of treatment

Table 2: Comparison of clinical parameters at baseline, 3 months, and 12 months

Variable	*Baseline*	*3 months*	*12 months*
FPG (mg/dL)	218.40 (±36.93)	123 (±16)	96 (±10)
PPPG (mg/dL)	343.94 (±60.85)	164 (±30)	146 (±16)
HbA1c (%)	9.47 (±1.56)	8.14 (±0.97)	6.14 (±0.43)
LDL (mg/dL)	123.47 (±34.65)	109.04 (±28.28)	90.55 (±28.14)

Table 3: Cross tabulation between different time periods and variation in drug dosage

Time	*Variation in drug-dosage*									
	Triple drug therapy (A1c ≥9%)		*Triple drug therapy with reduced dosage (A1c ≥7 to <9%)*		*Dual drug therapy (A1c <7 to ≥6%)*		*Single drug therapy (A1c <6%)*		*Total*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Baseline	137	100.0	0	0.0	0	0.0	0	0.0	137	100.0
3rd month	21	15.3	109	79.6	4	2.9	3	2.2	137	100.0
6th month	1	0.7	65	47.4	70	51.1	1	0.7	137	100.0
9th month	0	0.0	29	21.2	90	65.7	18	13.1	137	100.0
12th month	0	0.0	3	2.2	94	68.6	40	29.2	137	100.0

Chi-square value = 910.129; *p*-value < 0.001, significant; A1c = HbA1c

this study, we summarize the outcome of triple drug therapy used in newly diagnosed T2DM patients (HbA1c ≥9%) with respect to parameters such as changes in HbA1c level, lipid level (LDL), weight, waist circumference, hypoglycemic events, variation in drug dosages, changes in lifestyle and behavioral modification, patient well-being during the treatment, and corresponding result satisfaction. The age distribution in our study was from 20 to 80 years, with a mean age of 49.85 ± 8.12. The mean age among males was found to be 49.48 ± 8.26, and among females, it was 50.23 ± 7.99. These findings were comparable with the NHANES survey,[7] which reported that the mean age at diagnosis of T2DM in the United States decreased from 52 years (1988–1994) to 47 years (1999–2000). A cross-sectional study by Morkos et al.[8] demonstrated the mean age of patients as 49 ± 11.3 years. In our study, the mean BMI was 24.79 kg/m^2, with 25.05 ± 2.59 kg/m^2 among males and 24.2 ± 2.75 kg/m^2 among females. The Mayega and Rutebemberwa[9] study demonstrated the mean BMI of newly diagnosed diabetes patients as 24.7 (median 24; range 13.3–44.6), which was in concordance with our study. In our study, out of 137 patients, 92 (67.2%) were from rural backgrounds. In a cross-sectional study by Aung et al., the age-standardized prevalence of diabetes was much higher in the urban population (12.1%) than in the rural population (7.1%).[10] Educational status of the population had a noticeable impact on the prevalence of diabetes. Even in urban areas, the prevalence of T2DM was higher in populations with low education standards when compared with those with higher education levels. In rural areas, physical inactivity, lower intake of fruits and vegetables, and obesity culminated in a higher prevalence of DM than in those who were more physically active, took care of their diet, and managed their weight. The majority of the population in Himachal Pradesh belongs to rural areas (90%), so the chances of T2DM are higher in rural backgrounds. An increase in the prevalence of T2DM in rural populations could be the result of a lack of awareness and low education standards, which lead to ignorance of the symptoms and signs of T2DM.

Out of 137 patients, 58 (42.3%) had a positive family history of T2DM. These findings differ from the Mayega and Rutebemberwa study,[9] which reported only 20% of newly diagnosed diabetes patients with a family history of diabetes. In our study, 21 (15.3%) patients presented with a positive history of HTN. In Mayega and Rutebemberwa's study,[9] about 48% of newly diagnosed diabetes patients had high blood pressure at the time of enrollment. In the Venugopal and Mohammed study,[11] the prevalence of HTN was noted in 64 (25.6%) patients. Priya et al.[12] observed HTN in 42.7% of the patients. In a study by Ramachandran,[13] 38% of study subjects were hypertensive.

In our study, the most common presenting complaints were osmotic features seen in 83 (60.6%) patients, followed by others (Fig. 1). These were not consistent with the findings of a case series reported by Mayega and Rutebemberwa,[9] which stated increased urination as the most common symptom at presentation. It was followed by frequent drinking/thirst (79%) and easy fatigability (51%). Others had symptoms like blurred vision (38%), excessive sweating (27%), joint pains (22%), numbness (21%), and headache (21%). We observed a steady decline in the levels of the mean FPG, PPPG, and HbA1c from baseline to 12 months (Table 2 and Fig. 2). Thus, it was analyzed that the triple-drug combination of metformin, sulfonylureas, and thiazolidinedione was clinically effective in reducing HbA1c to a significant level. These observations were in concordance with a study done by Downes et al.,[4] which stated that all classes of drugs, in combination with metformin and sulfonylureas, provided a clinically relevant and statistically significant (>0.3%, >3.3 mmol/mol) decrease in HbA1c when compared to metformin and sulfonylureas dual therapy. Similar results were found in a multicentric study conducted by Meshram et al.[14] to determine the efficacy and safety of the triple-drug combination of glimepiride 2 mg, pioglitazone 15 mg, and metformin 500 mg for 2 months in 101 patients with T2DM. It was concluded that the goals recommended by the ADA can be achieved with the triple-drug combination. It was seen that after 2 months, the mean HbA1c, which was 10.32% at baseline, significantly reduced to 7.54% at the end of the study. The bad cholesterol (LDL) was shown to be reduced in our study from baseline 120.34 to 90.55 mg/dL at the end of the study; the reduction in mean value was statistically significant. Similar results were seen in the Meshram et al.,[14] which reported a significant reduction in levels of triglycerides, LDL, and total cholesterol with the triple-drug combination. In our study, there was no significantly documented hypoglycemic event (only 13 minor events), which is contrary to the study Downes et al.,[4] as this study was associated with major hypoglycemic events. In our study, none of the patients required hospitalization due to hypoglycemia. There was no case of poor tolerability to drugs reported as evaluated by patients as well as the investigator. No significant change in weight and waist circumference was observed in our study, as low-dose pioglitazone 15 mg was used. Also, the weight-gaining effect of thiazolidinedione might have been neutralized by metformin. These findings were consistent with the findings of the Praveen et al. study,[15] which stated that there was no significant increase in weight throughout the study period with the triple-drug combination therapy.

On having good compliance with the initial triple drug therapy of metformin, glimepiride, and pioglitazone, subsequent follow-up visits resulted in reduced doses of drugs due to significant reduction in HbA1c and better glycemic control. Due to better glycemic control, there was a reduction in both microvascular and macrovascular adverse events. The patient response, showing well-being and satisfactory results, was obtained in this study. All the subjects had satisfactory to very good improvement, assessed on the "Global Assessment of Efficacy of Treatment," evaluated by both the physician and patients at the 3rd and 12th months. Our study's observation could have been a step toward recommending the initiation of the triple drug combination of metformin, glimepiride, and pioglitazone in the treatment of newly diagnosed T2DM patients. However, stepwise add-on therapy is the existing recommendation for treating such patients. A longer-duration study within a multiethnic group may be needed to validate the observation in our study. It is also concluded that pharmacoeconomic studies of antidiabetic drugs should not be limited to the cost of drugs; emphasis should be given to other beneficial metabolic effects, such as a low risk of hypoglycemia, weight loss, and reduction of cardiovascular disease risk factors. Otherwise, these modalities may increase the overall cost of management in T2DM patients.

Conclusion

It is concluded that early induction of combination therapy with glimepiride, metformin, and pioglitazone results in a greater reduction of HbA1c levels with a lower incidence of hypoglycemia compared to the currently recommended add-on therapy with conventional agents, such as sulfonylureas and insulin. However, more studies with long-term follow-up are required to validate the favorable outcome of triple drug therapy in the management of newly diagnosed T2DM patients.

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