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Research Article

Combining Therapy of Vildagliptin with Metformin Improves Glycemic Control than Using Metformin Alone in The Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

The purpose of the trial was to determine whether combination medication for type 2 diabetes mellitus offers better glycemic control than monotherapy. Subjects whose ages were more than 18 years and with glycated hemoglobin levels higher than 7.5% were enrolled. Among the 664 patients enrolled, 332 received monotherapy, while 332 were treated with combination therapy. The treatment groups received either vildagliptin + metformin combination therapy or metformin monotherapy. Vildagliptin, as an adjunct to metformin treatment, was to be evaluated for its safety and efficacy in reducing HbA1c levels from baseline. The study included individuals with a history of T2DM for 3 to 4 years who had been treated with either combination therapy or monotherapy for at least three months. Statistical analysis was done using SPSS software. As per the findings, it indicated that combination therapy led to a considerably greater reduction in glycated hemoglobin levels compared to monotherapy. Adverse events were also observed to vary significantly between the two treatment cohorts. Outcomes suggest that combination medication should be started earlier than monotherapy for superior glycemic control. Additionally, it was thought that the combo therapy had a positive safety profile.

INTRODUCTION

Today, the prolonged non-infectious disease type 2 diabetes mellitus (T2DM) has become widespread.^[1] According to the International Diabetes Federation, in 2019, the overall occurrence of T2DM was around 10% (463 million) by 2045. It is predicted to increase by up to 10% (700 million).^[2] India's T2DM population is predicted to grow from 77 million in 2019 to 134 million by 2045, making it the next-largest T2DM population all over the world.^[3]

Although advancements in medical interventions for T2DM are increasing, changes in lifestyle continue to be the cornerstone of its management. Firstly, metformin monotherapy was the initial pharmacotherapy treatment

for type 2 diabetes. Studies have shown that patients with higher glycosylated hemoglobin (HbA1c) levels respond well to primary combination therapy; however, patients with lower HbA1c levels can now get this treatment as well.^[4,5] While escalating metformin monotherapy doses has indeed enhanced glycemic control, the uptick in adverse actions arising in the gastrointestinal system has led to a decline in patient adherence.^[6]

Hence, innovative treatment approaches are necessary due to the shortcomings of the stepwise intensive treatment approach. Initiating more vigorous combination therapy early on can prove to be an effective scheme prior to the decline in response to monotherapy.^[1,7,8]

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Enhancing glycemic control and targeting various disease pathways linked to glucose dysregulation are two advantages this approach might offer. Moreover, prevention of the evolution of type 2 diabetes and its related micro- and macrovascular problems is best achieved with early therapies.^[1]

Dipeptidyl peptidase-4 inhibitor (DPP4i) vildagliptin is both powerful and selective. It improves the sensitivity of alpha and beta cells to glucose, triggering an increase in weight or raising the condition of hypoglycemia.^[9,10] For T2DM patients, as per the INITIAL study and VERIFY trial-based study, combination therapy (metformin+vildagliptin) provides superior glycemic control than metformin alone,^[11-14] and no evaluation has been completed to compare the efficacy of metformin monotherapy versus combination treatment. With this evidence, doctors may better treat diabetic patients by offering personalized, all-encompassing care.^[15] With the early introduction of the diabetes intervention, an extra proactive, early, and intensive strategy has been suggested.

Metformin and DPP-4 inhibitors together are a commonly used combination that can be purchased as a combination pill, which improves patient compliance. A better FPG and HbA1c decrease were shown in a meta-analysis comprising five trials contrasting metformin monotherapy with beginning combination treatment. Neither the risk of hypoglycemia nor the duration of gastrointestinal adverse effects were elevated using the initial combination medication.^[16] A prior randomized controlled trial examined the safety and effectiveness of combination therapy in patients who were new to drugs.^[17] More information about the use of early combination therapy can be given to doctors by studying its effects in the population of western India, particularly in north Gujarat, where patients had high baseline HbA1c at diagnosis. Thus, we estimated the safety and efficacy of the first combination therapy (vildagliptin/metformin) in drug-naïve T2DM patients in the current non-interventional trial. When all patients were already taking the combination medication, the early combination strategy not only significantly and constantly decreased the comparative threat of time to first treatment defeat but also the comparative threat of time to second treatment defeat. Furthermore, a greater percentage of patients in the early combination treatment group were able to maintain reduced glycemic cut-off values and glycated hemoglobin A1C levels throughout the trial. Both methods of treatment were accepted just as well.^[12] As was previously mentioned, a typical medication combination used to treat T2D patients in clinical trials is metformin with DPP4 inhibitors. Researchers found that newly diagnosed T2D patients receiving combination medication with vildagliptin had superior durable glycemic control than those receiving metformin monotherapy alone in an initial 5-year follow-up study.^[18] Furthermore, it has been documented that the coadministration of

metformin and vildagliptin significantly reduces HbA1c while not significantly increasing the risk of adverse events. Therefore, this study's objective is to evaluate the properties of the former combination therapy by making running easier.

However, there is data from real-world Indian studies that compare the efficacy of combination therapy vs. monotherapy. This data will help treating physicians make decisions that will enable them to give patients personalized, all-encompassing care for improved diabetes control.^[19]

The primary goal is to match the potential and efficacy of antidiabetic drug therapy in the population with diabetes, determine the profits and damages of antidiabetic agents, define the best treatment regimen, and monitor the usefulness and welfare of DPP4 inhibitors in type 2 diabetes mellitus patients. Our main goal is to verify that vildagliptin is not inferior to glycosylated hemoglobin (HbA1c).

MATERIALS AND METHODS

Observational research was conducted here based on data collection through the questionnaires of patients with T2DM. In total, 664 patients who had been identified with type 2 diabetes, were female as well as male, and were between 18 and 75 years old, were suitable for this study. This experiment was open to type 2 diabetic patients who have been on metformin and vildagliptin together for at least three to six months. Patients are required to have two HbA1c results, a minimum of one recorded prescription, and one maintained follow-up period. The diagnosis is based on postprandial blood glucose, fasting blood glucose, and glycated hemoglobin. Individuals who had had type 2 diabetes for longer than five years were not accepted. As per the specifics of their usage, the patients were categorized into two groups: (a) those receiving monotherapy (metformin alone) and (b) those receiving combination therapy (metformin and vildagliptin). Both groups were analyzed in terms of gender, age, HbA1c, and extra-oral antidiabetic drugs (OADs).^[15]

Ethics Approval and Informed Consent

The study received approval from ethics committee, located in Gujarat, India (Ethics Approval Number: ECR/295/1ndt/GJ/2018). The study involves data collection, analysis, and informed consent form (ICF), etc. Hence, as per the "Declaration of Helsinki", confidentiality and compliance of patient data were maintained during the study, and the study did not need to acquire informed consent.^[20]

Design and Development of the Questionnaire

In this research, no questionnaire was available as per requirements, so a new self-administered questionnaire was developed with the help of thorough literature, experts, and personal experience. The list of all questions

was prepared first, and they were thoroughly examined to remove irrelevant information and classify the items. Lastly, the final wording and formatting were done for the proper layout of the questionnaire. Multiple-choice, closed-ended, or Likert scale-type questions were drafted to get more efficient data compared to open-ended questions. Open-ended questions are easy to write, but they are tough to analyze and understand, whereas closed-ended questions are more challenging to write, but they are great for slick data handling and analysis. The Likert scales for the question are quantifier and response categories, which show the intensity of the participant's decision.^[21] The different types of quantifiers used in the questionnaire are stated in table said. Quantifiers are classified on five scales, from 1 to 5. Where 1 is 'the lowest scale (intensity)' and 5 is 'the highest scale (intensity)' (Table 1).

Face Validity

It is a subjective assessment done by experts to see whether the questionnaire appears to be valid, clear, relevant, and reasonable or not. Also, input for the final layout of the print of the questionnaire can be taken with this validity test. The nine field experts were selected for face validity (Table 2).

Table 1: Likert scale for the questionnaire

Scale Part	1	2	3	4	5
Question 3	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Question 12	Never	Rarely	Sometime	Frequently	All the time
Question 13	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Question 14	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Content Validity

It is the degree to which the questionnaire fully assesses or measures the construct of interest. It is measured by a rational analysis of the questionnaire by a skilled professional with the paradigm or knowledge of the content or an expert in the research. It checks the relevance of items in the questionnaire. So, measurement errors can be minimised or eliminated that can be raised during work.^[22,23]

$$CVR = (N_e - N/2) / (N/2),$$

Where,

N_e = total number of experts divided by the number of experts saying the item essential

N = total number of experts on the panel.

As per the questions CVR values as 0.8 for 9 experts. All values of CVR (Table 3)

Statistical Analysis

With the SPSS program, all collected data will be analyzed. The Hba1c value and other parameters were calculated based on known scoring guidelines. The level of significance will be $p < 0.05$. Standard deviations, frequencies, and percentages are used to measure means for continuous parametric variables in descriptive statistics. For the determination of the substantial difference among the two groups, paired t-tests were utilized.^[24]

RESULTS

Out of the 662 patients who were recruited for the study, in a monotherapy group of 332 patients, 196 (59%) were male and 136 (41%) were female, with age ranges between 18 to 66 + years [(18–33) years 4 (1.2%), 34 to 49 years 92 (27.7%), 50 to 65 years 187 (56.3%), and 66 and above years 46 (14.8%)]. In the combination therapy group of 332 patients, 218 (65.7%) were male and 114 (34.3%) were female, with age ranges between 18 to 66 + years [(18–33)

Table 2: Results of face validity

No. of Expe Rts	Expert Answer														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
1	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
2	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
3	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES
4	YES	YES	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES	YES
5	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
6	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
7	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES
8	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
9	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
% of question Assessment	100	100	91	91	100	91	91	100	91	91	91	100	91	100	100
Overall assessment	95.2%														



Table 3: Minimum value of CVR

No.of experts	Minimum value	No.of experts	Minimum value
5	0.99	13	0.54
6	0.99	14	0.51
7	0.99	15	0.49
8	0.75	20	0.42
9	0.78	25	0.37
10	0.62	30	0.33
11	0.59	35	0.31
12	0.56	40	0.29

years 10 (3%), 34 to 49 years 69 (20.8%), 50 to 65 years 184 (55.4%), and 66 and above years 69 (20.8%)] (Table 4). As per the evaluation parameters for the monotherapy group, there is not enough statistical evidence to conclude a significant difference in PPBS levels and HbA1c between baseline and follow-up. For the combination therapy group, there is strong statistical evidence to conclude a significant difference in PPBS levels and HbA1c among baseline and follow-up. A considerably higher decline in the level of HbA1c was noted in the combination therapy group in comparison to monotherapy alone ($p < 0.05$). The combination group showed a reduction in HbA1c levels in males than in females, while the metformin-alone group showed a comparable fall in both genders (Table 5).

In patients, the frequency of side effects was assessed. Individuals in the monotherapy group experienced nausea and vomiting (22%), hypoglycemia (5%), megaloblastic anemia (75%), and muscle pain (80%). Adverse effects like nausea and vomiting (0.6%), megaloblastic anemia (1%), and muscle pain (7%) were common in a combination therapy group. During the treatment period, 0.1% of the patients noted hypoglycemia in the combination group. No statistically substantial variation was seen in the unfavorable interactions between the treatment groups (Table 6).

DISCUSSION

The findings imply that when starting pharmacologic therapy for type 2 diabetes, combination therapy is

preferable to metformin alone in terms of achieving better glycemic outcomes. Monotherapy is recommended for initial medication therapy in the ADA's recommended treatment approach.^[25] It may be necessary to start pharmaceutical therapy with an additional agent when a patient has a baseline A1c that is high—defined by the ADA as $\geq 9\%$ —because monotherapy is unlikely to attain glycemic targets.^[25] On the other hand, the AACE offers a therapy algorithm that groups the patient's initial pharmacologic treatment plan according to their current A1c level. According to this set of guidelines, patients whose A1c falls between 7 and 9.0% should have combination therapy, and those whose A1c is higher than 9.0% should receive triple therapy.^[26] According to both sets of guidelines, patients are unlikely to meet the glycemic target with monotherapy, which is why combination therapy should be started. This logic is supported by meta-analysis, which found a strong correlation between combination therapy and a higher chance of reaching the A1c target of less than 7%. The recommendation that early combination therapy be used in patients with baseline A1c values between 7 and 9% is further supported by previous analyses evaluating these patients, which show that a higher percentage of patients reach A1c with initial combination therapy than with monotherapy.^[27] When starting monotherapy in patients with type 2 diabetes, glycaemic objectives are frequently not met over a broad series of baseline A1c levels.^[28] This is most expected because, whereas combination therapy can target several mechanisms, the multiple pathophysiological reasons for diabetes cannot be addressed by monotherapy. Since all of the trials in our analysis had mean baseline A1c values between 7 and 9%, it demonstrates that introducing combination therapy could be a good course of action for patients with lower A1c levels as well as those with a wide range of A1c levels. Preliminary combination treatment may also possibly lessen certain adverse medication effects over time and potentially eliminate the need for dose intensification by optimizing glycaemic control with minor doses of the pharmaceutical components. Furthermore, research has demonstrated that those on monotherapy are

Table 4: Demographic details of patients

Demographic Details Mean $\pm$ SD		Metformin (n = 332)		Metformin + Vildagliptin (n = 332)			
		N	%	Mean $\pm$ SD	N	%	
Gender	Male	1.40 $\pm$ 0.49	196	59	1.34 $\pm$.47	218	65.7
	Female		136	41		114	34.3
Age	18–33 Years	2.84 $\pm$.067	4	1.2	2.93 $\pm$ 0.73	10	3
	34–49 Years		92	27.7		69	20.8
	50–65 Years		187	56.3		184	55.4
	65 and above		49	14.8		69	20.8

N= Frequencies, %= Percentage, Mean $\pm$ SD = Mean $\pm$ Standard Deviation,

Table 5: Evaluation parameters

Evaluation parameters	Metformin (n = 332)	Metformin + Vildagliptin (n = 332)
	p-value	p-value
FBS (baseline-follow up)	.000	0.000
PPBS (baseline-follow up)	0.06	0.000
HbA1C (baseline-follow up)	0.083	0.000

n = Sample size, Mean $\pm$ SD = Mean $\pm$ Standard Deviation, t- Test = Paired t-Test, p-value < 0.05

Table 6: Adverse effect in both groups

Side effects	Metformin (n = 332)		Metformin + Vildagliptin (n = 332)	
	Mean $\pm$ SD	p-value	Mean $\pm$ SD	p-value
Nausea& Vomiting	3.21 $\pm$ 0.41	0.000	1.00 $\pm$ 0.077	0.000
Hypoglycemia	2.05 $\pm$ 0.22	0.000	1.97 $\pm$ 0.15	0.000
Megaloblastic anemia	4.0 $\pm$ 0.41	0.000	1.01 $\pm$ 0.12	0.000
Muscle pain	3.82 $\pm$ 0.37	0.000	1.25 $\pm$ 0.57	0.000

n = Sample size, Mean $\pm$ SD = Mean $\pm$ Standard Deviation, t- Test = Paired t-Test, p-value < 0.05

more likely to follow their treatment plans than those on numerous prescriptions.^[29] The availability of fixed-dose combinations of antihyperglycemic medications might resolve this issue.^[30,31]

CONCLUSION

The study has determined similar findings for T2DM patients. Since the combination group reduced PPBS and HbA1c levels more than metformin alone, this study confirms that twin therapy increases glycemic management more than monotherapy. Generally, DPP-4 inhibitors were highly effective in reducing the rate of side effects when compared with metformin alone. When initially utilized, combination therapy did not increase the occurrence of any side effects.

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