RESEARCH ARTICLE

# Restoration of Euglycemia in Type 2 Diabetes Patients with Pioglitazone as Fourth Drug in Oral Combination Therapy: An Experimental Study

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**ABSTRACT**

The global burden of Type 2 diabetes mellitus (T2DM) is on the increase with over 500 million individuals of the world's population being affected and diabetes associated deaths reaching over a million yearly. The progressiveness of the disease coupled with poor adherence to treatment requirements and lifestyle modifications T2DM very challenging as patients on single drug treatment may eventually require combination therapy up to the level of triple therapy without achieving euglycemia. In this study we hypothesize that the addition of pioglitazone as a fourth drug, may restore euglycemia and prevent the use of insulin.

A total of 107 T2DM patients already on triple combination therapy were recruited and pioglitazone was introduced as a fourth drug in 66 patients (experimental group) while 41 patients served and as control. After 3 months, the mean post-treatment HbA1c in the experimental group was 7.00 ± 0.50% which showed statistically significant difference compared with the experimental group's mean baseline HbA1c of 8.47 ± 0.51% at $p < 0.05$. Also, the mean post-treatment HbA1c of the experiment group showed statistically significant difference when compared with the post-treatment HbA1c of the control group at $p < 0.05$, i.e. 7.00 ± 0.50% (experimental group) vs. 8.55 ± 0.73% (control group).

Our findings indicate that the addition of pioglitazone significantly improved the glycemic profile of the experimental subjects without necessitating the adoption of complex insulin-dependent strategies.

**Keywords:** Euglycemia, HbA1c, Insulin, Pioglitazone drug, Type 2 Diabetes.

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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) has a well-defined pathogenesis which starts when an initial genetic predisposition is coupled with unhealthy diet and sedentary lifestyle that culminates into elevations in body mass index and fasting plasma glucose level. This persistent hyperglycemia leads to the onset of insulin resistance which then transforms a normal glucose tolerance state to a condition of impaired glucose tolerance and eventually, loss of beta-cell function.[1]

Globally, the burden of T2DM, which is a major health concern, is on the increase with over 500 million individuals representing 6.5% of the world's population being affected – the prevalence of which is rapidly increasing and over a million deaths attributable diabetes yearly. For this reason, T2DM has been recognised as the 9$^{th}$ leading contributor to global mortality.[2] The morbidity of diabetes comes with severe financial implications as the cost of diabetes care is at about 3.2 times greater than the average per capita healthcare expenditure, which could increase to 9.4 times when associated complications sets in.[3] The challenges faced with control of the global spread of T2DM is attributable to poor financial status, inadequate health promotion and lack of awareness on the disease resulting to suboptimal control of blood glucose, blood pressure, and other associated complications.[4]

Although T2DM is a problem of response to insulin rather than production of insulin, the hallmarks of the disease are basically, increase in hepatic glucose production, impairment of insulin action i.e. insulin resistance, and eventually, reduction of insulin secretion.[5] Therefore, mechanism of action of the main classes of available oral antidiabetic drugs (OHDs) are; reduction of carbohydrate absorption in the gastrointestinal tract, i.e., α-glucosidase inhibitors, improvement of peripheral glucose disposal i.e. thiazolidinediones and biguanides, reduction of hepatic glucose release i.e. biguanides, and enhancement of insulin secretion i.e. incretin memetics, sulfonylurea & non-sulfonylurea.[6,7]

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Since the aim of diabetes treatment is timely and sustainable reduction of hyperglycemia (glycemic control), to prevent serious damage to the blood vessels and nerves, leading to development of both micro- and macrovascular complications, clinicians have over the last decade, recommended a strategic selection of more than two suitable pharmacodynamic agents that can provide the optimal metabolic benefits, in a combination therapy for patients with T2DM.[4] This strategy can enable the effectuation of rapid long term glycemic control, treat or minimize risk factors associated with development of T2DM, and reduce inflammation.[8] Studies have shown that conventional monotherapy is sequentially followed up with oral antidiabetic drugs to achieve effective long term treatment of T2DM as well as its associated complications.[9,10] Moreover, in comparison to monotherapy, the combination of oral drugs have shown to improve glycemic control faster and more effectively.[11,12]

The national institute for health and care excellence (NICE) guidelines for management of T2DM in adults recommends monotherapy i.e., the use of single non-insulin glucose lowering drug, for initial drug treatment. Dual therapy, which implies combination of 2 non-insulin drugs is recommended for first intensification treatment, while for second intensification treatment, combination of 3 non-insulin glucose lowering drugs (triple therapy) or any treatment combination that includes insulin, is recommended.[13] Interestingly however, the NICE guidelines limits combination therapy to only 3 non-insulin drugs as it recommends a combination therapy of metformin, a sulfonylurea and an incretion memetic for cases of T2DM where triple therapy is not effective or contraindicated.[14]

In this study we hypothesize that the addition of a fourth drug, in this case, pioglitazone may restore euglycemia and prevent the use of insulin as many T2DM patients dislike insulin therapy.

Pioglitazone is a potent antihyperglycaemic drug which inhibits hepatic gluconeogenesis and promotes splanchnic/peripheral glucose uptake by increasing insulin sensitivity of hepatic and peripheral tissues, thus correcting insulin resistance.[15] This thiazolidinedione is well tolerated, although weight gain, oedema are the common adverse effects. The drug has a bioavailability of 83% and is metabolised by the cytochrome P450 system with approximately 15–30% excreted in urine while the remainder is egested in faeces.[16] Short and long term improvement in glycemic control as well as serum lipid profiles have been recorded in clinical trials involving the use of pioglitazone either in monotherapy or combination therapy with metformn, repaglinide, a sulfonyurea or insulin.[17,18]

Therefore, we identified consented T2DM patients that have reached 3 maximum oral drug treatment and have refused insulin therapy. We then administered pioglitazone as a fourth drug for 3 months after which glycated haemoglobin was analysed and compared with baseline values as well as patients who had no change in treatment (control). The findings from this study could provide useful insights on possible treatment options that can achieve sustainable glycemic control even in T2DM patients where 3-drug combination therapy has been ineffective.

## METHODS

A total of 107 individuals with T2DM on routine clinical visit at the (Al-Hussein Medical City in Kerbala, Iraq), all of which had reached maximum of 3 orals non-insulin antidiabetic drug treatment (i.e., sulphonylurea, metformin, and one of the incretion mimetic) without achieving glycemic goal and have refused insulin therapy, were recruited for this study.

The exclusion criteria employed included individuals with volume overload state like renal failure, liver failure, or heart failure, current infection, pregnancy, CA bladder and type 1 diabetes mellitus. Ethical approval was obtained from the Hospital's Research and Ethics Committee of and informed consent was obtained from all the patients as the scope and purpose of the study was clearly stated. The participants were then grouped into two:

i. The experimental group, comprising of 66 patients which were given lifestyle recommendations and pioglitazone was administered as the fourth drug.
ii. The control group, comprising of 41 patients which were given lifestyle recommendation and had no change in treatment.

Sociodemographic data, treatment history, response to drugs that may affect diabetes i.e., hydrochlorothiazide and thyroxine, as well as duration of diabetes were extracted from the patients' hospital records.

Venous blood samples were collected, with minimal occlusion of the vein. Haemoglobin (Hb) was measured using an automatic hematology analyzer (automated Swelab counter Boule Medical, Stockholm, Sweden) and glycated haemoglobin (HbA1c) was measured using fully automatic chemistry analyzer (Smart -150, USA). Normal range was defined as HbA1c between 4.2–6.2%.[19] However, our target for euglycemia was set at HbA1c $\leq$ 6.5%.

### Statistical Analysis

Analysis of data obtained was performed with the software program SPSS (version 24.0). All data were presented as mean ± standard deviation and independent t-tests was used to determine statistically significant difference between the experimental and control group.

## RESULTS

The total number of T2DM patients recruited in this study was 106, out of which 66 individuals belonged to the experimental group which comprised of 32 females and 34 males, all with a mean age of 39.33 ± 7.95 years. The control group had 41 individuals comprising of 23 females and 18 males, all with the mean age of 39.98 ± 8.87 years.

Analysis of haemoglobin levels revealed no significant difference between the experimental and the control groups i.e., 12.46 ± 1.60% for experimental group against 12.29 ± 1.56% in the control group. Likewise, the difference in values for duration of disease condition as well as baseline HbA1c between the groups was not statistically significant at $p < 0.05$.

As shown in Table 1, the experimental group had a mean disease duration of 7.20 ± 2.84 years against 6.95 ± 1.71 years in the control group. Also, the experimental group has a mean baseline HbA1c of 8.47 ± 0.51% compared to 8.65 ± 0.44% in the control group.

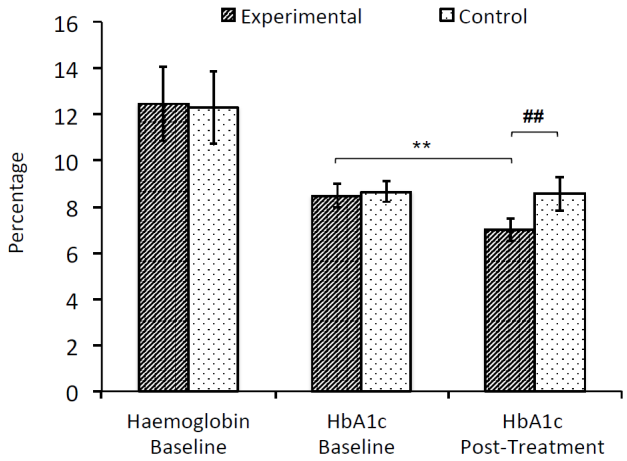


**Figure 1:** Baseline and post-treatment glycemic indices of the experimental and control subjects.
The patients had comparable baseline levels of haemoglobin and HbA1c, however while the post-treatment HbA1c in the control group remain relatively unchanged, there was significant reduction in HbA1c for the experimental group after treatment.
**indicates statistically significant difference between mean post-treatment HbA1c in the Experimental subjects compared to mean baseline HbA1c in the Experimental subjects at $p < 0.05$
##indicates statistically significant difference between mean post-treatment HbA1c in the Experimental subjects compared to mean post-treatment HbA1c in the Control subjects at $p < 0.05$

However, the mean post-treatment HbA1c in the experimental group was 7.00 ± 0.50% which showed statistically significant difference when compared with the experimental group's mean baseline HbA1c of 8.47 ± 0.51% at $p < 0.05$. Also, the mean post-treatment HbA1c of the Experiment group showed statistically significant difference when compared with the post-treatment HbA1c of the control group at $p < 0.05$, i.e., 7.00 ± 0.50% (experimental group) vs 8.55 ± 0.73% (control group). The graphical presentation of the data obtained is shown in Figure 1.

The HbA1c target of ≤ 6.5% was achieved in 14 patients from the experimental group, with a mean HbA1c of 6.30 ± 0.14% which showed significant difference in relation to the mean HbA1c of the overall experimental group.

It is noteworthy to report that some patients were already using drugs that could affect diabetes. Specifically, in the experimental group, 8 patients were using hydrochlorothiazide and 12 patients were on thyroxine while the control group had 4 patients using hydrochlorothiazide with 5 patients using thyroxine.

## DISCUSSION

The most prevailing challenges faced by clinicians in achieving T2DM patient-individualised glycemic goal are due to the progressive nature of the condition.[20] For newly-diagnosed T2DM patients, the widely accepted initiating therapy is placing the patient on metformin monotherapy, combined with recommendation of lifestyle modification. However, despite the competent efficacy of metformin coupled with weight loss and low risk of hypoglycemia, challenges with glycemic control are encountered in the clinical management of the disease and patients would eventually require to be placed on combination therapy.[21]

**Table 1:** Glycemic indices of the experimental and control subjects.

| | *All* | | *Achieved Target* | |
|---|---|---|---|---|
| | *Experimental (mean ± SD)* | *Control (mean ± SD)* | *Experimental (mean ± SD)* | *Control (mean ± SD)* |
| n | 66 | 41 | 14 | 0 |
| Age (years) | 39.33 ± 7.95 | 39.98 ± 8.87 | 40.79 ± 6.48 | NA |
| Gender (n) | | | | |
| Females | 32 | 23 | 8 | NA |
| Males | 34 | 18 | 6 | NA |
| Haemoglobin (%) | 12.46 ± 1.60 | 12.29 ± 1.56 | 12.06 ± 1.56 | NA |
| Baseline HbA1c (%) | 8.47 ± 0.51 | 8.65 ± 0.44 | 8.67 ± 0.49 | NA |
| Post-Treatment HbA1c (%) | 7.00 ± 0.50*# | 8.55 ± 0.73 | 6.30 ± 0.14† | NA |
| Drugs Affecting Diabetes (n) | | | | |
| None | 46 | 32 | 13 | NA |
| Hydrochlorothiazide | 8 | 4 | 0 | NA |
| Thyroxine | 12 | 5 | 1 | NA |
| Duration of disease (years) | 7.20 ± 2.84 | 6.95 ± 1.71 | 6.69 ± 1.77 | NA |

*indicates statistical significant difference between mean post-treatment HbA1c in the Experimental subjects compared to mean baseline HbA1c in the Experimental subjects at $p < 0.05$
#indicates statistical significant difference between mean post-treatment HbA1c in the Experimental subjects compared to mean post-treatment HbA1c in the Control subjects at $p < 0.05$
†indicates statistical significant difference between in mean HbA1c of the Experimental subjects with the target HbA1c compared to the mean post-treatment HbA1c in the overall Experimental group at $p < 0.05$

Clinicians have options of guidelines and treatment algorithms to choose from for non-insulin combination therapy as recommended by expert bodies such as NICE, the American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) or the American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE).[21] Based on these guidelines, the maximum drug combination is three non-insulin antidiabetic drugs i.e. triple drug therapy, should the target HbA1c remain unachieved after 3 months of dual drug therapy, after which more complex insulin strategies are adopted.[21-23] In this study, we specifically identified patients already on three drugs oral combination therapy, who are yet to achieve euglycemia, and placed them on pioglitazone as a forth drug. These patients were of a relatively young mean age (39 years) and of male and female gender, for both experimental and control groups - an indication that the challenges encountered with achieving glycemic goal was not gender based or associated with senescence and frailty care but could be as a result of poor adherence to treatment obligations or lifestyle changes.

Nevertheless, the introduction of pioglitazone resulted to the achievement of significant reduction in HbA1c levels after 3 months when post-treatment values of the experimental group when compared with the baseline HbA1c of the same group, representing a HbA1c change of -1.47%. Similarly, the post-treatment HbA1c of the experimental group was significantly lower than that of the control group i.e., -1.55% despite having comparable baseline HbA1c values i.e., a difference of -0.18 % as well as modest difference in baseline haemoglobin levels and duration of disease. This is indicative of the corroborative effect of introducing pioglitazone as a fourth drug on the effectiveness of combination therapy. The possible explanation for this finding is not farfetched. Being the only thiazolidinedione currently available in most countries following controversies with rosiglitazone,[24] pioglitazone targets the major problem of T2DM, which is insulin resistance by inhibiting the Peroxisome Proliferator activated receptor (PPAR) γ agonists which are key regulators of carbohydrate and lipid metabolism as they stimulate protein synthesis through wide variety of processes including energetic metabolism, cellular differentiation and proliferation.[25] Thiazolidinedione improve sensitivity to endogenous and exogenous insulin by liver, muscle and other tissues resulting to increase in glucose uptake and suppression of glucose output in the liver without risk of hypoglycemia.[26] Also, when used in monotherapy, pioglitazone has been shown to reduce HbA1c levels by 0.5–1.4%.[27] Moreover, pioglitazone has shown superior efficacy in glycemic control when in comparison with other antidiabetic drugs such as metformin,[28] insulin,[29] acarbose,[30] sulfonylurea[31] as well as the thiazolidinedione rosiglitazone.[32] Interestingly, pioglitazone has also shown to be competitively effective when used in combination therapy. In combination with repaglinide, pioglitazone has shown a -1.8% change in HbA1c,[33] while the reductions observed when combined with insulin, metformin, and a sulfonylurea were -1.3%, 1.0% and -1.2%, respectively.[34-36]

Despite the significant reduction in HbA1c observed in this study, our target HbA1c was only achieved in 21% of the experimental subjects as approximately 30% of the experimental patients were on either hydrochlorothiazide or thyroxine, which are known to aggravate the hyperglycemic state in T2DM. This suggests that the use of these diabetes-affecting drugs may have negatively affected the treatment drug combination impeded the conceivability of achieving our glycemic target. Notwithstanding however, the reduction in mean HbA1c of the patients in which our glycemic goal was achieved, when compared with mean baseline value is -2.07%. Such level of reduction in HbA1c to healthy normoglycemic ranges implies restoration of euglycemia and further support send the prowess of pioglitazone in achieving glycemic goal even as a fourth drug in oral combination therapy for T2DM patients.

In conclusion, the addition of pioglitazone in treatment combination of T2DM patients that have otherwise exhausted the number of non-insulin drugs in combination therapy, has not only reduced the progress of the disease as well as the risk of diabetes mismanagement and its associated complications, but has also significantly improved the glycemic profile of the experimental subjects with 21% euglycemia achieved without necessitating the adoption of complex insulin-dependent strategies.

The relatively small sample size and insufficiency in number of parameters evaluated, are some of the limitations of this study, hence it is recommended that future studies analyse other indices associated with the management of diabetes, prolong the treatment duration. Although thiazolidinediones have impressive tolerability and drug-interaction profiles in relation to other antihyperglycemic classes, as pioglitazone can be used by patients with impaired renal function,[37] it is important to explore any potential renal or hepatic adverse events that may arise from its usage as a fourth drug.

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