**RESEARCH ARTICLE**

# Evaluation of the Effect of Bromocriptine and Sitagliptin and Their Combination on Lipid Profile and Inflammatory Parameters in Induced Type 2 Diabetes Mellitus (T2DM) in Male Albino Rat

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**ABSTRACT**

The current study aimed to investigate the hypolipidemic and anti-inflammatory effects of recently used hypoglycemic drugs bromocriptine and sitagliptine alone and combined dosing regimen on induced type 2 diabetes mellitus (T2DM) in albino rats. Forty adult male rats divided equally into five groups including four diabetic groups and one non-diabetic representing control negative (C-ve). The four diabetic groups submitted to the following 90 day oral dosing regimens for (Control positive (C+ve), Bromocriptine (T1) at (0.07) mg/kg, Sitagliptine (T2) at (1.42) mg/kg and bromocriptine + sitagliptine (0.035 + 0.71) mg/kg B.W. Body-weight change and clinical observation were done throughout induction and treatment periods, while serum lipid profile (cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) as well as tumor necrosis factor (TNF) alpha were measured at 0, 45, 90 days after treatment. The result showed clear and significant improvement after the highest decline of body weight in all groups after T2DM induction with clear symptoms of diabetes both after alone drugs treatment in T1 and T2 with highest improvement in T3 at 45 and more at 90 day. Also lipid profile result showed clear and significant improvement in serum cholesterol, HDL, LDL, in T3, at 90 day treatment in comparison with alone drug treatment T1 and T2 after diabetic induction, while result of Triglyceride, VLDL, showed non-significant improvement between all drug treated groups in comparison with C +ve at 45 and 90 days. Such non-significant decline level was also recorded in serum TNF alpha in all drugs treated groups after 45 and 90 days after diabetes induction in comparison with the C +ve group that still at the high level. The superiority of combined therapy of Bromocriptine and Sitagliptine at half used doses over the alone therapy in combating hyperlipidemia and inflammatory effect as well as the decline in body weight of diabetic animals might attributed to the different mechanism of action of each used drug that probably exert potentiation in therapeutic effects against the studied parameters after induction of T2DM in rats.

**Keywords:** Bromocriptine, High-density lipoprotein, Sitagliptine, TNF alpha, Triglyceride.

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## INTRODUCTION

In type 2 diabetes (T2D), insulin resistance is associated with impaired glucose tolerance; concurrent islet beta cell injury may lead to insulin deficiency, which affects glucose utilization by skeletal muscle, liver, and adipose tissues.[1] Because of atherogenic abnormalities and dyslipidemia, patients with T2D are more likely to develop cardiovascular disease. The leading cause of morbidity and mortality worldwide is coronary artery disease, specifically myocardial infarction.[2] Hyperglycemia and atherosclerosis are associated with T2D.[3] Glycation of all proteins occurs as a result of persistent hyperglycemia, particularly collagen crosslinking and arterial wall matrix proteins. Endothelial cell dysfunction results, which contributes to atherosclerosis. Diabetes mellitus is linked to a 95% prevalence of dyslipidemia.[4] The early detection and treatment of hyperlipidemia in diabetic patients reduces their risk of cardiovascular and cerebrovascular disease.[5] Although lifestyle changes like diet and exercise can help improve diabetic dyslipidemia, pharmacological therapy is frequently required.[6]

Glycemic control and lower HbA1c levels can be maintained by combining two therapeutic drugs that target

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both insulin resistance and insulin secretion abnormalities.[7] For optimal glycemic control with minimal side effects, such as hypoglycemia and weight gain, the chosen regimen should also provide physiologically rapid postprandial insulin release. Combination therapy's mechanisms of action must be at least additive, if not synergistic. An insulin sensitizer in combination with an insulin secretagog, or two different insulin sensitizer drugs.[8]

Bromocriptine mesylate was recently approved by the FDA as a supplemental medication to help with glycemic control in adults with T2DM.[9] Bromocriptine is a dopamine D2 receptor agonist that was approved by the US Food and Drug Administration (FDA) in December 2018 as the first anti-diabetic drug. It improves insulin sensitivity by suppressing hepatic glucose production, reducing adipose tissue lipolysis, and suppressing hepatic glucose production.[10]

Sitagliptin is the first dipeptidyl peptidase 4 (DPP4) inhibitor that enhances the effect of incretins like GLP-1 (glucagon-like peptide-1),[11] which helps regulate blood glucose levels, insulin secretion, and fatty acid metabolism.[12] In diabetics and non-diabetics, sitagliptin has been shown to have anti-inflammatory effects by lowering CRP.[13]

## MATERIAL AND METHODS

### Experimental Animals

Total number of forty male albino rats was used in the experiment, they aged over 3 months with weight range from 200–300 gm. Animals were raised and bred in the Animal House of College of Veterinary Medicine/University of Diyala. They were accommodated in a quiet room in plastic cages with sawdust and allowed free access to water and pelleted food. The room temperature was kept at a 24 ± 1°C, and lights were turned on at 6:00 AM and turned off at 6:00 PM (12:12 h light: dark cycle). The experiment was performed in animals under the rules and ethics submitted by the University of Baghdad and College of Veterinary Medicine.

### Experimental Design

*Design of Study*

Forty adult male albino rats nearly at the same age and weight were divided equally in to five groups, four diabetic groups and one non diabetic group.

- First group is control negative group (C –ve) in which the eight male rat were given distilled water only orally for three months.
- Second group is control positive group (C +ve) in which eight diabetic male rats were administrated orally distilled water for three months.
- Third group (T1) in which eight diabetic rats given bromocriptine at dose 0.07 mg/kg orally for three months using gavage needle.
- Fourth group (T2) in which eight diabetic male rats given sitagliptin to diabetic rats at a dose (1.42) mg/kg daily orally for three months using gavage needle.
- Fifth group (T3) in which eight diabetic male rats given bromocriptine and sitagliptin in combination to diabetic rats at half therapeutic doses (0.035 and 0.71) mg/kg daily orally respectively for three months using gavage needle.

*Induction of T2DM*

DM type 2 was induced in male albino rats according to[14] in which alloxan at dose 120 mg/kg and nicotinamide 50 mg/kg were given IP to the different dosing diabetic animal groups. The assurance of diabetes were recorded according to estimation of FBS at level >200 mg/dL. Then the diabetic animals were allocated to different dosing animal groups.

### Studied Parameters

*Determination of Lipid profile*

Total cholesterol concentration, HDL-C concentration and triglyceride concentration was determined according to commercial kit (Human clinical system). While determination of VLDL-C concentration[15] by the following equation VLDL = 1/5 *triglyceride and LDL-C was obtained[15] by the

**Table 1:** Animal body weight changes /gm in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods groups* | *Before induction T2DM* | *After 30 days treatment* | *After 60 days treatment* | *After 90 days treatment* |
|---|---|---|---|---|
| C -ve | 230.6 ± 10.953<br>D a | 264.6 ± 10.769<br>C a | 303.3 ± 11.879<br>B a | 346.1 ± 7.790<br>A a |
| C +ve | 249.3 ± 20.437<br>A a | 227.2 ± 17.564<br>AB b | 204.5 ± 15.556<br>BC b | 188.6 ± 15.537<br>C d |
| T1 | 245.3 ±23.934<br>C a | 256.8 ± 13.097<br>BC ab | 280.8 ± 17.340<br>AB a | 303.6 ±14.471<br>A bc |
| T2 | 240.3 ± 17.622<br>C a | 258.1 ± 17.357<br>BC a | 278.8 ± 18.177<br>B a | 308.3 ± 12.176<br>A bc |
| T3 | 256.5 ±22.064<br>C a | 271.5 ± 11.489<br>BC a | 292.0 ±10.378<br>AB a | 319.6 ± 10.377<br>A ab |

Capital letters denote differences within groups, $p > 0.05$
Small letters denote significant differences between groups, $p > 0.05$.

following equation:- LDL-C = Total cholesterol –HDL-C – VLDL-C. While rat TNF-α (Tumor Necrosis Factor Alpha) level performed according to the commercial kit instruction (Elabscience). All this tests are estimated before induction T2DM, 45 and 90 days treatment.

*Statistical Analysis*

Statistical analysis of data was performed by Statistical Package for the Social Sciences (SPSS) on the basis of two-way Analysis of Variance (ANOVA) with a significant level of ($p < 0.05$). Specific group differences were determined using least significant differences (LSD) to compare between means has been indicated.[16]

## RESULTS

### Body Weight Changes

The results of body weight changes showed that there is a continuous higher increase in body weight rate of control negative group (C -ve) in comparison with all treated diabetic groups (T1, T2, T3 and C +ve) directly after induction. While T1, T2 and T3 showed significant increase ($p \leq 0.05$) from 30 day till the end of the study in comparison with the period directly before induction of T2DM. While control positive group (C +ve) recorded continuous significant decline in body weight in comparison with all treated groups till the end of the study (Table 1).

### Total Cholesterol (mg/dL) Level

Table 2 listed the result of total cholesterol level between the treated groups recorded a significant increase ($p \leq 0.05$) in T1, T2, T3 and C +ve at 45 days after induction, but after 90 days treatment the total cholesterol level showed improvement and recorded a significant reduction in treated groups (T2 and T3) in comparison with (C +ve) group.

### Triglyceride (mg/dL) Level

Table 3 listed the result of triglyceride level between the treated groups that showed a significant decrease ($p \leq 0.05$) in T2 and T3 at 45 days after induction, but after 90 days treatment the triglyceride level showed improvement and recorded a significant reduction in treated groups ( T2 and T3) in comparison with (C +ve) group.

**Table 2:** Total cholesterol (mg/dL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C - ve | 5.706 ± 105.15<br>A a | 5.406 ± 107.70<br>A c | 3.190 ± 102.97<br>A d |
| C +ve | 5.843 ± 104.91<br>B a | 8.273 ± 151.56<br>A a | 3.022 ± 160.73<br>A a |
| T1 | 5.292 ± 105.24<br>C a | 2.239 ± 140.23<br>A b | 4.415 ± 131.57<br>B b |
| T2 | 5.910 ± 106.01<br>C a | 3.356 ± 136.96<br>A b | 3.455 ± 121.38<br>B c |
| T3 | 5.654 ± 104.77<br>B a | 2.905 ± 134.31<br>A b | 2.929 ± 113.96<br>B c |

Capital letters denote differences within groups, p > 0.05
Small letters denote significant differences between groups, p > 0.05.

**Table 3:** Triglyceride (mg/dL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C -ve | 5.334 ± 105.45<br>A a | 6.072 ± 108.60<br>A d | 3.839 ± 110.33<br>A d |
| C +ve | 5.847 ± 105.01<br>B a | 4.963 ± 151.46<br>A a | 5.626 ± 153.46<br>A a |
| T1 | 5.193 ± 104.66<br>C a | 10.629 ± 142.46<br>A b | 5.527 ± 134.20<br>B b |
| T2 | 5.899 ± 106.52<br>C a | 6.679 ± 133.60<br>A c | 4.361 ± 119.46<br>B c |
| T3 | 5.291 ± 104.29<br>C a | 3.261 ± 136.33<br>A c | 8.440 ± 125.73<br>B c |

Capital letters denote differences within groups, p > 0.05
Small letters denote significant differences between groups, p > 0.05.

**Table 4:** HDL (mg/dL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C -ve | 2.512 ± 46.56<br>A a | 4.295 ± 44.51<br>A a | 3.265 ± 45.36<br>A a |
| C +ve | 2.318 ± 46.03<br>A a | 3.872 ± 32.72<br>B b | 2.438 ± 29.67<br>B c |
| T1 | 2.836 ± 46.87<br>A a | 3.113 ± 35.16<br>B b | 3.385 ± 37.93<br>B b |
| T2 | 2.093 ± 45.28<br>A a | 3.323 ± 36.92<br>B b | 2.881 ± 39.22<br>B ab |
| T3 | 2.629 ± 46.91<br>A a | 2.056 ± 35.96<br>B b | 3.655 ± 41.07<br>AB ab |

Capital letters denote differences within groups, p > 0.05
Small letters denote significant differences between groups, p > 0.05.

**Table 5:** LDL (mg/dL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C -ve | 6.307 ± 38.25<br>A a | 5.153 ± 41.47<br>A c | 4.949 ± 35.54<br>A d |
| C +ve | 6.393 ± 38.90<br>C a | 9.928 ± 88.54<br>B a | 3.991 ± 100.35<br>A a |
| T1 | 6.371 ± 38.53<br>C a | 3.216 ± 76.57<br>A b | 6.684 ± 66.79<br>B b |
| T2 | 6.184 ± 37.21<br>C a | 4.914 ± 73.31<br>A b | 5.067 ± 58.25<br>B b |
| T3 | 6.201 ± 37.94<br>C a | 2.932 ± 71.08<br>A b | 4.305 ± 47.74<br>B c |

Capital letters denote differences within groups, p > 0.05
Small letters denote significant differences between groups, p > 0.05.

**Table 6:** VLDL (mg/dL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods Groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C -ve | 1.068 ± 21.13 A a | 1.214 ± 21.72 A d | .7670 ± 22.06 A e |
| C +ve | 1.002 ± 20.19 B a | .9920 ± 30.29 A a | 1.125 ± 30.69 A a |
| T1 | 1.483 ± 21.37 C a | 2.125 ± 28.49 A b | 1.105 ± 26.84 B b |
| T2 | 1.754 ± 21.92 C a | 1.335 ± 26.72 A c | .8720 ± 23.89 B d |
| T3 | 1.970 ± 22.10 C a | 0.652 ± 27.26 A bc | 1.688 ± 25.14 B c |

Capital letters denote differences within groups, p > 0.05
Small letters denote significant differences between groups, p > 0.05.

**Table 7:** TNF alpha (pg/mL) level in induced diabetic rat groups dosed orally for three months with bromocriptine, sitagliptin and their combination.

| *Periods Groups* | *Before induction T2DM* | *After 45 days treatment* | *After 90 days treatment* |
|---|---|---|---|
| C -ve | 17.11 ± 2.257 A a | 18.01 ± 2.127 A c | 16.65 ± 1.819 A c |
| C +ve | 18.92 ± 2.637 C a | 40.08 ±7.909 A a | 37.04 ±2.727 B a |
| T1 | 17.08 ± 2.812 C a | 34.95± 2.092 A b | 25.13 ± 1.791 B b |
| T2 | 16.21 ± 2.045 C a | 31.23 ± 4.116 A b | 26.00 ± 3.384 B b |
| T3 | 16.43 ± 2.828 C a | 32.62 ± 4.654 A b | 24.83 ±3.872 B b |

Capital letters denote differences within groups, p> 0.05
Small letters denote significant differences between groups, p> 0.05.

### HDL (mg/dL) Level

The result of HDL level revealed that between the treated groups recorded a significant decrease ($p \leq 0.05$) in T1, T2, T3 and C +ve at 45, while at 90 day the result showed significant ($p \leq 0.05$) improvement and increase in all drug treated groups than control positive group (C +ve), especially in T3 that showed non-significant differences with control negative group (C -ve) (Table 4).

### LDL Level

The result of LDL level revealed that between the treated groups showed a significant increase ($p \leq 0.05$) in T1, T2, T3 and C +ve at 45 after induction, while at 90 day LDL level recorded a significant decrease ($p \leq 0.05$) in T1 and T2 in comparison with control positive, while T3 recorded the highest significant decline in comparison with other treated groups but still significantly higher than control negative group (C -ve) level (Table 5).

### VLDL Level

Between the treated groups VLDL level recorded a significant increase ($p \leq 0.05$) in T1, T2, T3 and C +ve at 45, while at 90 days the result showed a little improvement recorded continues significant decline ($p \leq 0.05$) in T1, T2 and T3 in VLDL level in comparison with C +ve group (Table 6).

### TNF Alpha Level

The results showed a significant increase ($p \leq 0.05$) in all drugs treatment groups TNF α level in comparison with (C - ve) group but they are lesser significantly than (C +ve) at (45) days of treatment, while after 90 days treatment the result recorded continues significant decrease ($p \leq 0.05$) in comparison with (C +ve) group (Table 7).

## DISCUSSION

The current study was designed and aimed to evaluate the effect of recently used oral hypoglycemic drugs (bromocriptine and Sitagliptin) at different dosing regimens as alone and combination on experimentally-induced T2DM in rats regarding to their effect on lipid profile and inflammatory parameters. Clear T2DM signs appeared after (14) day of induction in rats such as (Loss of appetite, Weight loss, Increased thirst, Smelly Ketone urea, Increase urination) except (C - ve) group, while after three months of drug treatment, the groups T1, T2 and T3 showed improvement in all diabetic signs that alleviated during the course of treatment especially T3 in comparison with control positive group (C +ve) that showed more worse signs, same results of improvement in body weight changes were recorded in all drug treated groups throughout treatment period after the significant decline in animal body weight after T2DM induction in comparison with (C +ve) that showed more declined body weight.

Diabetic dyslipidemia, which increases the risk of cardiovascular disease and atherosclerosis, has been associated to diabetes and insulin resistance/deficiency.[17] In insulin resistance/deficiency, which is often characterized by abnormal increases in triglycerides, total cholesterol, low-density lipoprotein cholesterol levels, and a reduction in high-density lipoprotein cholesterol levels, changes in lipid metabolism have been extensively reported. Lipoprotein lipase (LPL) is an enzyme that plays a critical role in lipid metabolism and has been implicated in the development of insulin resistance. The activity of LPL has been found to be reduced in diabetic patients, which invariably results in elevated triglyceride levels and dyslipidemia due to the enzyme's reduced ability to hydrolyze triglycerides.[18]

Hyperglycemia can affect vascular systems and cause circulation problems. Tissue hypoxia and excessive free radical production may result from the compromised circulation condition, resulting in the overexpression of growth factors and cytokines[19]. Bromocriptine has been shown to inhibit glucose stimulated insulin secretion (GSIS) in pancreatic beta cells, preventing long-term beta cell exhaustion.[20] It improves insulin sensitivity, however, which has been linked to the control of hypothalamic sympathetic output and prolactin secretion.[21]

However, the presence of active dopamine receptors in adipose tissue suggests that this drug may play a direct regulatory role in this tissue.[22]

When taken early in the morning, bromocriptine lowers plasma free fatty acids and serum lipids by increasing hypothalamic dopaminergic tone. Bromocriptine mesylate administration resulted in a significant reduction in plasma free fatty acid and cholesterol concentrations in obese subjects without a change in body weight.[23] On the contrary, intracerebroventricular (ICV) administration of bromocriptine, dopamine receptor 2 agonist, reduced insulin resistance, glucose intolerance and hyperlipidemia in seasonal animals.[24]

Sitagliptin, on the other hand, was discovered to enhance circulating glucagon-like peptide-1 (GLP-1) levels by inhibiting dipeptidyl peptidase IV (DPP-IV) activity, which, in turn, protects the heart through GLP-1's anti-inflammatory and anti-atherosclerotic properties. In both the postprandial and fasting states, it lowers blood glucose levels. These enzymes have a plethora of functions in the body, including blood sugar regulation, dyslipidemia, hypertension, oxidative stress, and silent inflammation.[25]

All the drugs regimen (Bromocribtine and Sitagliptine) alone and in combination showed improvement in all hyperlipidemia parameters in induced diabetic rats since it showed significant decline in HDL, Total cholesterol, Triglyceride, LDL and VLDL especially in T3 group also a significant decline level was recorded in serum TNF alpha in all drugs treated groups after 45 and 90 days after diabetes induction in comparison with the C +ve group that still recorded the high level values.

Sitagliptin at 10 mg/ kg/day orally for 4 weeks into diabetic rats resulted in significant improvement of blood glucose level, creatinine, urea, LDL, TC, triglyceride and significant increase in HDL level. Other study finding are in agreement with several studies,[26,28] which reported that HFSTZ-induced T2D is associated with significant increases in blood glucose, creatinine, urea, LDL, TC, triglyceride and significant decrease in HDL.

The superiority of hypolpidemic effects of combined half doses of both drugs might attributed to the differences in mechanisms by which the two drugs act and possible potentiate effect that might occur due to the increase in presence of dopamine receptor in adipose tissues that help to regulate lipid levels in this tissue potentiated by the mechanism of sitagliptine that effect on incrtin decreasing in the GIT food absorption and inhibition of glycolysis.

## CONCLUSION

The superiority of combined therapy of Bromocriptine and Sitagliptine at half used doses over the alone therapy in combating hyperlipidemia and inflammatory effect as well as the decline in body weight of diabetic animals might attributed to the different mechanism of action of each used drug that probably exert potentiation in therapeutic effects against the studied parameters after induction of T2DM in rats.

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