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A Comparative Assessment of Two Antidiabetic Medication on Glucose Level Lipid Profile and CBC in a Rat Model with Type II Diabetes Mellitus

Barakat Wathiq Al-Awdi[1], Jassem Hanoon Hashim[2]
[1,2]College of Science University of Kerbala, Iraq

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ABSTRACT
Objective: *Glycemic control is still the most important aspect of T2DM treatment sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin, and metformin therapy is effective and well tolerated in patients with T2DM and is the first of the several recommended treatment options. Since empagliflozin is poorly studied solely or in comparison with metformin, the current study aims to compare the influence of these drugs on glycemic levels individually in patients with type 2 diabetes mellitus (T2DM). this study aimed to evaluate both medication effects on the Lipid profile, glycemic level and CBC in comparison with control groups of the animals experimental.* ***Method:*** *The study was a quantitative experimental investigation (cross-sectional study) that contrasted the influence of metformin and empagliflozin on the short-term glycemic level. This study included an animal Experiment, forty healthy, Swiss male albino rats of approximately (10–12 weeks old) with weights of (150–200 g) were used in this research. The Induction of type 2 Diabetes Mellitus was performed through hyperlipidemia and insulin resistant model which was developed using the high fat and high sugar diet. Blood samples were analysed for basic and advanced investigations. electrochemiluminescence (E.C.L.) technology was used for immunoassay analysis to measure Lipid profile, Fasting blood glucose level, and Hemoglobin A1C (HbA1c) Test.* ***Results:*** *The results of the animal's experiment showed that the RBC number decreased significantly in rats-DM II group C treated with empagliflozin compared to the group A & B, the RBC decreased by 18% in group C, and 8% in Group B respectively. The blood sugar level decreased significantly in rats-DM II group B treated with metformin and in group C treated with empagliflozin compared to group A who was untreated, sugar levels decreased by 43% in Group B, and 35 % in group C respectively. results also showed a significant decrease in triglyceride concentration was observed in both treated diabetic rats groups (B&C) compared; the triglyceride level in the nontreated group (A) was, however, reduced by 44% in the diabetic treated with 500 mg/kg metformin and 40% in the diabetic treated with 10 mg/kg empagliflozin.* ***Novelty:*** *Metformin and empagliflozin have been shown through clinical studies an improve in the lowering of blood glucose. Both medications significantly improved glycemic control and lipid profile.*

INTRODUCTION

Management of DM is a multifaceted process wherein the patients need to attend checkups recurrently and also need to stick to a routine-prescribed regimen that includes a combination of a diet that is less fatty, planned exercise, medical therapy, and self-monitoring of blood glucose (SMBG). Since DM is a very complex disorder, combined efforts are required not only by a group of healthcare providers like dietitians, physicians, nurses, pharmacists, and psychological caretakers but also by the patients themselves and their household members [1]. Glycemic control is still the most important aspect of T2DM treatment. Lifestyle changes and pharmacologic treatment are often used to treat T2DM. Landmark studies have shown that poor glycemic control increases the risk of developing microvascular and macrovascular complications, while good glycemic control reduces the risk of these complications. Thus, reducing hyperglycemia is important to postpone the onset of complications and slow disease progression [2].

Metformin is currently the world's most widely prescribed oral anti-diabetic agent and is taken annually by over 150 million individuals. Metformin or dimethyl biguanide was synthesized in the 1920s [3].

Based on the official guidelines of the ADA, metformin has been recommended as the first-line, antidiabetic therapy for the treatment of T2DM over the past few decades and it has been widely used since the 1950s. Metformin, an insulin sensitizer, acts primarily on tissues that target insulin, such as the liver, muscle, and adipose tissues [4].

The glucose-lowering action of metformin is predominantly mediated by lowering hepatic glucose output by inhibition of gluconeogenesis and by increasing the sensitivity of peripheral tissues (such as skeletal muscle and adipose tissue) to the insulin action, also the drug has a minor effect of decreasing intestinal glucose absorption [5].

However, the main effect of metformin appears to be through decreasing hepatic glucose output due to inhibition of respiratory-chain complex 1 in the mitochondria. This transient reduction in the status of cell energy will promote stimulation of adenosine monophosphate-activated protein kinase (AMPK), which plays a task in regulating energy balance [6].

On the other hand, Empagliflozin (EMPA) was approved by the U.S. FDA in August 2014 as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM and by the European Medicines Agency (EMA) in May 2014, In 2016, the U.S. FDA approved EMPA to reduce the risk of cardiovascular death in adult patients with T2DM and cardiovascular disease [7].

Hyperglycemia augments the expression and activity of the SGLT2, which can cause an increase in glucose reabsorption by up to 20% in individuals with poorly controlled DM. Empagliflozin inhibits SGLT2 and therefore reduces the renal reabsorption of filtered glucose and lowers the renal tubular threshold for glucosuria. This results in increased urinary glucose excretion and reduction in hyperglycemia [8] SGLT2, located in the proximal convoluted segment of the proximal tubule, is a high-capacity, low-affinity glucose transporter. It integrates glucose transport to the electrochemical $Na+$ gradient and mediates 90% of renal glucose reabsorption, while the remaining 10% is reabsorbed by the high-affinity, low-capacity SGLT1 transporter. The mechanism of SGLT2 is that the sodium absorbed across the luminal cell membrane creates a gradient that permits the passive entry of glucose into the cell. Afterward, the sodium is returned to the bloodstream by the adenosine triphosphatase-mediated sodium–potassiu pump, and glucose diffuses to the basolateral glucose transporter 2, through which it passes back into the bloodstream [9]. To evaluate their effect, this study aimed to examine both medications on the liver and kidney functions in comparison with control groups of the animal’s experimental.

RESEARCH METHOD

Forty healthy mature albino white male rats were allocated at random into two groups. The hyperlipidemia and insulin resistant model were developed using the high fat and high sugar diet which were utilized to induce diabetic Mellitus type II in the rats. The mature albino male rats groups were then separated into four subgroups: Group 1 consisted of non-diabetic rats that were only administered distilled water (control), Group 2 consisted of diabetic rats that were not given any medications, Group 3 consisted of diabetic rats that were administered metformin at a dose of 500 mg/kg/day for three weeks, and Group 4 consisted of diabetic rats that were administered 10mg/Kg empagliflozin. After 3 weeks of therapy, the animals were slaughtered and their organs were harvested.

After grouping, the rats were weighed and fasted for 12 hours before the sacrifice. Each rat was anesthetized using a plastic container containing cotton soaked with chloroform as a volatile anesthetic agent. All rats were sacrificed by anesthetized using chloroform inhalation technique with a waiting period of about 5-10 mins. then blood samples were collected from the heart from the midline by using syringes(10ml) by intracardiac puncturing the right ventricle. All blood was collected in gel tubes and EDTA tubes, and then serum samples were obtained by centrifugation of blood samples at 3000rpm for 10-15 minutes at room temperature. serum samples were transferred to serum collecting tubes for further laboratory investigations and some serum samples were saved in Eppendorf tubes of 1-2 ml for freezing to be used for biochemical parameters measurement. Blood samples were analysed for basic and advanced investigations. electrochemiluminescence (E.C.L.) technology was used for immunoassay analysis to measure Lipid profile, Liver function test, Renal function tests, Fasting blood glucose level, Hormones (insulin, TSH), and Hemoglobin A1C (HbA1c) Test.

RESULTS AND DISCUSSION

In the present study, the effect of Metformin and Empagliflozin treatment on fasting blood glucose (FBG) concentration in Swiss male albino rats -induced diabetic was shown in Figure 1. HFHS-feeding rats were randomly divided into three groups (n=10), Group A rats with diabetes type II (DMII), Group B rates-DM2 treated with metformin, and Group C rats-DM2 treated with empagliflozin. The FBG concentration in diabetic animals was treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks.

After treatment, a Histopathological function study of the rat pancreas. results of hematological parameters showed that only RBC numbers were decreased significantly in rats-DM II group C that were treated with empagliflozin compared to groups A & B, the RBC was decreased by 18% in group C, and 8% in Group B respectively.

The high blood glucose concentration observed in this study in the untreated diabetic animals' group was significantly reduced ($p<0.05$) in the diabetic animals administered either metformin treatments or empagliflozin. This indicates that both can induce healing of wounded β-pancreatic cells thereby leading to increased production of insulin in rats resulting in glucose uptake from the blood to body cells.

The blood sugar level decreased significantly in rats-DM II group B treated with metformin and in group C treated with empagliflozin compared to group A who was untreated, sugar levels decreased by 43% in Group B, and 35 % in group C respectively.

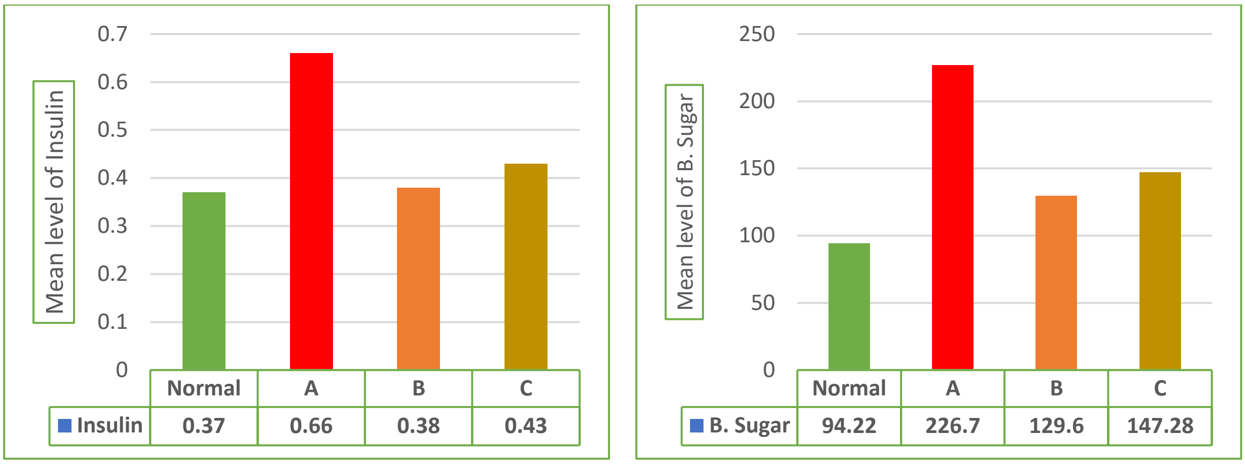


Figure 1. *The, B.sugar, and insulin in diabetic rats treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks*(ANOVA test was: significant at $p \leq 0.05$, N: number of cases; SD: standard deviation; S: significant; NS= Non-significant).

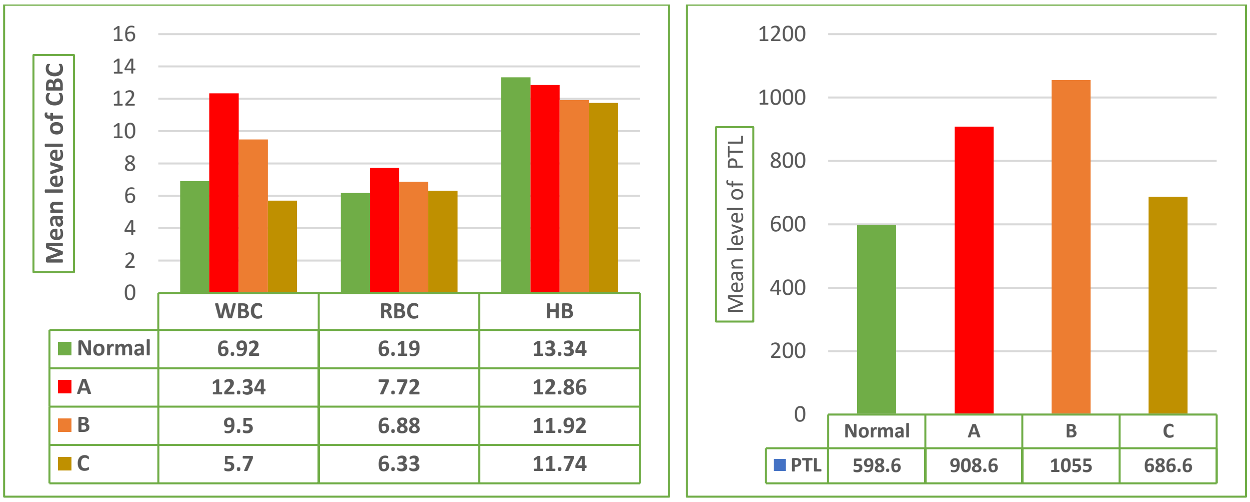
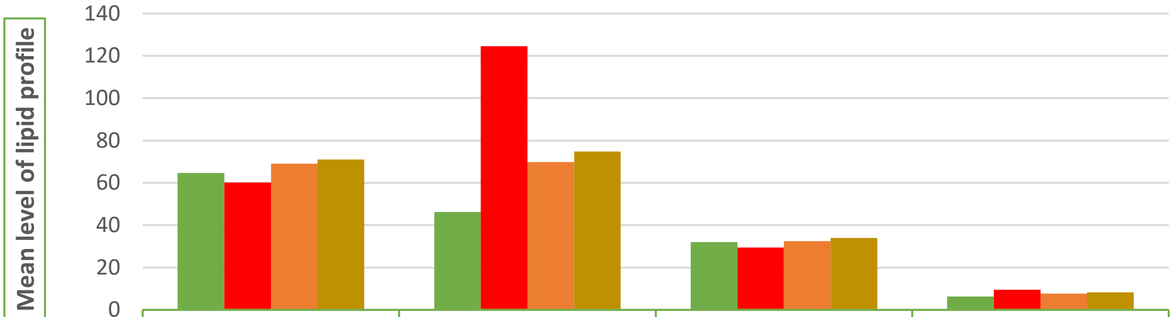


Figure 2. *The hematological parameters in diabetic rats treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks* (ANOVA test was: significant at $p \leq 0.05$, N: number of cases; SD: standard deviation; S: significant; NS= Non-significant).

Induction of diabetes in rats has been severally reported to culminate in alteration in body lipid profile. The presence of the appropriate proportion of fatty acids, triglycerides, cholesterols, and lipoproteins helps in the maintenance of the integrity of biological membranes. Alterations in lipid contents of bio-membranes and adipose tissues may sometimes be reflected in the blood as either hypolipidemia or hyperlipidemia. Significant variation in lipid profile has been implicated in the onset of many physiological disorders and or diseases including DM. In this study, the effect of both types of treatment on lipid profiles in induced diabetic rats was also investigated (Figure 3). A significant decrease in triglyceride concentration was observed in both treated diabetic rats groups (B&C) compared; the triglyceride level in the nontreated group (A) was, however, reduced by 44% in the diabetic treated with 300 mg/kg metformin and 40% in the diabetic treated with 500 mg/kg empagliflozin.



	S. Chol	S.TG	S.HDL	S.LDL
Normal	64.72	46.22	32.06	6.34
A	60.18	124.56	29.42	9.48
B	69.08	69.82	32.48	7.67
C	71.1	74.88	33.94	8.31

Figure 3. Mean level of lipid profile panel *in diabetic rats treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks* (ANOVA test was *: significant at $p \leq 0.05$, N: number of cases; SD: standard deviation; S: significant; NS= Non-significant).

Discussion

The high blood glucose concentration observed in this study in the untreated diabetic rats group was significantly reduced ($p<0.05$) in the diabetic animals administered either metformin treatments or empagliflozin.

A great attention re-given to the hematological indices as predictors of endothelial dysfunction and inflammation status [10].

Disturbances in hemorheological parameters can make a sort of complications in diabetes mellitus worse. Red blood cell (RBCs) count is a pivotal marker for the ability to recognize diabetic patients at risk of microvascular complications [11].

erythrocytes (RBCs) count revealed a significant decrease in patients treated with metformin and empagliflozin compared to the non-treated group, The decrease in RBCs counts in diabetic patients may be due to RBC membrane protein alterations, a decrease in hemoglobin levels and erythropoietin deficiency [12].

In diabetes, erythrocyte membranes are affected by chronic exposure to glucose, and several biochemical modifications are triggered, with subsequent structural and functional disruption of erythrocytes and decreased lifespan of RBCs [12] which may be related to RBCs count dimension. Meanwhile, RBC properties are critically affected by hyperglycemia and decreased deformability

In diabetes, there is an increased plasma viscosity, an enhanced red cell aggregation, and a reduced red cell deformability. erythrocytes of diabetic patients aggregate more readily is obviously enhances whole-blood viscosity, and adversely influences the microcirculation and finely leading to microangiopathy [13].

The protein oxidation and hyperglycemia in diabetics induced an elevation in the production of lipid peroxides that may lead to RBCs hemolysis [14] and subsequently decrease in RBCs count and hemoglobin levels.

Several studies found that metformin affected platelet activation [15] and aggregation [16].

both metformin and ***empagliflozin*** were shown to be a good reducer of fasting glucose concentrations by reducing rates of hepatic glucose production [17].

empagliflozin inhibitors have been shown to consistently improve glycemic control and pancreatic islet function, as well as preserve islet morphology in T2DM [18].

Empagliflozin has been shown to improve insulin sensitivity, reverse glucotoxicity, and normalize glucose homeostasis in T2DM [19]. One of the major patient benefits of empagliflozin is that blood glucose levels are reduced without increasing the risk of hypoglycemia or producing weight gain, both of which are major and unpreventable side effects of other classes of oral anti-hyperglycemic drugs. Accumulation of excess ROS in the body leads to oxidative stress, thus deleteriously affecting cell function. It is noteworthy that pancreatic islets are highly susceptible to oxidative stress, due to their low levels of intrinsic antioxidant systems [20]. Indeed, excessive ROS generation is one of the proposed mechanisms for glucotoxicity observed in diabetes. Chronic exposure of pancreatic β-cells to high concentrations of glucose causes suppression of insulin gene expression, as well as significant reductions in insulin content and secretion [21]. In the present study, empagliflozin significantly reduced the level of oxidative stress, which is believed to be induced by high blood glucose levels in T1DM. The maintenance of β-cell area and function is critical for the control of blood glucose levels within a narrow physiological range [22]-[31].

Since Diabetes mellitus, refers to a series of metabolic disorders with characteristic features, these complications may further lead to chronic complications such as dyslipidemia [32].

Although several hypotheses currently exist about the Metformin benefits, which include inhibiting hepatic gluconeogenesis, modifying hepatic fatty acid metabolism, increasing fatty acid oxidation, reducing lipogenesis, enhancing insulin sensitivity, and increasing antioxidant properties, all are well-established [33].

In this study, based on the study groups in diabetic rats treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks, both medication groups did not show any significant differences in the mean level of lipid panel except the serum level of HDL.

The group of empagliflozin was shown a high level of serum HDL compared to the metformin group, these results were consistent with other results that reported that an SGLT2 inhibitor (empagliflozin) was slightly increased in high-density lipoprotein (HDL) [34], [35] Several trials have addressed the potential role of empagliflozin on lipid metabolism and most ended up with a negative effect [36]. Briand et al [37] reported that empagliflozin moderately increased LDL cholesterol levels, ketone production, and energy metabolism from carbohydrate to lipid use. Despite the existing evidence, in the present study, no significant change was documented in lipid profiles between the preand post-addition of the empagliflozin to the groups. A possible explanation could be the neutralization of the negative effect on the lipid profile via the positive effect in terms of Hba1c decrease which then, improved lipid metabolism given that the HbA1c decrease in our study is much more than the reported in many previous studies in the literature [38].

A few investigators were looking for the effects of (empagliflozin) on plasma sterol markers of cholesterol absorption and synthesis in patients with type 2 diabetes [39].

Clinical studies have consistently demonstrated that treatment with empagliflozin inhibitors is associated with a small increase in both LDL and HDL cholesterol [40]. They were also found no significant correlation between changes in LDL cholesterol after treatment with empagliflozin, suggesting that augmented intestinal absorption of cholesterol might not contribute to the small increase in LDL cholesterol induced by empagliflozin inhibitors.

Previous studies demonstrated that the increase in LDL cholesterol caused by empagliflozin inhibitors may be due to increased conversion from VLDL to LDL, or reduced LDL clearance [41]. This study [39] confirmed that serum HDL cholesterol increased after empagliflozin but not after standard therapy. Studies have consistently shown that empagliflozin inhibitors, including empagliflozin, slightly but significantly increase HDL cholesterol in people with type 2 diabetes [35].

The mechanisms responsible for this increase in HDL cholesterol after treatment with empagliflozin remain unclear. One possible explanation is that empagliflozin inhibitors improve both insulin sensitivity and endogenous insulin secretion, decrease VLDL synthesis in the liver, and simultaneously increase catabolism of VLDL and chylomicrons by augmenting the activity of lipoprotein lipase, resulting in a reduction in triglycerides and an increase in HDL cholesterol. Furthermore, in previous studies, it was demonstrated that empagliflozin inhibitors alleviate hepatic steatosis or steatohepatitis in diabetic mice [42]. These results suggest that empagliflozin can increase HDL cholesterol by ameliorating insulin resistance in the liver [43]. This result suggests that an increase in plasma campesterol by empagliflozin was associated with an increase in HDL cholesterol. It was speculated that cholesterol absorption may be closely associated with HDL cholesterol, but not LDL cholesterol. Thus, serum levels of HDL cholesterol may depend on the intestinal absorption of cholesterol [44].

Others were reported that Increases in HDL-cholesterol was observed in some trials of empagliflozin inhibitors, which may be partly due to hemoconcentration effects [45].

Furthermore, mean differences of the biomarkers based on the study groups in diabetic rats treated with 500mg/kg metformin or 10mg/Kg empagliflozin for 3 weeks were found to not Significantly differ when compared to the renal function test of the two groups of treatment, but generally, metformin was reported to effective in the improvement of renal function. The possible explanation is that metformin regulates the mammalian target of the rapamycin (mTOR) signaling pathway by upregulating Klotho and protecting renal tubular cells, thereby delaying renal progression in patients with diabetic nephropathy. [46] unfortunately, these results were not agreed with the current study, since metformin does not reduce the level of urea and creatinine.

On the other hand, very few observations were reported about the renal function among DM patients receiving empagliflozin. The mechanisms behind the renal effects of empagliflozin are probably multifactorial, but direct renovascular effects may play an important role [47] Empagliflozin reduces proximal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula dense, which has been shown to activate tubuloglomerular feedback, leading to afferent Vaso modulation and a decrease in hyperfiltration [48]. In patients with diabetes, empagliflozin reduces the intraglomerular pressure [49].

Other effects, such as serum uric acid levels [50], and the systemic and renal neurohormonal systems [51], may also contribute to the improvements in the progression of renal disease observed with empagliflozin.

Furthermore, other research has proposed mechanisms of action which include the reduction of blood glucose, thus protecting the renal glomerulus from the effects of hyperglycemia. [52] Additionally, empagliflozin has been shown to cause hemodynamic effects due to their effects in nature is which results in actions similar to ACE inhibition [53]. There is some evidence in animal models that empagliflozin may downregulate the renin-angiotensin system activation caused by hyperglycemia. Although empagliflozin causes an initial decrease in eGFR, it provides protection in the long term and has been demonstrated to reduce urinary albumin and creatinine [54]-[58].

inflammatory markers play a direct role in impairing insulin signaling pathways which contribute to insulin resistance in diabetes. However, the anti-inflammatory action of various medications is partial and conflicting, most likely because of deficient normalization of metabolic dysregulation or because diabetes-related aggravation is multifactorial but is not restricted to hyperglycemia. Improved diabetes prevention and treatment modalities could benefit from a greater understanding of the inflammatory basis for diabetes, which could involve innovative targeted therapies in addition to existing pharmacologic and lifestyle strategies [59].

CONCLUSION

Fundamental Finding : Metformin and empagliflozin significantly reduced fasting blood glucose and triglyceride levels in high-fat and high-sugar diet–induced diabetic rats, while empagliflozin showed a greater reduction in red blood cell count and a higher serum HDL level compared to metformin. **Implication :** Both medications demonstrate therapeutic potential for improving glycemic control and lipid metabolism in type 2 diabetes mellitus, supporting their role as effective pharmacologic options for reducing hyperglycemia-related complications. **Limitation :** The study relied on a short-term animal experimental model with a limited sample size, which restricts the generalizability of the findings to long-term clinical outcomes in human patients. **Future Research :** Further longitudinal clinical studies are needed to clarify the long-term hematological effects, renal outcomes, and lipid profile changes associated with metformin and empagliflozin in diverse human populations.

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***Barakat Wathiq Al-Awdi (Corresponding Author)**
College of Science University of Kerbala, Iraq
Email: barakatwathiqbarakat2020@gmail.com

Jassem Hanoon Hashim
College of Science University of Kerbala, Iraq