

# Effect of medroxyprogesterone injection on liver function and histological features of the liver in albino rats

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**Abstract.** Medroxyprogesterone is a synthetic progestin that is widely used as a hormonal contraceptive and has a potential for hepatotoxicity. The present study aimed to evaluate the effects of medroxyprogesterone administration on the hepatic functions of female albino rats. For this purpose, a total of 20 female albino rats were divided into two groups of 10 rats each. The first group represented the rats prior to medroxyprogesterone administration, and the second group included the same rats after receiving an intramuscular injection of medroxyprogesterone (3.5 mg/rat/week) following an 8-week study period. In addition, the study included group 3, which represented the control female albino rats at the start of the study and group 4 represented the same rats of group 3, but at the end of the experiment. Blood samples were obtained for the evaluation of liver function, including the analysis of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin levels. Additionally, samples of hepatic tissues were histologically assessed. The results revealed a statistically significant elevation in AST, ALT and total bilirubin levels, with a reduction in ALP levels in the treated group (group 2) compared to the other groups at  $P < 0.001$ . The histopathological examination of the liver tissues revealed the vacuolar degeneration of hepatocytes, the congestion of sinusoids and inflammation in the treated group compared to the control groups. These findings point to the negative impact of medroxyprogesterone on rat liver function, with hepatic cell injury being observed. These findings highlight the potential hepatotoxic effects of this drug and urges the routine monitoring of liver function in clinical settings.

## Introduction

The well-known injectable hormonal contraceptive, medroxyprogesterone (MdP), is a long-acting progestin. A progesterone-based contraceptive injection is a highly effective birth control method (1). The contraceptive efficacy of MdP involves the inhibition of the secretion of gonadotropin-releasing hormone, preventing the maturation of ovarian follicles and ovulation that leads to a thin endometrial lining. This renders the endometrium unsuitable for implantation (2). The most commonly associated side-effects of MdP are irregular bleeding and weight gain (3). Depression, mood swings, decreased sexual interest and a slight increase in the risk of developing breast cancer have also been reported. However, there is evidence of a protective role of MdP against cancer, such as decreasing the risk of developing ovarian cancer (4).

MdP is commonly used as a family planning method due to its availability, effectiveness with a low failure rate and easy administration as a single intramuscular injection every 12 weeks (5). However, the careful use of MdP is required in patients with diabetes mellitus, as insulin sensitivity and glucose tolerance are affected. Additionally, patients with renal impairment may exhibit elevated levels of urea and creatine with the deterioration of the oxidative stress status. Moreover, the parenteral use of MdP is contraindicated in patients who are at a risk of developing cardiovascular diseases, such as stroke (6,7). The use of MdP with estrogen in menopausal women is associated with an increased risk of cardiovascular disorders and thromboembolic complications (8,9). It is considered that the underlying complications of cardiovascular disorders in women on injectable progestin-only contraceptives are caused by the abnormal lipid status (10-12).

MdP is exclusively cleared by the metabolism of the liver, and this may involve hepatobiliary complications (13-15). Over the years, conflicting data have been reported concerning the use of MdP in women with liver dysfunction. In 2009, The World Health Organization recommended the use of injectable progestogen-only contraception in women with liver disease (14) and it was found that MdP does not affect liver function (16,17). However, MdP was then used in women with liver disease and was classified as category 3 (risks outweigh benefits) (18,19). In 2022, Sathe and Gerriets (20) considered a contraindication of MdP usage in females with hepatic

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disorders and suggested discontinuing the MdP in case of liver function disturbances. Accordingly, the present study aimed to evaluate the effects of MdP on liver function and histological changes in the livers of female albino rats. The present study aimed to provide clinical insight into the liver-associated risks in users of MdP.

## Materials and methods

**Study protocol and animals.** The study protocol was approved by the Medical Ethical Committee at the University of Mosul, Mosul, Iraq with code number CCMRE-phA-22-13 on 18/10/2022. A total of 20 adult female Wistar albino rats (age range, 3-4 months; weight range, 200-315 g) were obtained from the Animal House at the College of Veterinary at the University of Mosul. A sample size of 20 female albino rats was based on previous studies investigating the effect of MdP on different organs (6,21,22). These rats were healthy and exposed to a light cycle of 12 h light/12 h dark with ~50% humidity at 22±2°C. The housed animals were hosted in cages for a 14-day adaptation period, which were enriched with bedding, nesting material and environmental supplements to promote natural behaviors and reduce stress. In addition, the rats were caged in small groups to allow social interaction, and were provide with access to water *ad libitum* and were fed a standard rodent laboratory diet. Animal handling was minimized, and all procedures were performed by trained personnel to reduce stress. To ensure compliance with ethical standards by minimizing pain and distress without compromising the scientific integrity of the study, meloxicam was used subcutaneously (1 mg/kg) on need. The animals were monitored, on a daily basis, for body weight, food and water intake, and for any signs of distress. The behavior of animals was recorded twice daily. The specific criteria for predefined humane endpoints used to determine when animals should be euthanized included either the end of the experiment, so that the liver could be examined for microscopic studies, or if any animal exhibited severe weight loss, inability to drink and eat, or severe irreversible distress signs. The 20 rats were randomly assigned to receive MdP (10 rats) or to serve as a control group (10 rats). All rats were euthanized at the end of the study, and none died during the experiment. The 10 rats in group 1 (G1) represent those prior to MdP administration, while those in group 2 (G2) represent the same rats as those in group 1, but after receiving an intramuscular injection of MdP (3.5 mg/rat/week for 8 weeks). The rats in group 3 (G3) represent the untreated control group at the baseline (starting point of the experiments), which included 10 female Wistar albino rats. The rats in group 4 (G4) are the same rats as those in G3, but at the end of the experiments (after 8 weeks). The animals were weighed and blood samples were drawn from the lateral tail vein at two time points: At the start of the experiments and at 8 weeks following the MdP administration. Blood samples were allowed to clot and centrifuged for 5 min (1500 x g at room temperature). The supernatant of the blood samples was then collected and stored at -20°C until tested at the same time in triplicate. Liver function tests were performed using the serum by enzyme-linked immunosorbent assay (ELISA) were purchased from CORMAY (Poland) and included alanine transaminase (ALT) (cat. no. 7-216),

aspartate transaminase (AST) (cat. no. 7-214) and alkaline phosphatase (ALP) (cat. no. 7-212) in addition to total bilirubin (cat. no. 7-254). At the endpoint of the 8-week MdP treatment period, the animals were euthanized by an intraperitoneal injection of phenobarbital sodium (150 mg/kg) according to the American Veterinary Medical Association (AVMA) guidelines. The death of the rats was verified by the absence of a heartbeat, corneal reflex and respiration. The total period of the study lasted 10 weeks, including 2 weeks of adaptation and 8 weeks of treatment.

**Histopathological examination.** The livers of the rats were immediately collected through surgery, washed with cold saline, preserved in 10% neutral buffered formalin and fixed for ~48 h at room temperature (25°C). The fixed tissues then washed with running water for 6-8 h. The samples were then hydrated through a graded alcohol series, and cleared with xylene, were embedded in paraffin, after which 5-μm-thick sections were prepared. The specimens were deparaffinized and stained with hematoxylin and eosin (H&E; Bio Optica staining kit) as outlined in the instructions provided with the kit, which involved three clearing stations of 3 min each at room temperature (25°C). The slides were analyzed using a light microscope (Olympus BX43; Olympus Corporation), and images were captured using a digital camera (Olympus XC30; Olympus Corporation).

**Statistical analysis.** Statistical analysis was performed using GraphPad Prism 8.0 software (Dotmatics). All data are expressed as the mean ± standard deviation (SD). The Student's t-test was used for two paired variables (pre-and post-administration of MdP), while one-way ANOVA followed by Tukey's post hoc test were used to calculate a significant difference of the means between different examined groups. A P-value ≤0.05 was considered to indicate a statistically significant difference.

## Results

**Effects of MdP on serum liver biomarkers.** As demonstrated in Table I, a considerable increase was observed in the serum levels of ALT, AST and total bilirubin at 8 weeks following the administration of a weekly dose of MdP, with a significant decrease in the levels of ALP (P<0.001) in G2 compared to the serum levels prior to the administration of MdP (G1). On the other hand, no changes in the liver function tests were noted in the control rats before the start (G3) and after the end of the study (G4), as demonstrated in Table II.

When comparing the examined liver function parameters of the four groups, the results revealed that the serum ALT, AST and total bilirubin levels significantly increased following the administration of 3.5 mg of MdP (G2) in comparison to G1, G3 and G4, respectively (P<0.001), as shown in Fig. 1A, B and D. On the other hand, there was a substantial decrease in the serum levels of ALP in G2 following treatment compared to the other groups (G1, G3 and G4; P<0.001, as shown in Fig. 1C).

**Immunohistochemistry of hepatic tissues in rats.** Immunohistochemistry of the liver (G1) revealed the classical histological observation of the liver section in the rats prior to

Table I. Effect of medroxyprogesterone on liver function parameters.

Parameter	Pre-MdP	Post-MdP	P-value
ALT (IU/l)	68.41±5.67	85.90±5.03	<0.001
AST (IU/l)	71.91±6.95	169.927±5.03	<0.001
ALP (IU/l)	259.72±24.32	201.86±14.14	<0.001
Total bilirubin (mg/dl)	0.76±0.1	1.01±0.06	<0.001

Data are presented as the mean ± standard deviation. Data were analyzed using a paired-test. Significant differences were found (P<0.05) between pre- and post-MdP. MdP, medroxyprogesterone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table II. Liver function tests in the control group at the start and end of the study.

Parameter	Before	After	P-value
ALT (IU/l)	61.24±7.34	66.43±6.63	NS
AST (IU/l)	66.93±5.49	72.09±4.99	NS
ALP (IU/l)	238.86±12.70	253.77±13.20	NS
Total bilirubin (mg/dl)	0.77±0.08	0.78±0.07	NS

Data are presented as the mean ± standard deviation. NS, not significant (P>0.05). MdP, medroxyprogesterone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

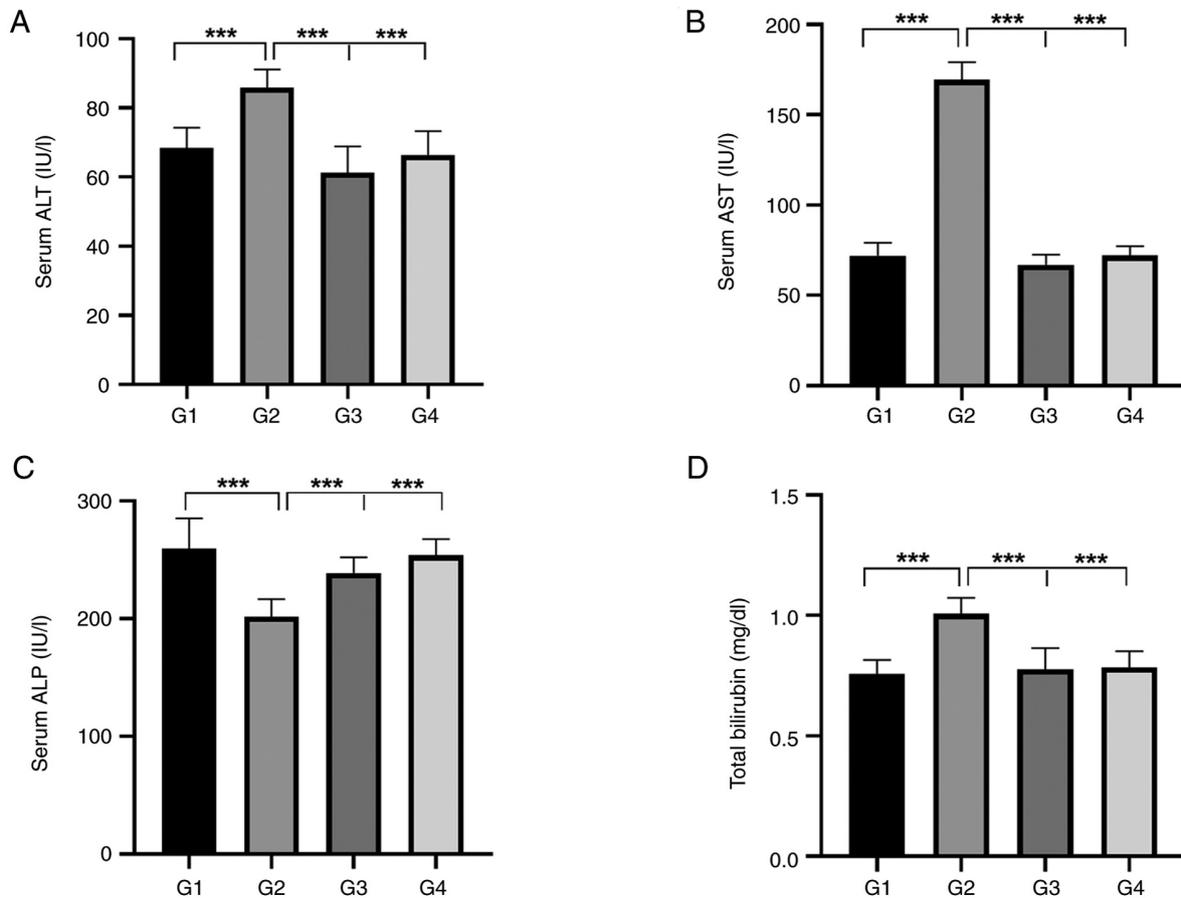


Figure 1. Effect of medroxyprogesterone administration on liver function parameters: (A) ALT levels, (B) AST levels, (C) ALP levels and (D) total bilirubin levels. Data are presented as the mean ± standard deviation. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. \*\*\*P<0.001. G1, group 1 (after 8 weeks of treatment with MdP); G2, group 2 (treated with MdP); G3, group 3 (untreated control group at the baseline) and G4, group 4 (same rats as those in G3 but after 8 weeks). ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

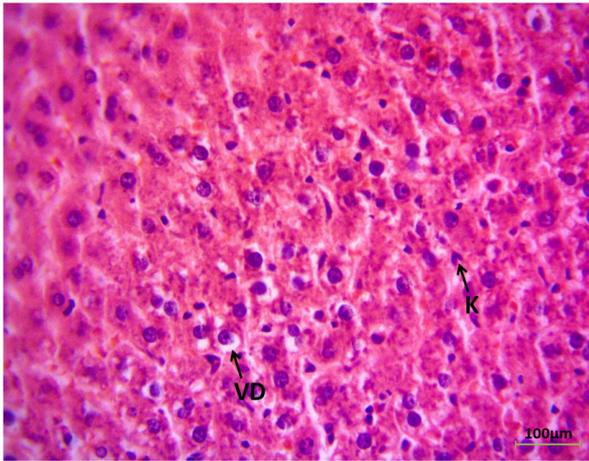


Figure 2. Photomicrograph of the liver prior to the administration of medroxyprogesterone (group 1). The image shows the mild vacuolar degeneration of hepatocytes (VD) and increased numbers of Kuepfer cells (K). Hematoxylin and eosin staining, x400 magnification.

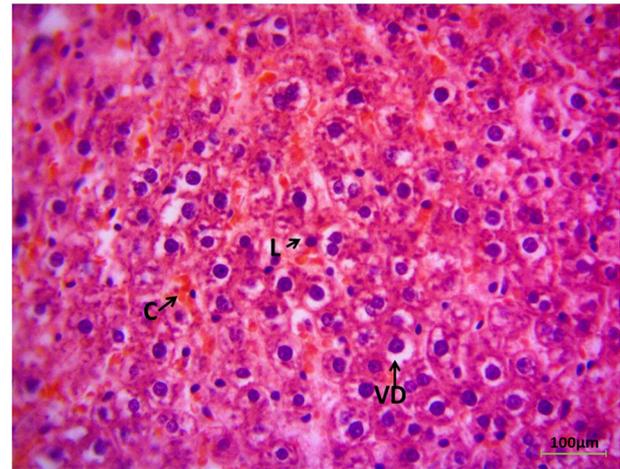


Figure 3. Photomicrograph of the liver following the administration of medroxyprogesterone (group 2). The image shows the vacuolar degeneration of hepatocytes (VD), the congestion of sinusoids (C) and inflammatory cell infiltration (lymphocytes). (L) Hematoxylin and eosin staining, x400 magnification.

MdP, apart from mild vacuolar degeneration of hepatocytes (Fig. 2). However, the liver histological sections exhibited a pathological appearance following the administration of MdP for 8 weeks, as demonstrated in Fig. 3. Some areas exhibited the congestion of sinusoids with hepatic tissue infiltration of inflammatory cells (lymphocytes).

## Discussion

In the present study, the 8-week use of MdP was found to be linked to an increase in AST, ALT and total bilirubin levels, aligning with findings of previous research (23-25). As regards ALP, the present study demonstrated a decreased level in the MdP group compared to the animals not administered MdP. Furthermore, MdP was found to cause the vacuolar degeneration of hepatocytes, the congestion of sinusoids and the infiltration of hepatic tissues with inflammatory cells.

The liver is a crucial organ for several metabolic processes, including the detoxification of medications. AST, ALT, ALP and total bilirubin are among certain biochemical tests that can be used to monitor the overall function of the liver (26). The abnormal levels of any of these markers may be a sign of liver damage, and such tests are required for the determination of the location of liver injury and differential diagnosis (27).

The elevations in the levels of AST and ALT observed in the present study indicate possible MdP-induced hepatocellular damage. Hepatic cell injury results in the release of AST and ALT enzymes in the circulation. This observation is in line with the findings of previous studies that attributed the rise of such liver enzymes to the effect of ethinylestradiol (26-28). Hepatic, cardiac, renal, skeletal muscles, white blood and red blood cells in addition to the brain and lungs contain AST as cytosolic and mitochondrial enzymes. An increase in AST levels may be due to non-hepatic sources and it is not as specific or sensitive as ALT for the liver (31). Conversely, ALT is a cytosolic hepatic enzyme that is found in high concentrations in the liver. An increase in ALT levels is highly specific to liver injury (32).

The significant reduction in the levels of ALP in the present study is contradictory to the results of other studies (21,31) that demonstrated an elevation in the levels of ALP. It is known that hormonal contraception containing progestin is metabolized by the liver, potentially affecting the activity of liver enzymes (34), leading to a decrease in the production or release of ALP or even lowered levels due to damage to the biliary system.

The total bilirubin levels were substantially higher in the present study following the administration of MdP compared with the controls, which is a potential indicator of hepatobiliary damage or issues with the excretory roles of the liver (35). This outcome is consistent with the findings of previous studies demonstrating liver complications with the use of progesterone (21,23,34).

The outcomes of the present study collectively revealed that the use of MdP was associated with increased levels of ALT, AST and total bilirubin, suggesting that the use of MdP is associated with integrity and functionality alterations of the liver. It is a consequence of how medications can alter the metabolic activity of the liver and how injectable contraception leads to elevated levels of hepatic enzymes (37).

The present study also found histopathological lesions in the livers of female rats following hormonal therapy. Hepatocyte vacuolar degeneration, sinusoidal congestion and lymphocyte infiltration by lymphocytes were observed. Previous research has explained vacuolar degeneration, stating that an increase in endoplasmic reticulum, mitochondrial swelling and cellular granularity is caused by the metabolism of female sex hormones in hepatocytes (38); however, mild vacuolar degeneration does not essentially indicate severe liver damage. Additionally, the activation of the inflammatory immune system is reported by the infiltration of immune cells that are potentially responsible for the acceleration of hepatic damage (39).

MdP induces hepatic toxicity via several mechanisms, including an increase in oxidant molecules with a reduction in antioxidant enzymes that may be associated with

hepatocellular injury (6). The levels of inflammatory markers increase with the administration of MdP, resulting in inflammation. The alteration of bile acid metabolism associated with MdP indicates a possibility of cholestatic damage (40). Elevated levels of inflammatory cytokines, and the interruption of mitochondrial oxidation further exacerbate hepatocellular injury through cellular homeostasis disruption and provoke apoptosis (41).

MdP is commonly used in hormonal therapies, including birth control and hormone replacement therapy. The present study confirmed the hepatotoxic effects of MdP, suggesting comparable adverse effects in humans. These data may help clinicians monitor liver function in patients with MdP or may provide a safer therapy or an adjuvant treatment for the likely development of hepatotoxicity.

The present study demonstrates the hepatotoxic effects of MdP through liver function tests and histological damage; however, the present study was an observational study. Further studies at the molecular levels, examining inflammatory cytokines, mitochondrial chain reaction, gene expression and oxidative stress markers are recommended to determine the mechanisms through which MdP induces liver damage. Despite this limitation however, the results of the present study highlight the negative effects of MdP on hepatic cells with the need for future research in this area.

In conclusion, the present study confirmed that MdP induces liver injury through mechanisms that are not yet entirely clear. Hepatotoxicity can be caused through induced metabolism, as MdP is metabolized by the liver, during which a reactive metabolite could be formed and cause further liver damage. The activation of the immune response through medication can result in inflammation and injury to hepatocytes, or can cause liver injury via direct MdP toxicity that more likely depends on the dose and duration of the treatment. However, the results of the present study highlight the necessity for the routine monitoring of liver function and status in the case that MdP is to be used by females for birth control.

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### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

FAA and MNA were involved in the conceptualization and methodology of the study. FAA, MNA and MEQ were involved in the investigative aspects of the study and in the formal analysis. FAA and MNA were involved in preparation of the figures and in the writing of the original draft of the manuscript. All authors edited and revised the manuscript. All

authors confirm the authenticity of all the raw data. All authors have read and agreed to the final version of the manuscript.

### Ethics approval and consent to participate

The Medical Ethical Committee at the University of Mosul, Mosul, Iraq approved the study protocol with code number CCMRE-phA-22-13 on 18/10/2022.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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