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Influence of Combination Therapy of Oral Anti Diabetics on HbA1c Values

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Abstract: ***Type 2 diabetes mellitus has been one of the most common chronic, metabolic diseases whose prevalence is steadily increasing worldwide. The choice of therapy (either mono or dual therapy) or the choice of agent is based on the blood glucose levels and patient characteristics. When metformin alone is insufficient to achieve the glycemic target, adding basal insulin or a sulfonylurea is recommended as a well - validated therapy strategy, whilst pioglitazone or glucagon - like peptide - 1 (GLP - 1) agonists are suggested as less well - validated combination therapies. If a patient is on dual therapy and the HbA1c value remained above 7.5%, it is recommended to have a third - line treatment with a glitazone or insulin. An observational study was carried out for a period of three months to estimate the influence of oral hypoglycemic agents in combination therapy in improving the hba1c levels. After eliminating all the individuals who do not met the criteria, the observation was carried out in 257 individuals and their hba1c values were collected during follow - up. The mean values of hba1c are calculated for each category of hypoglycemic agent and the effective agent that can actually improve the hba1c value is estimated.***

Keywords: Diabetes mellitus, Hypoglycemic agents, Hba1c values, Metformin

1. Introduction

In approximately 92% of the patients, Insulin resistance (IR) is the core metabolic defect that contributes to the development of T2DM[1]. Type 2 diabetes mellitus is characterized by hyperglycemia with elevated levels of glycated hemoglobin A1c (HbA1c) which leads to micro - vascular and macro - vascular diseases in patients[2, 3].

In general, A HbA1c level of 6.5% or under was set for people with diabetes according to NICE guidelines on type 2 diabetes mellitus, released in May 2008[4]. The choice of therapy (either mono or dual therapy) or the choice of agent is based on the blood glucose levels (RBS, FBS, and HBA1C) and patient characteristics. If a patient is on dual therapy and the HbA1c value remained above 7.5%, it is recommended to have a third - line treatment with a glitazone or insulin[5]. It was always said that treatment for diabetes usually start with lifestyle measures, but it was accepted that these would fail in most cases. Unless overweight or obese, the First - line therapy for T2DM should be metformin for people.

Metformin was the most commonly prescribed hypoglycemic drug in the United States in 2007, being prescribed in 54 percent of all diabetes treatment visits, either as monotherapy or in combination with insulin, sulfonylureas, thiazolidinediones (mainly pioglitazone), or dipeptidyl peptidase 4 (DPP - 4) inhibitors.6 According to experiments, it lowers glycated haemoglobin (HbA1c) levels by 1–2 percent (11–22 mmol/mol).7, [8] A recent systematic review[9] indicates that this is an overestimation of effect, but the meta - analysis only included seven studies of metformin and did not look at it independently as a monotherapy or in conjunction with other antihyperglycemic medicines.

Sulfonylureas have been used to treat diabetes for a long time, and they were the first oral glucose - lowering drugs to be used in clinical practice. They're still commonly used in the UK, and they're the second - most - recommended oral glucose - lowering medication after metformin.1[0] Sulfonylureas reduced HbA1c by 1.5 percent (equivalent to 16 mmol/mol) when used an individual drug according to a consensus study published by the American Diabetes Association and the European Association for the Study of Diabetes[11]. Several other systematic reviews have looked at the impact of sulfonylureas in combination with other drugs on HbA1c levels[12 - 14].

DPP - 4 inhibitors are a novel type of oral hypoglycemic medication. The US Food and Drug Administration and the European Medicines Agency have already approved a few drugs from the class of gliptins such as sitagliptin, vildagliptin, saxagliptin, and linagliptin, while other drugs are seeking approval or under research. If there is a significant risk of hypoglycemia or if a sulfonylurea is contraindicated or not tolerated, the National Institute for Health and Clinical Excellence (NICE) clinical guideline for type 2 diabetes recommends using a DPP - 4 inhibitor as a second - line treatment to first - line metformin.

Between the years 2012 and 2014, the US Food and Drug Administration (FDA) [15, 16, 17] and the European Medicines Agency (EMA) [18 - 21] approved three sodium - glucose co - transporter 2 inhibitors (SGLT2 - i) from a wide range of drugs, canagliflozin, dapagliflozin, and empagliflozin, for the treatment of type 2 diabetes patients. SGLT2 - i inhibits glucose reabsorption in the kidney's proximal tubules, increasing urine glucose excretion and lowering blood glucose levels[22].

Thiazolidinediones (TZDs) are the only antidiabetic (AD) agents that bind to and activate the nuclear peroxisome proliferator - activated receptor (PPAR) expressed in peripheral and hepatic tissues, primarily as insulin sensitizers. Although pioglitazone, the only thiazolidinedione medication in clinical use, is under review

due to documented side effects, its unique insulin sensitising action gives justification for its continued use in the treatment of type 2 diabetes (T2DM).2[3] If metformin is not tolerated or if metformin alone fails to attain the desired HbA1c level, pioglitazone monotherapy can be administered instead[24]. Despite these benefits, pioglitazone's usage in routine clinical practise is limited due to a slew of side effects, including weight gain, peripheral edoema, and congestive heart failure, as well as debate over the possibility of bladder cancer. As a result of its unique insulin sensitising effect, a risk - benefit analysis of pioglitazone medication in T2DM patients is critical for evaluating its role in the current and future glucose - lowering treatment algorithm.2[5]

This study is an attempt to estimate the capacity of the available oral hypoglycemic agents in combination in lowering the elevated glycated hemoglobin levels in patients suffering from long term type 2 diabetes mellitus.

2. Methodology

We conducted a prospective cohort study considering combination therapies for its efficacy in T2DM patients. The efficacy is calculated in terms of improvement in the mean hba1c values. Mean changes in hba1c levels were calculated and improvement in the hba1c levels after consistent use of a hypoglycemic agent was estimated.

The study was carried out considering the individuals with type 2 diabetes mellitus in and around our locality in Vijayawada, Krishna district, Andhra Pradesh (India) over a period of three months. A total of 211 individuals who met the inclusion criteria were recruited in the study. For an individual to participate in the study, he/she should have a history of diabetes mellitus for at least 5 years and age not less than 30 years and not more than 50 years. Patients who have a prior history of cardiac disease are excluded from the study. In January 2022 the HBA1C value of each individual at that time was collected from the reports and after 3 months, in April 2022 after consistent use of a particular combination of anti diabetic medication, HBA1C values were collected from each individual. Patients were categorized according to the class of hypoglycemic agent they were using consistently and two values of hba1c were collected for each individual over a period of three months.

The mean of collected hba1c value for each category of drug was performed and tabulated. A paired t test was performed using Graph pad Prism Software Version 9.2.0 to observe the influence of anti - diabetic drug on Hba1c level.

3. Results

Table 1: Number of individuals using combination of oral hypoglycemic agents

Drug Combination	Number of Individuals Using The Combination	Percentage of Males (%)	Percentage of Females (%)
Metformin+Sulfonyl urea	131	54.198	45.80
Metformin+ DPP4I's	64	46.875	53.125
Metformin+SGLT2I's	2	100	0
Metformin +Voglibose	2	50	50
Metformin + Sulfonyl urea + Pioglitazone	3	66.66	33.33
Metformin + Sulfonyl urea + Voglibose	9	55.55	44.44

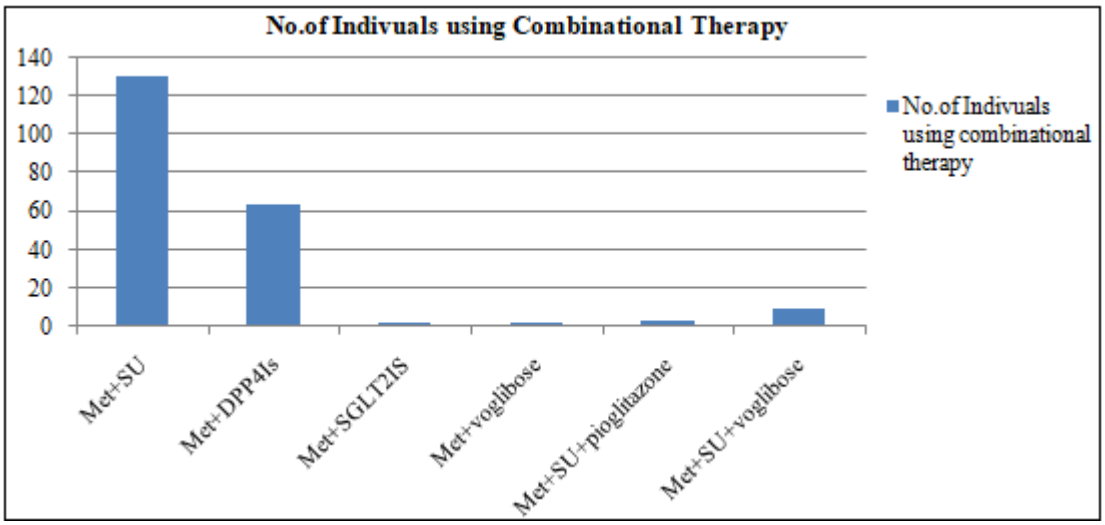

Figure 1: Total Number of Individuals using each category of oral hypoglycemic agent

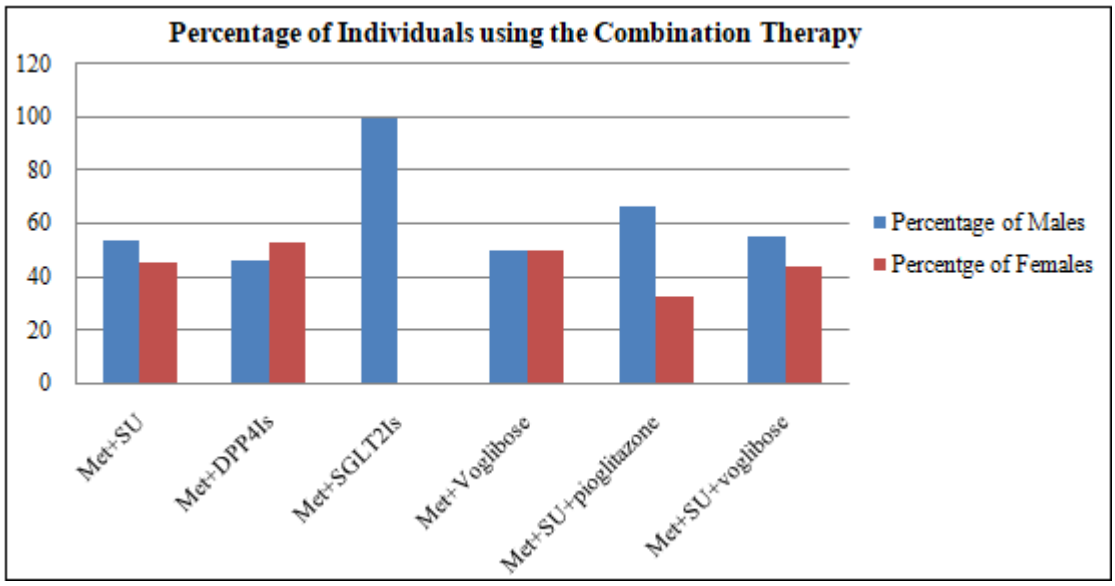

Figure 2: Percentage of Individuals using each category of the combination of oral hypoglycemic agents

Table 2: Categorized HBA1C values of patients using anti diabetic medications

	MET+DPP4i	MET+SU	MET+SGLT2	MET+ VOGLIBOSE	MET+SU+ GLITAZONE	MET+SU+ VOGLIBOSE
HBA1C						
6.0 - 7.5	04	33	01	0	01	02
7.6 - 9.0	21	35	0	02	02	02
9.1 - 11	19	37	01	0	0	04
>11.0	20	26	0	0	0	01

All the hypoglycemic agents (combination therapy) mentioned in the study are grouped according to the Patients Hba1c values

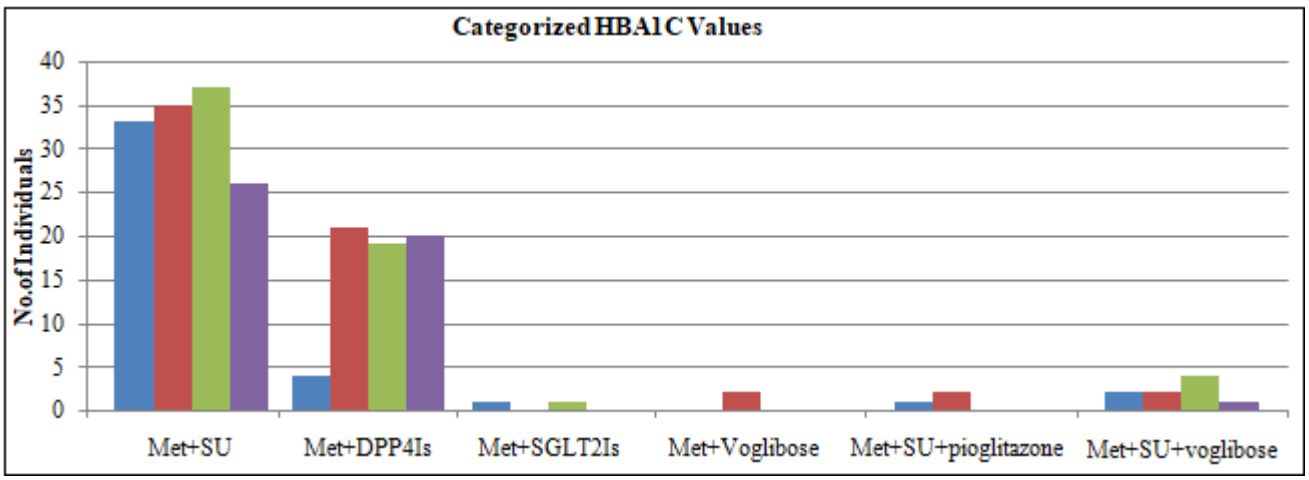

Figure 3: Categorized HBA1C values for each combination therapy

Table 3: This table shows the results obtained in the paired t - test

DRUG	N	MEAN		STANDARD DEVIATION (SD)		P value	
		Hba1c – 1	Hba1c - 2	Hba1c - 1	Hba1c - 2	Hba1c - 1	Hba1c - 2
METFORMIN+ SULFONYL UREAS	131	8.94	8.89	1.8840	1.8107	<0.0001	<0.0001
METFORMIN+ DPP4Is	64	9.87	9.87	2.1309	2.0337	<0.0001	<0.0001
METFORMIN+ SGLT2Is	2	6.90	7.20	6.0340	5.5860	- -	- -
METFORMIN+ VOGLIBOSE	2	8.30	8.55	0.989	0.919	0.0535	0.0483
METFORMIN+SU+PIOGLITAZONE	3	8.06	7.96	0.757	0.450	0.0029	0.0011
METFORMIN+SU+VOGLIBOSE	9	9.23	9.20	1.694	1.5842	<0.0001	<0.0001

The paired t - test is also known as the dependent sample t - test. For the paired t - test, we need two variables, one variable defines the pairs for the observation and the second variable is the measurement. In this study paired t - test is performed for the drugs and Hba1c values during first and second follow - ups. The results have shown significance between different drug therapies and Hba1c values.

The results for hba1c during first time and different drug combinations are as follows, Metformin + Sulfonyl urea (N: 131, mean: 8.94, SD: 1.8840, p: <0.0001) Metformin + DPP4I's (N: 64, mean: 9.87, SD: 2.1309, p: <0.0001), Metformin + SGLT2I's (N: 1, mean: 6.9, SD: 6.034, p: -), Metformin + Voglibose (N: 2, mean: 8.3, SD: 0.989, p: 0.0535), Metformin + Sulfonyl urea + Pioglitazone (N: 3, mean: 8.06, SD: 0.757, p: 0.0029), Metformin + Sulfonyl urea + Voglibose (N: 9, mean: 9.23, SD: 1.694, p: <0.0001).

The results for hba1c during the follow - up and different combinations are as follows, Metformin + Sulfonyl urea (N: 131, mean: 8.89, SD: 1.8107, p: <0.0001) Metformin + DPP4I's (N: 64, mean: 9.87, SD: 2.0337, p: <0.0001), Metformin + SGLT2I's (N: 1, mean: 7.20, SD: 5.5860, p: -), Metformin + Voglibose (N: 2, mean: 8.55, SD: 0.919, p: 0.0483), Metformin + Sulfonyl urea + Pioglitazone (N: 3, mean: 7.96, SD: 0.450, p: 0.0011), Metformin + Sulfonyl urea + Voglibose (N: 9, mean: 9.20, SD: 1.5842, p: <0.0001).

4. Discussion

After vigorous research and review, it is evident that there is an association between consistent use of anti diabetics and the level of hba1c levels of a diabetes patient. Our study aimed to establish the extent of influence that each drug class has on the glycated hemoglobin value. To estimate the effect a group of 211 individuals were recruited in the study where each individual is categorized according to their hba1c values collected during each follow up conducted during the study. After all the statistics being performed we managed to find that a few drug classes have a really good impact in lowering the hba1c values over continuous usage.

Results from our study clearly show that sulfonyl ureas used in combination with metformin for consistent time reduced the mean Hba1c value from 8.94 to 8.89. Similar kind of results were observed in a systematic review of double - blinded, randomized controlled trials where it was found that sulfonylurea monotherapy reduced HbA1c by an average of 1.5% (16 mmol/mol), and sulfonylurea in combination other oral medications reduced HbA1c by 1.6% (18 mmol/mol) compared with placebo groups.2[6]

Considering the DPP - 4 inhibitors, when used in combination with metformin was taken for a consistent period there was no significant improvement in the mean value. This is contrast to the results obtained in other study. In patients who do not achieve their glycaemic targets with metformin mono - therapy, two recent meta - analyses[27, 28] assessing the efficacy and safety of hypoglycemic drugs combined with metformin concluded that DPP - 4 inhibitors achieved relative reductions in HbA1c similar to other active drugs when compared with placebo.

Our study findings reveal that, in usage of few drug combinations, metformin+SGLT2 inhibitors, metformin+voglibose, the hba1c values are elevated. This may be due to insignificant sample size. Further investigations are necessary to confirm the results.

The triple therapy anti diabetic combinations like metformin+sulfonyl urea+pioglitazone and metformin+sulfonyl urea+voglibose slightly improved the values. These combinations might be useful considering patient characteristics as there are many mono - therapy and dual therapy options available which can greatly reduce the Hba1c values and cause hypoglycemia.

5. Conclusion

Based on the findings of this study, we concluded that Dual therapy of sulfonyl ureas in combination with metformin can be used as an alternative to metformin or insulin monotherapy if metformin cannot be tolerated or as if metformin alone fails to achieve target HbA1c level. Triple therapy should be the least considered option in case all the alternatives fail and the patient requires immediate treatment of hyperglycemia despite the improvement in hba1c values.

Abbreviations

AD – Anti Diabetic, DM - Diabtes Mellitus, DPP - 4 I – Dipeptidyl peptidase 4 inhibitor, IR – Insulin resistance, GLP - 1 - Glucagon - like peptide - 1, Hba1c – Glycated heamoglobin, SU – Sulfonyl Urea, TZD - Thiazolidinediones

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