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**Original Research Article**

# Clinical effectiveness of a combination of metformin and ipragliflozin in the management of patients with type-2 diabetes mellitus

**Xiaojie Tan[1], Guijuan Sun[2], Fei Yuan[3], Linfang Qu[3], Aiqiang Han[4]***
*[1]Department of Pharmacy, Jiaozhou Central Hospital of Qingdao, [2]Department of Encephalopathy, [3]Department of Internal Medicine, Shandong Qingdao Integrated Traditional Chinese and Western Medicine Hospital, Shandong, [4]Department of Health, The Second People's Hospital of Weifang, Weifang, China*

**For correspondence:* ***Email:*** *qianghuiaoaohkx@163.com*

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## Abstract

***Purpose:*** *To investigate the clinical effectiveness of combination of metformin and ipragliflozin in the treatment of patients with type-2 diabetes mellitus (T2DM).*
***Methods:*** *Patients with T2DM (n = 100) aged 35 – 68 years (mean age = 51.5 ± 16.5 years) were recruited over a 1-year period and randomly assigned to 2 groups (50 patients/group): control and study groups. Control group patients were treated with metformin orally at a dose of 500 mg/kg body weight twice a day, while patients in the study group received 50 mg ipragliflozin/kg, orally once a day, in addition to metformin. Fasting blood glucose (FBG), 2-h postprandial blood glucose (PBG), bedtime glucose (BBG) and glycated hemoglobin (HbAlc) concentrations were measured in patients' plasma before and after treatment. Incidence of adverse reactions, changes in body fat and clinical effectiveness were also determined.*
***Results:*** *FBG, 2-h PBG, BBG, HbAlc, body fat and incidence of adverse reactions were markedly reduced in T2DM patients treated with the combination of metformin and ipragliflozin, relative to those treated with metformin alone ($p < 0.05$). After treatment, the proportion of outcomes categorized as 'markedly effective' and 'total effectiveness' was higher in the study group than in the control group ($p < 0.05$).*
***Conclusion:*** *The combination of metformin and ipragliflozin is safer and more clinically effective in the treatment of T2DM than metformin monotherapy.*

***Keywords:*** *Blood glucose, Diabetes mellitus, Clinical effectiveness, Ipragliflozin, Metformin*



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## INTRODUCTION

Improved standard of living particularly among the younger population has contributed significantly to drastic rise in cases of diabetes mellitus (DM). Diabetes mellitus (DM) is characterized by reduced pancreatic function and insufficient insulin secretion, which result in hyperglycemia (elevated blood glucose level) and glucosuria (elevated urine glucose level) [1-3]. Diabetes mellitus (DM) is classified as type-1 or type-2 DM. Type-1 diabetes mellitus (T1DM) is

congenital, and the treatment involves insulin injection from birth. Type-2 diabetes mellitus (T2DM), with characteristics with insufficient insulin secretion is attributed to impaired pancreatic function caused by acquired lifestyle habits (lifestyle modification), genetics and other factors. Patients with T2DM are generally treated with oral hypoglycemic drugs in combination with exercise and diet. In the event that oral hypoglycemic drugs fail to meet the desired goal, insulin injections are administered [4-6]. Metformin, the most commonly used oral medication for DM, has the advantages of satisfactory hypoglycemic effect and low side effects. As DM progresses, oral metformin and other hypoglycemic drugs are usually combined. Gliflozin drugs are a class of newly developed oral hypoglycemic agents used for the treatment of T2DM. They act as inhibitors of sodium-glucose cotransporter-2 (SGLT2). Examples of gliflozin drugs are dapagliflozin, empagliflozin and ipragliflozin [7-9]. This study was to investigate the clinical effectiveness of the combination of metformin and ipragliflozin in the treatment of patients with T2DM.

## METHODS

### Drugs

Metformin was a product of Beijing Taiyang Pharmaceutical Co. Ltd, while ipragliflozin was obtained from AstraZeneca AB (England).

### Patients and general information

Patients with T2DM (n = 100) aged 35 – 68 years (mean age = 51.5 ± 16.5 years) were recruited over a 1-year period and randomly assigned to 2 groups (50 patients/group): control and observation groups. Patients in the study group were aged 36 - 66 years (mean age = 51 ± 15 years), while those in control group were aged 35 - 68 years (mean age = 51.5 ± 16.5 years).

### *Inclusion criteria*

The following categories of patients were included in the study: (1) patients diagnosed with T2DM; (2) adult patients aged ≥ 18 years; (3) patients with normal heart, function, lung function and kidney function, without other systemic diseases; (4) patients with no history of drug allergy or drug abuse, and (5) patients who signed written informed consents with their family members. Patients with T1DM, coagulation disorder, or patients on anticoagulant drugs, as well as those with history of insulin treatment were excluded from the study. The study protocol was reviewed and approved by the Human Ethics Committee (approval no. 2017-234) of The Second People's Hospital of Weifang, Weifang, China [10].

### Study design

The control group patients were given orally with metformin at a dose of 500 mg/kg twice a day, while patients in study group received 50 mg ipragliflozin/kg, once a day orally, in addition to metformin. Treatment in the two groups lasted 3 months, during which the patients paid close attention to their diets, carried out moderate exercise, and were not allowed to use other antidiabetic drugs.

### Treatment indices

Peripheral venous blood (5 mL) was drawn from patients before and after treatment, and centrifuged at 3000 rpm for 10 min to obtain plasma that was used for analysis. Fasting blood glucose (FBG) and 2-h PBG were determined employing automated biochemical analyzer. Fasting blood glucose (FBG) of 3.9 - 6.1 mmol/L and 2-h PBG < 11 mmol/L were taken as normal. Glycated hemoglobin (HbAlc) concentration was determined using immuno-turbidimetric method. Glycated hemoglobin concentrations within the range of 4.99 - 6.79 % were considered normal. Body fat of patients was measured every 1 month for 3 months.

### Determination of curative effect

Curative effect was determined by following reductions in blood glucose and improvements in clinical symptoms. Curative effect was classified into three: *remarkably effective*, *effective* and *ineffective*. The conditions applicable to each classification were: *remarkably effective*: clinical symptoms disappeared, FBG < 6.1 mmol/L, 2-h PBG < 11.0 mmol/L, and HbAlc < 6.79 %; e*ffective*: obvious improvements in clinical symptoms, with FBG, 2-h PBG, and HbAlc within normal ranges; *ineffective*: no improvements in clinical symptoms, and no appreciable reductions in blood glucose levels. The total effectiveness was calculated as shown in Eq 1.

*A (%) = B + C ……. (1)*

*Note: A-Total effectiveness; B-remarkably effective cases; C-effective cases*

### Measurement of safety

Adverse reactions such as gastrointestinal reaction, duration of hypoglycemia and abnormal

liver and kidney functions were recorded and analyzed.

### Statistical analysis

Data analysis was performed with SPSS (20.0), expressed as mean ± SEM. Inter-group comparison was conducted by using Student *t*-test and Chi-squared test. GraphPad Prism version 7 was used to construct graphs. Values of $p < 0.05$ were declared as significant differences.

## RESULTS

### Clinicopathological data

No significant differences between the two groups in clinicopathological data for the patients such as gender, age, course of disease, and comorbidities, were detected ($p > 0.05$; Table 1).

### Blood glucose levels of patients

The levels of FBG, 2-h PBG and BBG observed a sharp decline in both groups of patients after treatment ($p < 0.05$). However, the study group yielded lower levels of FBG, 2-h PBG and BBG ($p < 0.05$; Figure 1).

### Levels of glycated hemoglobin of patients in each group

As shown in Figure 2, after treatment, in comparison with the control group in terms of the HbAlc level, the study group garnered an apparently lower result ($p < 0.05$).

### Comparison of curative effect

After treatment, a larger number of remarkably effective cases and a higher total effectiveness were observed in the study group ($p < 0.05$; Table 2).

### Effect of treatment on incidents of adverse reactions

There were adverse reactions such as nocturnal hypoglycemia, low vision, chronic nephritis, and constipation in both groups. However, incidents of adverse reactions were markedly reduced in the study group ($p < 0.05$). See Table 3.

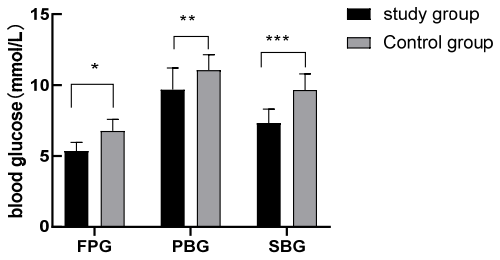


**Figure 1:** Comparison of blood glucose levels. $^{*}P < 0.05$ (FBG of study group compared with control group); $^{**}p < 0.05$ (2-h PBG of study group compared with control group); $^{***}p < 0.05$ (BBG of study group compared with control group)

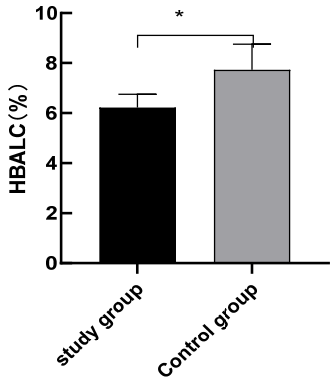


**Figure 2:** Comparison of glycated hemoglobin level; $^{*}p < 0.05$, as compared to the control group

**Table 1:** General patient profile

| Parameter | Group *Study* | *Control* | $\chi^2$ | *P*-value |
|---|---|---|---|---|
| Gender<br>Male<br>Female | 26<br>24 | 27<br>23 | 0.04 | 0.84 |
| Age (years) | 53.29 ± 6.38 | 53.40 ± 6.59 | 0.08 | 0.93 |
| Height (cm) | 173.26 ± 8.81 | 173.59± 8.66 | 0.19 | 0.85 |
| Weight (kg) | 71.04 ± 5.39 | 70.99 ± 5.42 | 0.05 | 0.96 |
| Course of disease (years) | 6.47 ± 2.08 | 6.38 ± 2.11 | 0.21 | 0.83 |
| History of smoking (years) | 5.81 ± 1.33 | 5.76 ± 1.41 | 0.18 | 0.86 |
| History of drinking (years) | 10.00 ± 2.34 | 9.86 ± 2.05 | 0.32 | 0.75 |
| Hypertension (cases) | 13 | 15 | 0.20 | 0.66 |
| Hyperlipidemia (cases) | 8 | 7 | 0.08 | 0.78 |

**Table 2:** Comparison of effectiveness of treatment

| Group | Markedly effective | Effective | Ineffective | Total effectiveness (%) |
|---|---|---|---|---|
| Study | 35 | 13 | 2 | 96 |
| Control | 10 | 26 | 14 | 72 |
| $\chi^2$ | | | | 10.710 |
| *P*-value | | | | 0.001 |

**Table 3:** Comparison of incidents of adverse reactions

| Group | Nocturnal hypoglycemia | Impaired vision | Chronic nephritis | constipation | Incidence of adverse reactions (%) |
|---|---|---|---|---|---|
| Observation | 0 | 1 | 0 | 3 | 8% |
| Control | 8 | 5 | 1 | 6 | 40% |
| $\chi^2$ | | | | | 14.04 |
| *P*-value | | | | | < 0.001 |

**Effect of treatment on body fat**

Two groups did not differ regarding body fat between the two groups before treatment ($p > 0.05$). However, after treatment, body fat of patients in study group was notably and time-dependently reduced ($p < 0.05$; Figure 3).

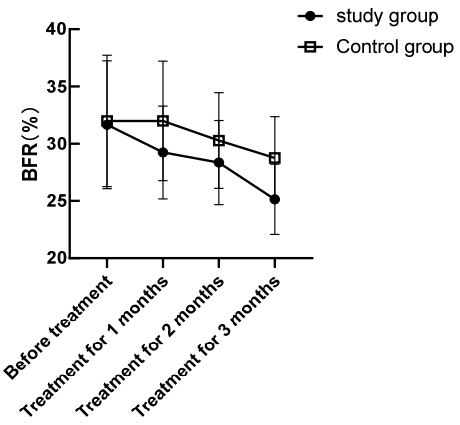


**Figure 3:** Changes in patients' body fat after treatment

## DISCUSSION

Diabetes mellitus (DM) impacts negatively on the quality of life of patients. The disease is characterized by micro- and macrovascular complications, and high morbidity. Diabetics rely on long-term hypoglycemic medication which puts considerable economic pressure on them and their family members [1-13]. Hypoglycemic therapy alone cannot sufficiently protect the secretory function of pancreatic β cells, since this may decline with duration of the disease. Thus, diabetic patients are advised to pay close attention to their diets and carry out regular exercises.

Treatment of asymptomatic DM requires constant monitoring of FBG, 2-h PBG and BBG [14-16]. The goals in diabetic care are to eliminate diabetes symptoms and to prevent, or at least slow the development of complications. Type-2 diabetes mellitus (T2DM) is managed with non-insulin medications, insulin (in extreme cases), weight reduction and dietary changes. Long-term hyperglycemia results in cardiovascular and cerebrovascular diseases, nephropathy, retinopathy, neuropathy and endocrine disorders. Thus, maintenance of blood glucose within a safe range is of utmost importance [17-20]. The simultaneous use of different hypoglycemic drugs predisposes patients to persistent hypoglycemia due to drug interactions, and fatality may result in severe cases. Adverse reactions often accompany such drug combinations. Ipragliflozin and metformin are common oral hypoglycemic drugs used for the treatment of T2DM.

This study evaluated the clinical effectiveness of combination of metformin and ipragliflozin in the treatment of patients with T2DM. The results showed that FBG, 2-h PBG, BBG, HbAlc, body fat and incidents of adverse reactions were markedly reduced in T2DM patients treated with the combination of metformin and ipragliflozin, relative to those treated with metformin alone. These results is indicative of that the combination therapy may exert an effective efficacy in stabilizing blood glucose. Since effectiveness of DM treatment is majorly determined by blood glucose and glycated hemoglobin indices, as well as incidents of adverse reactions, the combination therapy of metformin and ipragliflozin may be more effective than monotherapy with metformin in alleviating the complications of DM. These results are in agreement with previous reports [21].

### Limitations of the study

This study has several limitations with respect to interpretations of results. First, this study was conducted in a single region, and they might not have representability. Second, the study population was small, so the results should be interpreted with caution.

## CONCLUSION

The results obtained in this study show that the combination of metformin and ipragliflozin is safe and more clinically effective in the treatment of T2DM than metformin monotherapy.

## DECLARATIONS

### *Conflict of interest*

No conflict of interest is associated with this work.

### *Contribution of authors*

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

### *Open Access*



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