



Assessment of Metformin's Impact on Liver, Kidneys and Spleen Tissues in Normoglycemic Female Albino Rats

Aveen Abdullah Mohammed Ameen¹ and Malika Kassim Najeeb²

¹ Department of Scientific Research Center, College of Science, University of Duhok, Kurdistan Region- Iraq.

² Department of Biology, College of Science, University of Duhok, Kurdistan Region- Iraq.



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Abstract

METFORMIN is one of the medications used to treat diabetes most frequently nowadays, which is also used in non-diabetic patients to treat fatty liver, weight reduction, infertility, polycystic ovarian syndrome, prevention of pregnancy complications, prevention of diabetes and obesity. However, its use may have several serious adverse effects such as hepatic injury, renal toxicity and spleen damage. This study was designed to assess the potential pathogenic impact of metformin on the liver, kidneys and spleen in normoglycemic rats. Two equal groups of twelve adult female rats were randomly selected. First group was intraperitoneally injected with metformin (200 mg/kg) as a single dose for three days and the second group was used as a control received an intraperitoneal injection of the similar-volume of physiological saline. The animal weight, organs weight, creatinine, lactate and vitamin B₁₂ were measured. Histopathological changes in the liver, kidneys and spleen were also studied. The blood parameters levels didn't alter with metformin use. The metformin treated group showed structural damage of varying degrees in all three organs; liver, kidney and spleen. Metformin like any medication may be helpful in treating certain medical issues. However, the results of the current study confirms that the metformin use can cause hepatic injury, renal toxicity and moderate damage to the spleen tissues, which may contribute to the clinical effects of the drug; physicians and patients alike need to be aware of these possible side effects.

Keywords: metformin, liver, kidneys, spleen, normoglycemic rats, antidiabetic medication, histopathological examination

Introduction

Metformin is a widely-used oral hypoglycemic agent that is commonly used in the treatment of type II diabetes [1]. It is also used in the treatment of polycystic ovarian syndrome [2, 3], fatty liver [4], impaired glucose tolerance [5], weight reduction, infertility, prevention of pregnancy complications, prevention of diabetes and obesity [3] in non-diabetic patients.

Metformin is biguanide that was synthesized from galegine [6]. Galegine is a guanidine

derivative found in *Galega officinalis* (French lilac) utilized as a herbal therapy that lowers blood sugar in medieval Europe in the 1920s, but it was discovered to be too toxic and was withdrawn as a consequence for its toxicity [7].

Metformin, similar to any other medications, has adverse effects. These are mainly related to the digestive system (heartburn, diarrhea, vomiting, nausea, abdominal pain, bloating, flatulence and anorexia) [2, 8]. It has been reported that metformin cause reductions in serum (vitamin

*Corresponding author: Aveen Abdullah M. Ameen, E-mail: aveen.ameen@uod.ac, Tel.: 96407504870422

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B12 and folic acid) levels [9], pancreatitis [8], damage in spleen function and liver or kidney problems [10-12]. A rare but potentially it was found that metformin associated with serious side effects such as hypersensitivity reactions, dehydration, hypoglycemia and lactic acidosis [10, 11]. Clinically, metformin-associated lactic acidosis develops rapidly and is characterized by drowsiness, unconsciousness and overbreathing [13]. Metformin has been withdrawn from most countries because of lactic acidosis which is the most serious and important adverse effect seen with metformin use and not administered to patients with many chronic hypoxemic conditions such as cardiovascular, hepatic, renal and pulmonary disease, and advancing age [2, 14, 15]. In addition, it has been reported that, even young patients with previously normal renal function may develop metformin-induced lactic acidosis [14]. Metformin's widespread use necessitates a comprehensive understanding of its potential side effects. Despite its established benefits in glycemic control, questions persist regarding its impact on organ histology in normoglycemic conditions. This study aims to address this gap in knowledge. However, due to the availability of limited studies on its effects in nondiabetic individuals and since most of the studies related to the use of metformin in the treatments of diabetes focused on the beneficial effects of it, whereas very little is known about the side effects of metformin. Thus, this research has been designed to assess the potential pathogenic effects of metformin on the liver, kidney and spleen in nondiabetic rats.

Material and Methods

Experimental animals

Twelve adult female rats (*Rattus rattus norvegicus*) (200-260gm) were obtained from Animal House, College of Science, University of Zakho, Kurdistan Region of Iraq. All animals were housed in an environmental-controlled space with a 12-hour light/dark cycle, free access to a rodent diet and tap water. Ethical approval was obtained from Animal Ethics Committee, University of Zakho, Kurdistan Region-Iraq.

Experimental protocol

Normoglycemic rats were subjected to controlled experiments. Metformin administration protocols were followed, with meticulous attention to dosage and duration. Blood parameters were measured using

standardized techniques, and histopathological examinations were conducted on liver, kidney, and spleen tissues. Rigorous controls were employed to ensure the validity of results.

The animals were weighed and divide randomly into two groups of six rats each:

Group 1: metformin-treated group (200 mg/kg as a single dose for three days through intraperitoneal injection), according to the Reagan-Shaw approach, this dose is comparable to approximately 1000 mg for a human of average weight (human equivalent dose (mg/kg) = animal dose (mg/kg) × animal (km)/human (km) [16]. Metformin (Awamedica, Iraq) was purchased from a local pharmacy.

Group 2: control group was injected intraperitoneally with the identical volume of physiological saline

Sacrifice of rats and samples collection

At the end of the experiment, rats in each group were weighed, blood samples were collected by cardiac puncture and then sacrificed them [17]; creatinine, lactate and vitamin B₁₂ were measured by Cobas Integra-400 plus automated chemistry analyzer (Roche/Germany). For histological study, organs (liver, kidney and spleen) were removed, after which the tissue was fixed in 10% neutral buffered formalin (NBF)[18] for histopathological study.

Statistical Analysis

Data were expressed as mean ± SE. A student's two-tailed unpaired t-test was used to analyse statistical differences between metformin group and control group. For statistical analysis Graph Pad Prism 6 program (GraphPad Software, USA) was used. P value < 0.05 was considered as significant.

Results

Data analysis revealed notable histological changes in the liver, kidney and spleen tissues. Visual representation of the results through tables and figures provides a clear overview. Statistical analyses, including p-values, were conducted to ascertain the significance of observed effects.

Effect of metformin on the animal weight and the weight of the animals' selected organs (liver, kidney and spleen)

In metformin treated rats, the weight of the

body, liver, kidney and spleen did not differ from that of the control group (Table 1).

Effect of metformin on blood (creatinine, lactate and vitamin B₁₂)

The rats' data are shown in Table 2, In metformin treated group, the serum creatinine (0.44 mg/ dl) was found to be close to the control group (0.42 mg/ dl). The metformin treated group didn't show any significant alteration in the lactate level (15.2 mg/ dl) as compared with that of the control group (32.23 mg/ dl).

Intraperitoneal treatment with metformin showed non-significant increase (805.5 pg/ mL) in the concentration of plasma vitamin B₁₂ as compared to the control group (1127 pg/ mL).

Effect of metformin on liver histology

The liver of control group showed normal architecture; normal hepatic cord, central vein and sinusoid capillary with hepatocytes presenting a homogenous cytoplasm and a large central nucleus with dark heavy chromatin materials. While, the liver tissue in metformin treated group showed structural damages with variable degrees such as; moderate of infiltration of inflammatory cells (leukocytes), necrosis, follow by odema, congestion in hepatic central vein, hemorrhage, sinusoidal dilation, macro and micro vascular fatty deposition with vacuole in hepatocytic cytoplasm and different stages death in the nucleus of hepatocytes, as shown in (Fig. 1 A, B1 and B2).

Effect of metformin on kidney histology

In the control group, kidney tissues showed almost normal cytoarchitecture appearance of renal corpuscle (glomerulus and Bowman's capsule) and convoluted renal tubules (proximal and distal). In metformin treated rats, kidney sections showed variable damages through degeneration in glomerulus, dilatation of Bowman's space, necrosis in convoluted renal tubules (proximal and distal), congestion and hemorrhage (Fig. 2 A, B1 and B2).

Effect of metformin on spleen histology

Spleen sections of the control group showed the normal histological appearance of parenchyma consists of regular red pulp and white pulp with germinal center and central arteriole. In the metformin group showed moderate degrees in damaging tissue of the spleen such as; necrosis and odema in both red and white pulps, conges-

tion, hemorrhage with filtration of inflammatory cells, moderate reduction in white pulp size and fibrin deposition in central arteriole (Fig. 3 A, B1 and B2).

Discussion

Interpreting our findings in light of existing literature, we discuss the potential implications of metformin-induced changes in histology of the liver, kidney and spleen tissues. Insight into the mechanisms underlying these effects is crucial for a comprehensive understanding.

Metformin is one of the most frequently used medications for diabetes worldwide. It has surfaced new indications for metformin use in clinical practice, besides diabetes [19].

In the current study, intraperitoneal injection of metformin to non-diabetic rats didn't show variations in the weight of the organs (liver, kidney or spleen) and the body or almost similar to the control rats. Similarly, these results were reported [20]. However, metformin has been shown to induce weight loss in obese non-diabetic populations [21].

The levels of serum creatinine before and after treatment of metformin in normal rats were not altered. Similarly, these results have been reported previously [14]. It has been reported that there is a significant risk of all-cause mortality for individuals with type 2 diabetes who use metformin and have a serum creatinine concentration higher than 5.99 mg/dl. Therefore, it is not recommended to encourage metformin use in this patient group [22].

In this research, the serum level of lactate was not changed obviously. However, it has been reported a steep decrease in the plasma levels and a corresponding rise in pH indicated that the patients had lactic acidosis induced by metformin. Not just those with pre-existing risk factors are at risk for metformin-induced lactic acidosis. In fact, metformin-induced lactic acidosis is identified when no other lactic acidosis causes are present [14].

In metformin-treated group, plasma concentration of vitamin B₁₂ was elevated considerably but statistically was non-significant as compared to the control group. Dissimilarly, it has been indicated that there was no alteration in the plasma concentration of B₁₂

in metformin treated rats [18]. Since the liver is the organ responsible for metabolizing B12, it is known that low liver function can be predicted by raised B12 levels. Consequently, elevated B12 levels may be a sign of poor liver function [25].

From the data, we have found that metformin use is associated with hepatic toxicity. In parallel to this finding, it has been reported that the metformin use is rarely associated with hepatic toxicity by which patients treated with metformin started to show signs of mixed type hepatocellular and cholestatic hepatic injury within two months after starting metformin treatment [10, 24]. In addition, as potential for increased idiosyncratic hepatotoxicity associated with metformin use is likely to occur [25]. Furthermore, it has been reported that the hepatocellular and cholestatic hepatic damage can result from the use of metformin in the treatment of fatty liver patients [4]. However, the exact mechanism underlying metformin-induced liver damage is unknown. Metformin-induced acute liver injury may have a metabolic cause and arising after weeks to months of treatment [26].

According to the result of this study, kidney histology showed abnormal glomeruli, congestion, haemorrhage and renal tubular necrosis in the metformin group. Similarly, these results have been reported previously [10, 24]. Also, it has been diagnosed that the lactic acidosis caused by metformin when there are no other underlying reasons for it. It appears that neither metformin nor lactate nor creatinine levels can predict the development of lactic acidosis in metformin users. Renal injury was found to occur in younger patients without any other concomitant illnesses and those with previously normal renal function due to the development of metformin-induced lactic acidosis [14].

The metformin-treated group in the current research displayed altered splenic contours, irregularities in the appearance of the white pulp, necrosis with hemorrhage and congestion in both white and red pulp. Previously, the same results have been reported [27]. Also, parallel to our findings, it was shown that metformin treatment changed some subsets of B cells, preventing the development of mice's germinal centres, marginal zones and plasma

cells [28]. This may be because metformin is known to impact mTOR (mechanistic target of rapamycin), AMPK (AMP-activated protein kinase) and suppresses the activity of STAT3 (phosphorylation at tyrosine 705) in vitro, which in turn causes the suppression of splenic B cells and their subsets [29]. It has been proposed that metformin acts on the mitochondrial respiratory chain in humans, which lowers cellular ATP, raises the AMP: ATP ratio, and activates AMPK [30].

The metformin-treated group exhibited decreased Bcl2 expression across all zones. In line with these findings, metformin treatment was shown to inhibit spleen germinal center B cell formation in mice, resulting in lower Bcl2 expression [26, 31]. Additionally, it has been reported that metformin can decrease the expression of the anti-apoptotic protein Bcl2 in the synovial fluid of rats with collagen-induced arthritis [32].

Conclusion

Metformin like any medication may be helpful in treating certain medical issues. However, the results of the current study confirms that the metformin causes different degrees of histological changes in the liver, kidneys and spleen tissues, this is consistent with some of the biochemical factors that were studied in the current study, which may contribute to the clinical effects of the drug. Thus, from these results, metformin should be used cautiously to prevent any potential risks. Patients and doctors should both be aware of these possible adverse effects.

Conflict of Interest

None

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Author's contribution

Aveen Abdullah M. Ameen designed the study, analysed the data, performed the statistics study. Malika K. Najeeb performed the histopathological study. Both authors interpreted the results, edited and revised the manuscript and approved the submitted version.

TABLE 1. Effect of metformin on the weight of animals' body and organs (liver, kidney and spleen) (n = 6/group)

Weight (g)/group	Control	Metformin
Body weight at injection	189.2 ± 33.60	226.3 ± 8.476
Body weight at sacrifice	233.5 ± 13.76	236.5 ± 11.13
Liver weight	8.59 ± 0.10	8.16 ± 0.56
Kidney weight	0.84 ± 0.04	0.90 ± 0.13
Spleen weight	0.66 ± 0.08	0.76 ± 0.08

Values are expressed as mean ± SE (no statistical differences were found between groups)

TABLE 2. Effect of metformin on blood creatinine, lactate and vitamin B₁₂ of the animals (n = 6/ group)

Parameter/group	Control	Metformin
Creatinine (mg/ dl)	0.42 ± 0.08	0.44 ± 0.05
Lactate (mg/ dl)	15.20 ± 1.90	32.23 ± 5.96
Vitamin B ₁₂ (pg/ mL)	805.5 ± 95.75	1127 ± 135.1

Values are expressed as mean ± SE (no statistical differences were found between groups)

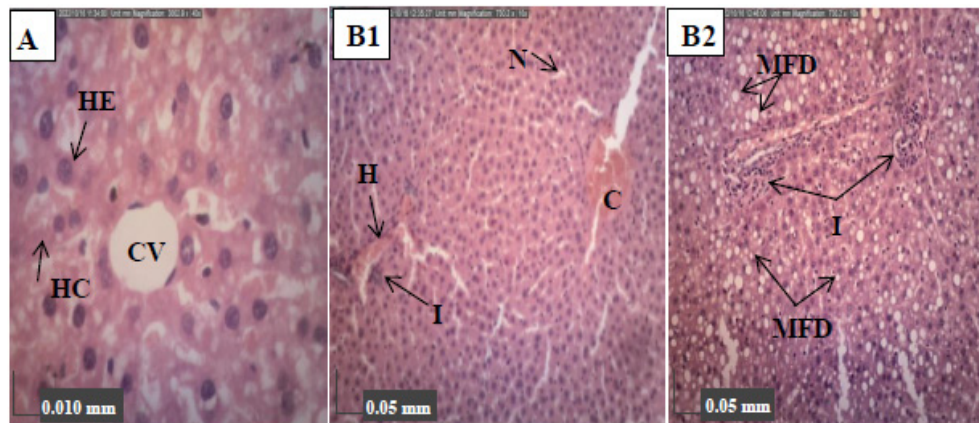


Fig. 1. Cross section through the liver (H and E): Controls group (A), showing normal structure of central vein (CV), hepatic cord (HC) and hepatocyte (HE). Metformin treated group (B1 and B2) showing different damage in the liver tissue; congestion (C), hemorrhage (H), necrosis (N), macro and micro vascular fatty deposition (MFD) and inflammatory cells (I).

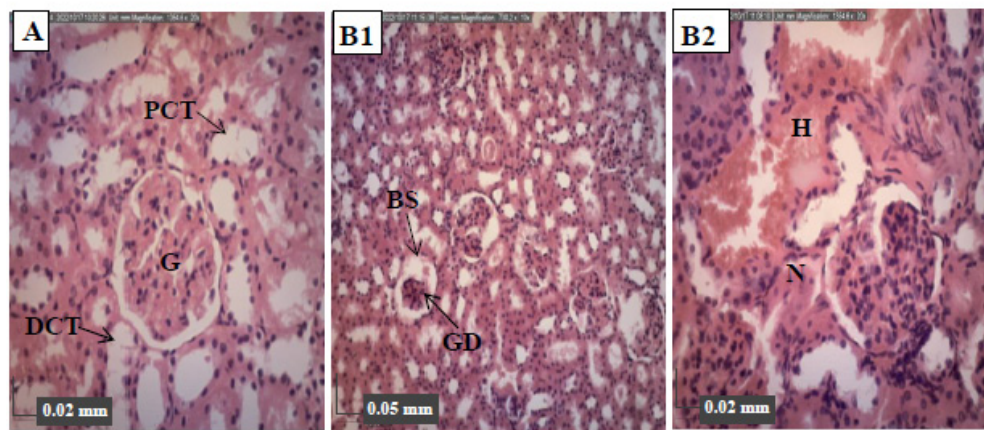


Fig. 2. Cross section through the kidney (H and E): Controls group (A) showing normal glomerulus (G), proximal convoluted renal tubules (PCT) and distal convoluted renal tubules (DCT). Metformin treated group (B1 and B2) showing different types of kidney damages; glomerulus degeneration (GD), increase in Bowman's space (BS), hemorrhages (H) and necrosis in the wall of convoluted renal tubules (N).

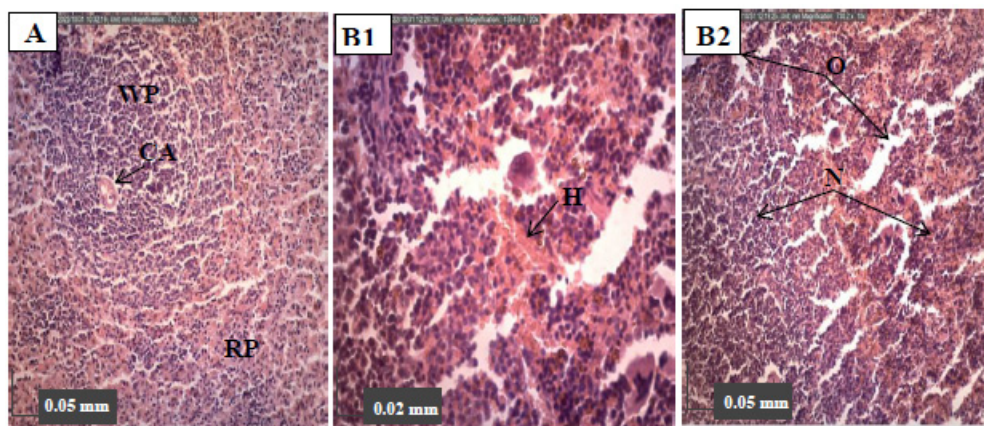


Fig.3. Cross section through the spleen (H and E): Control group (A) showing normal parenchyma architecture of red pulp (RP), white pulp (WP) and central arteriole (CA). Metformin treated group (B1 and B2) showing spleen damage; hemorrhage (H), odema (O) and changes in the red and white pulps through scattered necrotic areas in the parenchymal tissue of the spleen (N).

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تقييم تأثير الميتفورمين على أنسجة الكبد والكلى والطحال في إناث الجرذان البيضاء ذات مستوى السكر الطبيعي في الدم

أفين عبدالله محمد أمين^١ و مليكة قاسم نجيب^٢

^١ قسم مركز الأبحاث العلمية - كلية العلوم - جامعة دهوك - إقليم كردستان - العراق.

^٢ قسم الأحياء - كلية العلوم - جامعة دهوك - إقليم كردستان - العراق.

المستخلص

الميتفورمين هو أحد الأدوية المستخدمة لعلاج مرض السكري بشكل متكرر في الوقت الحاضر، والذي يستخدم أيضاً في المرضى غير المصابين بالسكري لعلاج الكبد الدهني، وتخفيض الوزن، والعقم، ومتلازمة المبايض المتعددة الكيسات، والوقاية من مضاعفات الحمل، والوقاية من مرض السكري والسمنة. ومع ذلك، قد يكون لاستخدامه العديد من الآثار الضارة الخطيرة مثل إصابة الكبد، وتسمم الكلى وإلحاق الضرر بالطحال.

تمت هذه الدراسة لتقييم التأثير المرضي المحتمل للميتفورمين على الكبد والكلى والطحال في الجرذان الغير المصابة بمرض السكري.

تم اختيار مجموعتين متساويتين من اثني عشر جرذاً بالغاً بشكل عشوائي. تم حقن المجموعة الأولى بالميتفورمين (٢٠٠ ملغم/كغم) داخل طبقة البريتون كجرعة وحيدة لمدة ثلاثة أيام، واستخدمت المجموعة الثانية كمجموعة كونترول وتلقّت حقنة داخل طبقة البريتون من نفس الحجم من المحلول الملحي الفسيولوجي. تم وزن الحيوانات والأعضاء وقياس الكرياتينين واللاكتات وفيتامين ب١٢. كما تمت دراسة التغيرات النسيجية المرضية في الكبد والكلى والطحال.

لم تتغير مستويات بارامترات الدم مع استخدام الميتفورمين. أظهرت المجموعة المعالجة بالميتفورمين تلعفاً هيكلياً بدرجات متفاوتة في الأعضاء الثلاثة؛ الكبد والكلى والطحال.

قد يكون الميتفورمين مثل أي دواء مفيداً في علاج بعض المشكلات الطبيعية. إلا أن نتائج الدراسة الحالية تؤكد أن استخدام الميتفورمين يمكن أن يسبب إصابة كبدية وتسمم كلوي وتلف متوسط في أنسجة الطحال، مما قد يساهم في التأثيرات السريرية للدواء؛ يجب على الأطباء والمرضى على حد سواء أن يكونوا على دراية بهذه الآثار الجانبية المحتملة.

الكلمات الدالة: الميتفورمين، الكبد، الكلى، الطحال، الجرذان ذات مستوى السكر الطبيعي في الدم، الفحص النسيجي المرضي.