Biochemical Evaluation of Metformin and GLP-1 Therapy in Amelioration Metabolic Disturbance in Rats Induced Type II Diabetes

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Abstract:

Type 2 diabetes mellitus (T2DM) is a chronic worldwide disease characterized by significant consequences. T2DM is linked to impaired insulin sensitivity and/or secretion, as well as disturbed glucose and lipid balance. The principal effects of metformin, a first-line treatment for T2DM, are to enhance insulin sensitivity and glucose absorption while suppressing gluconeogenesis. GLP1 receptor agonists, such as dulaglutide, are prospective therapeutic medicines for the management of diabetes mellitus **(DM)**. Thus, the purpose of the current research was to evaluate how GLP1 and metformin affected rats' T2DM.

The study involved 35 healthy male rats, which were categorized into 2 groups: the control group and the T2DM group, the latter being induced by a high-fat diet **(HFD)** and streptozotocin **(STZ)**. Three groups of diabetic rats were randomly assigned: two treatment groups received metformin and dulaglutide, while the control group was untreated diabetic. Rat weight was assessed at the conclusion of the experiment. Serum concentrations of insulin, blood glucose, lipid profile, and hepatic and renal function were evaluated after an overnight fast.

Serum blood glucose, insulin, body weight, lipid profile, and liver and kidney function were all significantly elevated in diabetic rats. Dulaglutide markedly decreased blood glucose levels, improved liver and kidney functions, and outperformed metformin. In conclusion, we investigated how dulaglutide and metformin treat T2DM. We discovered that they all reduce the hyperglycemia and dyslipidaemia linked to T2DM. In addition to reducing hyperglycemia and dyslipidaemia, the current work offers a plausible mechanism for the protective effects of GLP-1 on the kidneys and liver in a rat model of diabetes.

Keywords: Diabetes, Dulaglutide, GLP1, Glucose, Metformin

Introduction

DM ranks high among metabolic non-communicable diseases. There has been a sharp rise in diabetes worldwide in recent years. According to an estimate by the International Diabetes Federation **(*IDF*)**, there will be 642 million diabetics by 2040, up from 415 million in 2015 **(*Peng et al., 2018*).** Microvascular and macrovascular problems associated with the degree and duration of hyperglycemia are hallmarks of DM. Diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy are examples of microvascular problems **(*Wang et al., 2020*).**

The conventional first-line therapy for T2DM is metformin. According to ***Ding et al. (2019)***, it exhibits anti-inflammatory, cardio-protective, and anti-oncogenic properties. According to one explanation, the effects of metformin include lowering intestinal glucose absorption, hepatic gluconeogenesis, increasing the activity of pancreatic beta cells and improving insulin sensitivity.

Individuals with T2DM are often managed with glucagon-like peptide-1 **(GLP-1) (*Wajcberg and Tavaria, 2009*)**. It stimulates GLP-1 receptors, which have been found in the kidney, gut, lung, and CNS, among other extra-pancreatic organs **(*Takashima et al., 2016*)**. Dulaglutide, a weekly GLP-1 receptor agonist **(GLP-1RA)** and analogue is utilized for the treatment of T2DM. By promoting glucose-dependent insulin production and preventing glucagon release, it enhances glucose metabolism. Enhancing lipid profiles, obesity, and hypertension reduces cardiovascular risk factors **(*Drucker, 2018*)**.

As a long-acting human GLP-1RA, dulaglutide (Trulicity) was approved by the FDA in 2014 and is used to treat T2DM in addition to diet and exercise. Dulaglutide is made up of two disulfide-linked chains with a GLP-1-like sequence. To enhance glycemic management, dulaglutide is used in conjunction with other medications, as well as via diet and exercise. Every week, a 0.75-mg dosage of dulaglutide is administered subcutaneously at any time, regardless of when a meal is scheduled **(*Fala, 2015*)**.

The goal of this study is to determine if metformin and dulaglutide, a GLP-1 receptor agonist, can help male rats with STZ-induced T2DM maintain glucose homeostasis.

Material and Methods

A- Material:

1) Animals:

The current investigation involved 35 healthy male rats, each weighing between 110-120 g, procured from the Animal House at the Faculty of Veterinary Medicine (FVM), Suez Canal University (SCU). The Ethical Committee approved the animal study protocol for

Laboratory Animal Welfare of the FVM, SCU.

Diet & Management of rats:

They were kept at the Animal House of FVM, SCU. They were contained in individual metal enclosures inside a regulated atmosphere (20-24ºC & 55-60% relative humidity) and nutritional conditions. They were maintained on a standard balanced ratio, in accordance with **(*Tae-Yoal et al., 1995, and Brichard et al., 1996*)** for one week of accommodation. The animals were granted unrestricted access to water and food. The rats were subsequently categorized into two groups based on food regimens. The control group, including 5 rats, received a conventional balanced diet, while the remaining 30 rats were administered an HFD formed of 58% fat, 25% protein, and 17% carbohydrates for an initial duration of 7 weeks, consistent with **(*Reed et al., 2000*)**. The formulation and manufacture of HFD closely resemble the methodology outlined by ***Srinivasan et al. (2005)***.

2) Drugs and chemicals:

a- STZ

Sigma-Aldrich (United States). It is provided as a powder with a purity exceeding 99% and is to be dissolved in freshly produced sodium citrate buffer at pH 4.5.

b- Metformin

Metformin hydrochloride, a biguanide derivative, is supplied in 500 mg tablets by Cidophage, a CID firm for the pharmaceutical and chemical sectors. The solubility in water is unrestricted. Distilled water was used to dissolve it prior to usage.

c- Dulaglutide (GLP-1 Receptor Agonist)

Eli Lilly, USA produces trulicity. Each pre-filled injection pen contains 1.5 milligrams of dulaglutide in a 0.5 milliliter solution. It was administered s/c on a weekly basis in rats.

3) Experimental Design:

The experiment lasted 4 weeks from the initiation of medication delivery. Rats were randomly allocated into four groups as follows:

Control Group (Five Rats): Functioned as a -ve control group and was administered a standard balanced diet during the 12-week trial duration.

Diabetic Group (10 Rats): Administered an HFD for 7 weeks, followed by an injection of STZ at a dosage of 25 mg/kg body weight via **i/p**, serving as the +ve control diabetic group throughout the experimental duration of 4 weeks.

The Metformin Group (10 rats) was administered an HFD for 7 weeks, followed by an injection of STZ (25 mg/kg body weight, intraperitoneally). Subsequently, they were treated with Metformin (Metformin HCl 500 mg/kg body weight) for 4 weeks **(*Rachel et al., 2012*)**.

The GLP1 Agonist Group (10 rats) was administered an HFD for 7 weeks, followed by an injection of STZ at a dosage of 25 mg/kg body

weight via **i/p**. Subsequently, they were given Trulicity at a dosage of 1.5 mg/kg body weight subcutaneously once weekly for 4 weeks **(*Tuttle KR et al., 2017*)**.

***Induction of DM**

Following seven weeks of an HFD, 30 HFD-fed rats were administered an **i/p** injection of a low dose of STZ at 25 mg/kg body weight **(*Srinivasan et al., 2005; Latt et al., 2013*)**. Glucometer readings were taken one week after STZ injection using an Accu-Chek Meter from Roche Diagnostics GmbH in Germany. Rats with fasting blood glucose levels above 11.1 mmol/l or 200 mg/dl were chosen for further studies.

***Drug Administration**

Metformin was solubilized in distilled H_2O_2 for daily oral delivery via gavage to fasted mice **(*Lauro et al., 2012*).**

Trulicity was injected s/c once weekly **(*Tuttle et al., 2017*).**

* Body weight in different groups is measured weekly

4) Sampling:

Blood samples were obtained from all groups following 4 weeks of nighttime fasting via ocular vein puncture in rats, utilizing micro-hematocrit tubes. Serum was subsequently isolated through centrifugation at 3000 rpm for 15 minutes. The serum samples that had been purified were quickly tested for lipid and glucose profiles and then kept at -20°C until they could be used for additional biochemical evaluations.

5) Statistical analysis:

The analysis of statistics was conducted using SPSS software, version 16. All data will be presented as mean ± standard error. A one-way analysis of variance **(ANOVA)** will be employed to compare groups of rats. Statistical results were deemed significant when the p-values were less than 0.05.

II - Biochemical parameters estimation:

1- Determination of FBG:

Ultraviolet assay, enzymatic reference technique utilizing hexokinase. Hexokinase **(HK)** facilitates the phosphorylation of glucose to glucose 6-phosphate utilizing ATP, as per the method described by ***Tietz, 2006***.

2- Determination of Fasting Blood Insulin (FINS):

The ALPCO Rat Insulin ELISA Kits (Catalog Number 80-INSRT-E01, E10) are used for insulin estimation **(*Finlay and Dillard, 2007*)**

3-Determination of Serum Lipid Profile:

A- Total cholesterol (TC):

The concentration of TC in the serum was measured using the procedure outlined in **(*NCEP, 1988*)**.

B- Triacylglycerol (TAG):

We used ***Stein's (1987)*** approach to find the concentration of serum TAG.

C- High-density lipoprotein-cholesterol (HDL-c):

Using a method developed by ***Finley et al. (1978)***, the colourimetric kit was able to measure the serum HDL-C content.

D- Calculation of serum low-density lipoprotein-cholesterol (LDL-c):

Based on the concentrations of total cholesterol, HDL-c, and TAG, the LDL-c concentration in serum was determined using the method described by ***Friedewald et al. (1972).***

LDL-c (mg/dl)= Total cholesterol – ([triglycerides ÷ 5] – HDL-c)

4-Determination of kidney function tests:

The kinetic colorimetric assay for serum creatinine determination is based on the ***Jaffé et al., 1886*** method, whereas the kinetic test with urease and glutamate dehydrogenase is used to assess urea level according to ***Rock et al., (1987)***.

5- Determination of Liver function tests:

Based on the method outlined by ***Breuer (1996)***, the enzymatic determination of alanine aminotransferase **(ALT)** and aspartate aminotransferase **(AST)** was carried out using reagent kits acquired from Spectrum Diagnostics.

Results

The body weight of diabetic rats was significantly higher than that of normal control rats ($P<0.0001$), as demonstrated in Table (1). Metformin dulaglutide-treated groups lost significantly more weight than diabetic rats.

Table (2) shows that when compared to normal rats, diabetic rats exhibited significantly higher levels of FBG and FINS ($P < 0.05$). Additionally, as compared to normal rats, animals in the Metformin and GLP-1 agonist groups exhibited substantial increases ($P<0.05$) in FBG and FINS levels, while both groups outperformed diabetic rats in terms of FBG and FINS levels.

In comparison to normal rats, diabetic rats exhibited a significant decrease ($P < 0.05$) in HDL-c levels and a significant increase ($P < 0.05$) in TC, TAG, and LDL-c levels (Table 3). In contrast, the groups treated with GLP1agonist or Metformin exhibited a significant increase ($P<0.05$) in HDL-c levels and a significant decrease ($P < 0.05$) in TC, TAG, and LDL-c concentrations when compared to diabetic rats.

Serum creatinine and serum urea levels in diabetic rats were significantly higher ($P < 0.05$) than in normal rats, as seen in Table (4). In contrast, animals treated with GLP-1 and metformin exhibited significant ($P < 0.05$) reductions in serum urea and creatinine levels when compared to diabetic rats.

As shown in Table (5), the ALT and AST activities of diabetic rats were noticeably greater ($P<0.05$) than those of normal rats. The ALT and AST activities of all treatment groups were significantly higher ($P < 0.05$) than those of

normal rats. In contrast, the ALT and AST activities of diabetic rats (Group 2) were significantly reduced ($P < 0.05$).

Table (1): *Changes in Body weight in different groups.*

Groups Parameters	Control	Diabetic	Metformin	GLP-1 Agonist	P value
Body Weight (gm)	$250^{d} \pm 70$	$360^{a} \pm 90$	$260^{b} \pm 75$	$245^{c} \pm 48$	0.0000005

M ± SE is used to express the data. The $P \leq 0.05$ indicates that the means with varying superscripts are significantly distinct.

Table (2): *Changes in serum FBG and FINS levels in different groups.*

Groups Parameters	Control	Diabetic	Metformin	GLP-1 Agonist	P value
FBG (mg/dl)	$80.86^{d} \pm 8.51$	$386.22^{a} \pm 45.45$	$120.57^{b} \pm 24.35$	$117.39^{c} \pm 17.66$	0.0000008
FINS (IU / ml)	$9.54^{d} \pm 0.69$	$35.12^{a} \pm 3.56$	$27.01^{bc} \pm 3.49$	$23.47^{c} \pm 3.68$	0.0000006

M ± SE is used to express the data. The $P \leq 0.05$ indicates that the means with varying superscripts are significantly distinct.

Table (3): *Levels of serum TC, TAG, HDL-c and LDL-c in different groups.*

Groups Parameters	Control	Diabetic	Metformin	GLP-1 Agonist	P value
Total Cholesterol (mg/dl)	$56.50^{d} \pm 0.85$	$148.00^{a} \pm 2.30$	$123.13^{b} \pm 1.62$	$105.11^{bc} \pm 1.03$	0.0000004
Triglycerides (mg/dl)	$136.6^{d} \pm 4.4$	$236.43^{a} \pm 3.9$	$139.45^{b} \pm 3.3$	$135.3^{c} \pm 2$	0.0000001
HDL-c (mg//dl)	$52.33^{a} \pm 1.07$	$25.2^{d} \pm 8.3$	$42.6^{c} \pm 2.8$	$50.7^{b} \pm 8.3$	0.0000003
LDL-c (mg/dl)	$54.17^{d} \pm 2.08$	$89.91^{a} \pm 1.61$	$52.16^{b} \pm 1.6$	$50.9^{c} \pm 1.9$	0.0000001

M ± SE is used to express the data. The $P \leq 0.05$ indicates that the means with varying superscripts are significantly distinct.

Table (4): *Serum Urea and Creatinine levels in different groups***.**

Groups Parameters	Control	Diabetic	Metformin	GLP-1 Agonist	P value
Creatinine (mg/dl)	$0.71^{d} \pm 0.17$	$1.6^{a} \pm 0.63$	$0.81^{b} \pm 0.3$	$0.73^{bc} \pm 0.11$	0.0000001
Urea (mg/dl)	$51.06^{d} \pm 14.08$	$70.33^{a} \pm 11.8$	$57.43^{b} \pm 6.48$	$55^{bc} \pm 9.8$	0.0000003

M ± SE is used to express the data. The $P \leq 0.05$ indicates that the means with varying superscripts are significantly distinct.

Table (5): *Serum AST and ALT activities in different groups.*

Groups / Parameters	Control	Diabetic	Metformin	GLP-1 Agonist	P value
ALT (IU/ L)	69.67 [d] ± 1.05	106.57 [a] ± 2.95	89.75 [b] ± 0.62	86.89 [bc] ± 0.48	0.0000003
AST (IU /L)	90.50 [d] ± 2.53	163.43 [a] ± 2.19	134.50 [b] ± 1.20	131.00 [b] ± 1.08	0.0000002

M ± SE is used to express the data. The $P \leq 0.05$ indicates that the means with varying superscripts are significantly distinct.

Discussion

The prevalence of T2DM, a prevalent medical illness, exceeds 415 million individuals globally **(*Wang et al., 2020*)**. Genetic, environmental, and lifestyle variables all play a role in the development of insulin resistance and β-cell dysfunction, which in turn promote hyperglycemia and dyslipidemia **(*Trinh et al., 2021*)**.

Our mouse successfully demonstrated hyperinsulinemia, elevated blood glucose concentration, lipometabolic abnormalities, and increased ALT/AST levels after seven weeks of an HFD, followed by a single administration of STZ. Dyslipidemia, characterized by elevated serum TAG and LDL and lower HDL levels, is linked to the protracted hyperglycemia observed in diabetic rats. Additional research by **(*Veneti and Tziomalos, 2020*)** confirmed these findings. Chronic consumption of HFD contributes to IR development, followed by compensatory hyperinsulinemia (***Kraegen et al., 1986***). Due to their high secretary activity, β-cells are continuously subjected to two types of stress: glucolipotoxicity and oxidative stress. (***DeFronzo, 2004***). This leads to the demise of β-cells, a common feature of T2DM marked by elevated insulin and glucose levels (***Rhodes, 2005***). Dyslipidemia, characterized by elevated serum TG, TC, and LDL and decreased HDL levels in the blood, is a consequence of the protracted hyperglycemia observed in diabetic rats. These results were confirmed by additional research conducted by (***Veneti and Tziomalos, 2020***). The insulin-inhibited hormone-sensitive lipase is the main factor responsible for the excessively high levels of serum lipids in DM, perhaps because it enhances the release of free fatty acids from the peripheral fat reserves. This could result from either an increase in the absorption of TGs or a decrease in their peripheral uptake (***Magalhaes et al., 2019***).

Biochemical markers of diabetic nephropathy, including elevated blood urea and creatinine levels, were seen in the diabetic rats in this investigation, as compared to the healthy control group. Like the

current study, ***Abdel Aziz et al. (2014)*** found that the rise in creatinine and urea levels in the blood after STZ treatment is one of the most significant and sensitive markers of renal damage. Another explanation was discovered by ***Mousa et al. (2016)***, who hypothesized that the kidneys' morphological and/or functional alterations might be the cause of the elevated blood urea and creatinine levels in STZ diabetic rats.

Metformin is the ADA-recommended first-line treatment for diabetes; however, on its own, the majority of patients do not achieve their target blood glucose level **(*Prasad and Isaacs, 2015*)**. Nowadays, adverse drug responses are taken into account when prescribing diabetic drugs to individual patients (***Inzucchi et al., 2012***).

In the current study, the diabetic rats were given metformin, which resulted in a considerable reduction in body weight, blood glucose levels, and insulin levels. This was in comparison to the diabetic control group. A lower blood glucose level is linked to a better lipid profile, which includes lower levels of serum cholesterol, TAG, and LDL, as well as higher levels of HDL. In accordance with the findings of ***Derosa et al. (2020)***, the findings confirm the findings.

Metformin also reduces lipogenesis in adipocytes, muscles, and the liver and increases glucose consumption and GLP-1 synthesis. Metformin affected hyperglycemia and hypertension **(HTN)**, two important counter-regulators that modify DN in rats by substantially reducing blood insulin, glucose, TAG, TC, LDL, creatinine, and urea **(*Figueiredo et al., 2020*)**. In order to get plasma lipids back to normal, metformin was also administered to increase plasma GLP-1 levels.

Compared to the diabetic control group, rats given metformin for their diabetes exhibited markedly reduced creatinine and urea levels. Research conducted by ***Mostafa et al. (2021)*** lends credence to our findings. The researchers observed that diabetic mice given low doses of metformin had improved renal function, lower levels of blood urea and creatinine, and less renal fibrosis linked to diabetic nephropathy.

Results showed that diabetic rats treated with dulaglutide had significantly lower levels of insulin, blood glucose, and body weight compared to the diabetic control group. Additionally, the rats' lipid profiles improved, showing lower blood triglycerides and LDL and higher blood HDL levels.

In a glucose-dependent way, GLP-1RA increased insulin secretion. GLP-1RA help with weight loss primarily by lowering body fat, improving glucose regulation, and decreasing the occurrence of hypoglycemia **(*Wang et al., 2019*)**. When comparing the two drugs, our research showed that dulaglutide increased serum HDL

levels more effectively than metformin. Dulaglutide significantly reduced TGs in diabetic rats as compared to animals treated with Metformin.

One reversible risk factor for renal damage, especially in T2DM, is dyslipidaemia, which is caused by persistent hyperglycemia. According to ***Kawanami et al. (2016),*** it causes lipid buildup in the kidneys, which exacerbates nephropathic aetiology. Elevated TGs and LDL-C levels were indicative of aberrant lipid metabolism in diabetic rats. This might be the result of either a decrease in TG peripheral uptake or an increase in TG absorption **(*Magalhaes et al., 2019*)**. In the meantime, treated diabetic rats with GLP-1 showed a significant improvement in this dyslipidaemia. Hepatic lipoprotein secretion and intestinal chylomicron synthesis are both directly lowered by GLP-1 (***Drucker, 2016***).

The action of GLP-1 RAs to reduce high blood glucose levels is multifaceted. Beyond the glucose-lowering effect of GLP-1 RAs, there are a plethora of additional routes that contribute to the preservation of renal functioning **(*Lyseng, 2019*)**.

According to the current study's findings, diabetic rats given dulaglutide had lower blood levels of urea and creatinine than the diabetic control group. ***Leon et al. (2020)*** also found similar results, finding that glomerular filtration preservation was the primary basis for GLP-1's renal effects. Additionally, our findings demonstrated that, in comparison to the diabetic rats, dulaglutide administration markedly reduced AST and ALT levels. The group that received GLP-1 treatment had notable improvements in renal and hepatic indices and functioning. Metformin and GLP-1 can significantly decrease insulin/glucose levels and effectively treat lipometabolic problems and liver dysfunction.

Conclusion:

Both Metformin and GLP-1 therapy ameliorate hyperglycemia and dyslipidemia associated with T2DM. The best result is given with GLP-1 rather than Metformin, besides its protective effect on hepato-renal tissues.

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الملخص العربي

دراسة كيميائية حيوية حول فعالية الببتيد الشبيه بالجلوكاجون-1 والعلاج بالخلايا الجذعية كطرق لعلاج الجرذان المصابة بمرض البول السكري

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يعتبر داء السكري من النوع الثاني مرض عالمي مزمن له مضاعفات خطيرة، و يرتبط باختلال توازن الجلوكوز والدهون مع حساسية غير طبيعية للأنسولين و / أو إفرازه.

الميتفورمين هو علاج الخط الأول لمرض داء السكري من النوع الثاني والذي تتمثل إجراءاته الرئيسية في قمع تكوين الجلوكوز وتحسين امتصاص الجلوكوز وحساسية الأنسولين.

تعتبر منبهات الببتيد الشبيه بالجلوكاجون 1 عوامل علاجية واعدة في علاج داء السكري. ولذلك، تهدف الدراسة الحالية إلى تقييم آثار الميتفورمين و منبهات الببتيد الشبيه بالجلوكاجون 1 ضد مرض السكري في الجرذان.

تمت الدراسة على عدد 35 من ذكورالجرزان الأصحاء ، وتم تحفيز الإصابة بداء السكري من النوع الثاني بواسطة STZ.

تم تقسيم الجرذان المصابة بداء السكري بشكل عشوائي إلى 3 مجموعات، مجموعة مصابة بمرض السكري بدون علاج ومجموعتين تم علاجهما باستخدام الميتفورمين و الدولاجلوتيد وفي نهاية التجربة تم تقدير وزن الجرزان. بعد الصيام طوال الليل، وكذا قياس مستويات مصل الجلوكوز والانسولين في الدم والدهون ووظائف الكلى.

أظهرت الجرذان المصابة بداء السكري زيادة كبيرة في وزن الجسم، ومستوى السكر في الدم، ومستوى الدهون في الدم، واختلال وظائف الكلى. كان الدولجلوتايد متفوقًا على الميتفورمين وكان له تأثير كبير في خفض مستوى السكر في الدم ومستوى الدهون في الدم وتحسين وظائف الكلى.

تم استكشاف تأثير كل من الميتفورمينو دولجلوتيد، الببتيد الشبيه بالجلوكاجون-1 على داء السكري من النوع الثاني. وقد وجد أن دولجلوتيد يحسن وزن الجسم، ومستوى السكر في الدم، ومستوى الدهون في الدم.

توفر الدراسة الحالية آلية محتملة للتأثيرات الوقائية للكلى والكبد للببتيد الشبيه بالجلوكاجون- في نموذج الجرذان المصاب بالسكري.