

# Outcome of Patients Compliance to Fixed-Dose Combinations Oral Hypoglycemics: A Prospective Study

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## Abstract

**Background:** single pill combinations is proved to achieve patient compliance and hence better blood sugar control and less occurrence of complications of type two diabetes. **Objectives:** to assess the outcome of fixed dose combination management of diabetic patients by monitor blood glucose and HbA1c, renal function test and body weight, and test its significancy in regard to the previous management. **Methodology:** Prospective follow up study carried out for a period of 28 weeks, combined pills of pioglitazone 30mg with glyburide 2mg as a single dose drug taken before breakfast-and dapagliflozin 10mg combined with 1000mg metformin as a single dose taken at dinner, measurement of fasting blood sugar, HbA1c, blood urea, creatine and weight and renal function test and weight were done at the start of the study and then repeated 28 weeks later, compliance was assessed using Morisky Medication Adherence Scale (MMAS-8) with 3 level Likert scale. **Results:** The eligible subjects who were involved in the study were 72, their mean blood sugar and HbA1c at start of the study was 302.09, 10.40respectively, mean blood urea and creatinine 41.34, 0.72respectively, mean weight was 80.03 kg, by the end of the study period all the reading was reduced to the following levels: , 198.33, 8.43, 40.67, .69 in the same previous order, apart from the mean weight which showed an increase to 81.82. While compliance was increased from score of 6 up to score of 8. **Conclusion:** Drug combination and single pills have assured compliance and hence blood sugar control and have a negative impact on the occurrence of complications.

**Keywords:** Compliance, diabetes, oral hypoglycemia, fixed dose.

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## INTRODUCTION

Type 2 Diabetes (T2D) remains a massive global health crisis, with nearly 1 in 9 adults (around 589 million) having diabetes (mostly T2D), over 40% undiagnosed, and rising dramatically in low-to-middle-income countries. [1]

Adherence to treatment represents a major challenge, with low rates often leading to poor blood sugar control and complications, the main reason for lack of adherence is the multimerizations and complexity of treatment that are used as multidose, making forgetfulness the main barrier to compliance and hence poor control and complications development thus simpler medication plans is the best option. [2,3]

Besides, improving diabetics adherence to medications is recognized as one of the most impactful and cost-effective strategies for improving the health of

the general population through complications reduction and hence less admissions are required.[4]

Pioglitazone is related to thiazolidinedione drug class, which is FDA approved for type two diabetes for adults, its activates {peroxisome proliferator-activated receptor gamma nuclear receptor of fat, liver and thereby improving insulin sensitivity, also decreases gluconeogenesis in the liver, it involves also lipid metabolism (specifically triglycerides), and preserve the function of pancreatic Beta cells.[5]

Pioglitazones eventually reduce HbA1c, increase body insulin sensitivity without causing hypoglycemia because they do not force insulin secretion but rather enhancing its effect.[5]

Glimepiride is a third-generation sulfonylurea, acts by stimulating pancreas to secrete insulin, which can cause hypoglycemia.[6]

Dapagliflozin is a SGL2 inhibitor (sodium-glucose co transporter 2 inhibitor) in the kidneys, which cause glucose excretion in urine rather than absorption, such mode of action will collectively improve blood sugar control, improves heart failure and slow chronic kidney disease progression, on the other hand this increases urinary tract and genital infections.[7]

Metformin is considered the 1<sup>st</sup> line treatment of type two diabetes, it acts by both decreasing intestinal glucose absorption and hepatic gluconeogenesis and thereby hypoglycemia, on the long run may cause vitamin B 12 deficiency.[8]

Reliance of type two diabetes management on monotherapy unlikely achieve and maintain the required glycemic target, hence early combination hypoglycemic drugs is essential for required results. [9]

The combined pill containing pioglitazone 30 mg and glimepiride 2 mg is a recognized fixed-dose medication used to treat type 2 diabetes, must be taken with the 1<sup>st</sup> meal, while fixed-dose combination tablet containing dapagliflozin 10 mg and metformin 1000 mg (extended-release form) is available as a single daily dose medication at night, such regimen confers tight control of blood sugar which is a necessity not only for short term control noted by HbA1c level but also on the long run to improve overall condition such as body weight and prevents complications assessed by blood urea and creatinine. [10,11]

So, the aim of the study is to compare glycemic control of fixed dose combination drugs to multiple

drugs of different timing on the base of patient compliance as ease and feasibility of use.

## METHODOLOGY

This is a prospective follow up study included 67 type two diabetic patients who fit the following Inclusion Criteria:

Age range within 18-65 years with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) for at least 1 year with HbA1c levels between 7.5% and 10.5% at screening, and were on loose dose combination.

Before the study patients were assessed for compliance by Morisky Medication Adherence Scale, weight was measured, blood investigations include of fasting blood sugar, HbA1c, blood urea, creatinine, then patients were prescribed a combined pill of pioglitazone 30 mg and glimepiride 2 mg to be taken with the 1<sup>st</sup> meal, and a combined tablet of dapagliflozin 10 mg and metformin 1000 mg at night, then patients were followed up for 28 weeks by repeating weight measurements blood investigations of fasting blood sugar, HbA1c, blood urea, serum creatinine, adherence to medications was reassessed by Morisky Medications scale.

Data entry was done to Excell sheet, analysis of data was done using SPSS version 26, mean and standard deviation were calculated for quantitative data, number and percentage were calculated for qualitative data, paired T test was calculated for significance of difference, while association was assessed by Chi square test, P value was set below 0.05 for significance.

## RESULTS

**Table 1: Test of significance for patient's blood readings and weight before and after treatment regimen**

Mean	N	Std. Deviation	Std. Error Mean	Correlation	T test	P value
FBS before	302.09	67	106.736	13.040	.559	.000
FBS after	198.33	67	83.111	10.154		
HbA1c before	10.40	66	2.014	.248	.742	.000
HbA1c after	8.43	66	1.721	.212		
Weight before	80.03	65	18.152	2.251	.980	.000
Weight after	81.82	65	17.012	2.110		
Urea before	41.34	58	16.776	2.203	.698	.000
Urea after	40.67	58	13.755	1.806		
Creatinine before	.72	54	.369	.050	.633	.000
Creatinine after	.69	54	.285	.039		

Table 1 shows FBS (Fasting Blood Sugar): Dropped by 103.76 mg/dL (from 302.09 to 198.33), while HbA1c: Decreased by 1.97% (from 10.4% to 8.43%), regarding weight it was Increased slightly by

1.79 units (80.03 to 81.82), for Urea & Creatinine: Both showed very slight decreases:

Urea from 41.34 to 40.67, while Creatinine from 0.72 to 0.69, All correlations are (Sig. = .000) so are highly significant (p<.001).

**Table 2: Association of weight change with gender**

Gender	Increase	Decrease	Stable	Total
Female	37	7	3	47
Male	13	6	1	20
Total	50	16	6	67

The chi-square statistic is 0.969. the *p*-value is .325. the result is not significant at *p*<.05.

Among 47 female, 37(78.7%) experienced an increase, while for the 20 male, 13(65%) showed increased 65%, the *p*-value of .325, which indicates no

statistically significant association between gender and weight change.

**Table 3: Statistical Significance of HbA1c Reduction and its Interaction with Patient Age (ANOVA)**

Variable	Sum of Squares	df	Mean Square	F	Sig.
HbA1c	9.088	1	9.088	9.667	.003
HbA1c * Age	.674	1	.674	.717	.400
Error(HbA1c)	60.166	64	.940		

There is significant reduction of HbA1C (.003) but no significant variation based on age (*p*=.400).

## DISCUSSION

Patient compliance to fixed dose combination is high, which in turn leads to improved glycemic control in comparison to loose-dose combination.[12]

So our sample were at the start of study on multiple separated oral hypoglycemic medications(LDCs), with poor compliance as assessed by Morisky Medication Adherence Scale(3),with poor glycemic control expressed by mean fasting blood sugar(302.09 g/dl), HbA1c (10.4), after the introduction of the fixed dose combination of single combined pioglitazone and glimepiride breakfast pill and night single combined dapagliflozin and metformin tablet through period of 28weeks of follow up, improvement in blood glycemic control was noticed (mean fasting blood sugar 198.33g/dl and mean HbA1c 8.43), without affecting renal function as noted by blood urea and serum creatinine at the start of the study and thereafter, (41.34, 4067),(72,69)alternatively, in comparison to another study with 1 year follow up showing similar results of better glycemic control and moreover blood pressure control of diabetics who were on monotherapy and were assigned FDCs.[13]

On the other hand, body weight expressed a minor increase up to two kg to the mean body weight (80.3 to 81.82) which did not impact blood sugar control, this can be related to both pioglitazones which sensitize insulin, which by itself reflects positive treatment response. [14]

Glimepiride use has been shown to actually decrease body weight although its main function is insulin secretion.[6]

Our results show no significant association of gender with therapeutic effects reflected by glycemic improvement (the *p*-value is .325.), such fact have been

documented by the review of article that explored the effect of gender for treatment adherence, that declared mixed results and the main barrier to adherence was the and suggested instead the single pill use regimen to ascertain compliance and hence good control.[15]

Adherence to treatment in regard to age is U shaped relation, in which adherence increase till the age of 60-69 thereafter adherence decline due to impaired cognition, a review of article in this regard has supported this finding, but showed that when drugs number exceeds 9, the adherence declines regardless the age , which supports our finding in which blood sugar control was noticed regardless the age effect(*p*=400).[16]

In conclusion, FDCs is more reliable than LCDs in type two diabetic patients regardless age and gender, glycemic control was achieved without affecting renal function, although slight weight increase was noted, poor compliance at the start of study was noted with LDCs.

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