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Original Article

Effect of dexamethasone and contraceptive pills in Female Rats (Rattus *norvegicus)*

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ABSTRACT

The present study aimed to investigate the effect of dexamethasone and contraceptive pills on glucose level, liver function of female rats. Methods: contraceptive pills (EE 0.03 ml, LE 0.075 ml), and dexamethasone were used, and the animals were treatment for three months. The result indicated a significant increase ($p<0.05$) of glucose level in the second, third and fourth groups compared with the control group. The results showed a significant increase in liver enzymes (AST, ALT) in the second, third and fourth groups compared with the control group. This study showed that the treatment with dexamethasone caused a damage for liver. No morphological damage was observed in the control group, while (dilated central veins, proliferation of portal and congestion in the sinusoids and enlargement of hepatocytes with, dilated portal spaces) was observed in the second group. In the third group moderate damage (minimal disorganization of the hepatocyte plates, congested sinusoids, central vein, and enlargement hepatocytes was observed. While, the same but moderate changes in the hepatocytes, minimal vacculation of center lobular hepatocytes, enlargement sinusoids, congested central vein and enlargement hepatocytes was observed in the fourth group.

Keywords: Dexamethasone, contraceptive pills, glucose level, liver enzymes

INTRODUCTION

One of five major classes of cholesterol-derived steroid hormones, known as corticosteroids, which also include, mineral corticoids, progestagens, androgens and estrogens. In humans and corticosterone in rats are naturally circulating glucocorticoids - such as cortisol (hydrocortisone) synthesized within the mid-zone of the adrenal cortex, the zona fasciculate, in response to adrenocorticotrophic hormone (ACTH) secretion from the anterior pituitary gland [1]. The side effects of glucocorticoids are widely used drugs with diabetogenic [2;3]. Syndromes of cortisol excess and chronic glucocorticoid therapy are associated with increase of glucose concentration, diabetes and glucose intolerance [4]. The underlying mechanisms are suppression of insulin secretion from the pancreas, promotion of gluconeogenesis in the liver, and inhibition of glucose uptake in peripheral tissues [4].

Clinical studies and several basic have investigated the rapid effects of glucocorticoids on glucose metabolism. Rodent studies and in vitro experiments have known non-genomic glucocorticoid signaling in pancreas, liver, and adipose tissue [5;6]. Oral administration of hydrocortisone was observed to decrease insulin secretion within 30 min In humans [7]. Administered a single oral dose of dexamethasone 150 min before an oral glucose tolerance test impairs glucose tolerance without changing insulin sensitivity [8]. Clinically, dexamethasone is administered for the inhibition of inflammation [9]and the alleviation of emesis associated with chemotherapy [3;10]. When administered increased, dexamethasone induces adverse effects such as increased insulin resistance[11;12;13,] increased adiposity[14; 15], and muscle catabolism[16], hyperplasia[17]. In rodents dexamethasone has been used to rapidly generate insulin resistance [18;19]. Over the years, concerns have been increased about the possible association between hormonal contraceptives and various chronic diseases, including breast cancer, cardiovascular disease and metabolic dysfunction. However, little is known about hormonal contraceptive use and its role in the development of gestational diabetes (GDM). Research has established a relationship between oral, hormonal contraceptive use and increased levels of serum glucose, altered lipid profiles and insulin [20;21]. The present study aimed to investigate the effect of dexamethasone and oral

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contraceptive pills (OCs) on glucose level and liver function of female rats.

MATERIALS AND METHODS

Experimental Animals: Twenty four female rats (*Rattus norvegicus*) were used in the present study. Rats supplied from the animal house of Biology department, Science collage, Thi-Qar University, Iraq with weights ranging from 200 to 250 g. Animals were divided into four groups (6 for each group). The first group (A) was a control treated with normal saline for three months, the second group (B) was treated with dose (0.15 ml/animal/day) of dexamethasone (0.5 mg in 5 ml) for three months. The third group (C) treated with (EE 0.03 ml, LE 0.075 ml) of contraceptive microgeynon for three months. The fourth group (D) treated with (0.15 ml/animal/day) of dexamethasone and (EE 0.03 ml, LE 0.075 ml) of contraceptive pills for three months.

Specimens Collection: At the end of experiment the rats were generally anaesthetized by inhalation of chloroform and then sacrificed. Blood samples were collected directly from the heart by the use of disposable syringes of 5 ml capacity, and the blood samples were poured into test tubes without anticoagulant, and allowed to clot at room temperature and then centrifuged at velocity (3000 rotation/minute) for (15 minutes) to isolate blood serum and froze at -20 centigrade to estimate the biochemical parameters included glucose level and liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Liver was isolated for histological sections [22].

Statistical Analysis: Standard analysis of the data of different studied groups was performed using the computerized statistical program: The SPSS program (Statistical Program for Social Sciences). The results were expressed as mean± S.E. Analysis of variance (ANOVA) was used to compare the results of different groups. The differences are considered to be significant at the level 0.05($P \leq 0.05$).

RESULTS

Biochemical parameters

Glucose Level: The results showed a significant increase ($P \leq 0.05$) in the glucose level in the second group, third and fourth groups (B, C and D) compare with the control group (A). Also, there was a significant increase in the glucose level in the second and fourth groups (B and D) compare with the third group (C).

Table (1): Effect of dexamethasone and contraceptive on glucose level of female rats.

Animal groups	Glucose level (mg/Dl)
Control (A)	124.00±1.74 [c]
Dexamethasone(B)	233.00±8.61[a]
Contraceptive(C)	133.00±2.10 [b]
Dex.+ Contraceptive(D)	235.00±1.95 [a]
LSD	9.00

Values are means ± S.E.; Different letters refer to significant differences ($p<0.05$); Same letters refer to no significant differences ($p<0.05$).

Liver enzymes: In the table (2) the results showed a significant increase ($P \leq 0.05$) in the liver enzymes, aspartate aminotransaminase (AST) in the second group(B), third group(C) and fourth group (D) compare with control group (A). Also there was a significant increase in (AST) of group (D) compare with the (B and C) groups, whereas alanine aminotransaminase (ALT) increased significantly in (B, C and D) groups comparison with the control group (A).

Table (1): Effect of dexamethasone and contraceptive on (AST) and (ALT) of female rats.

Animal group	SGOT (AST) IU/L	SGPT (ALT) IU/L
Control A	8.55c ± 1.46	8.60c ± 1.41
Dexamethasone (B)	11.15b ±3.55	12.73ab ± 3.84
Contraceptive (C)	10.83b ± 1.99	10.17b ± 2.817
Mixed of dex+ Contraceptive (D)	15.77 a ±2.88	15.17a ±3.31
LSD	3.32	4.500

Values are means ± S.E.; The different letters refers to significant differences among groups ($P \leq (0.05)$.; Same letters refer to no significant differences ($P \leq 0.05$)

Histological Changes: No morphological damage was observed in liver of the rats in the control group (figure 1). In the treated group with dexamethasone, severe damage (dilated central veins, proliferation of portal and congestion in the sinusoids and enlargement of hepatocytes with, dilated portal spaces) was observed (figure 2). In

contraceptive dose, moderate damage (minimal disorganization of the hepatocyte plates, congested sinusoids, central vein, and enlargement hepatocytes was observed (figure 3). While, the same but moderate changes in the hepatocytes, minimal vacculation of center lobular hepatocytes, enlargement sinusoids , congested central vein and enlargement hepatocytes was observed in the dose dexamethasone and contraceptive group (figure4).

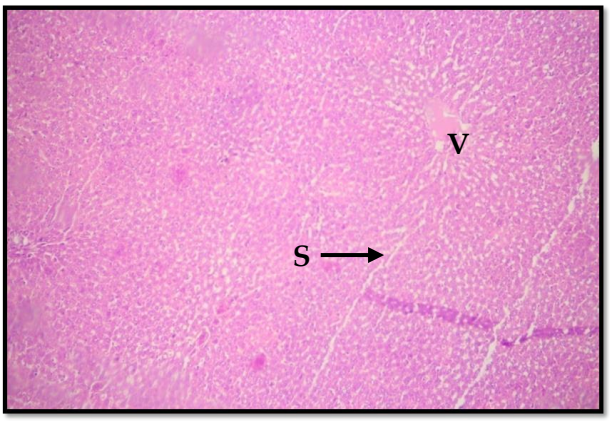
DISCUSSION

In this study, used of dexamethasone and contraceptive pills oral for three month was shown a significant increase in glucose level in both rats treated with dexamethasone dose(group B) and mixed of dexamethasone with contraceptive(group D), while the low a significant increase in rats treated with contraceptive pills (group C) compared with rats control (group A). This increase may due to that glucocorticoids caused in the liver increased in gluconeogenesis [23]. Increase of blood glucose may be due to decreases of glucose transmitters in cell membrane, then decrease entry of glucose in to the cells and lead to its increase in the blood [24]. Increase in the blood glucose in treated groups significantly ($P \leq 0.05$) by dexamethasone in the present study consistent with [25] in the rats, [26] in the rats. In the mice [27], and in human [28]. In our study observed the administered contraceptive pills only effect low significant in glucose level confirms that this formula does not cause significant changes in glucose levels compared with dexamethasone doses, the possibility that use of OCs may be associated with a lower odds of diabetes may have important clinical implications,

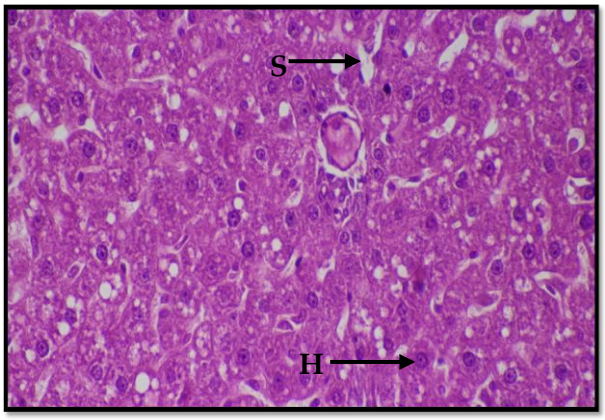
The results indicated a significant increases ($P \leq 0.05$) in the aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) in all treated groups. These enzymatic changes may take place as a result of destruction of hepatocytes which are responsible for detoxication and their accompanying exodus the entrance enzymes to blood. These results agree with [29;30] in human, in dog [31] , and [32] in piglets. These results may be due to that the catabolic effects of hydrocortisone, as measured by the gluconeogenic marker glutamate-oxaloacetate transaminase enzyme (AST) [31]. Increase of ALT more than AST consistent with [33], that may due to that the high gluconeogenic potency of the substrates of this enzyme (glutamate, alanine, and pyruvate). This suggested that "the control of hepatic levels of glutamicpyruvic transaminase by glycol corticosteroids is importantly related to the mechanism whereby these compounds exert their gluconeogenic activity [34].

The liver is a major target organ of dexamethasone action in both physiological and pathological conditions. The effects of dexamethasone on amino acid and glucose metabolism by modulation of tyrosine-aminotransferase and phosphoenolpyruvate carboxykinase gene expression are well known [35]. Furthermore, glucocorticoids play an important role in the treatment of certain liver diseases [36]. Glucocorticoids modulate acute-phase reaction by interaction with the interleukin-6 pathway [37], therefore dexamethasone consist have major effects on the liver, particularly when given long term and in higher than physiologic doses. Dexamethasone can result in hepatic enlargement and glycogenosis. Also the present study shows that OCPs treated to female rat indicated the histopathological change on rat livers including damage and, congested sinusoids ,central vein, and enlargement hepatocytes was observed compare with control group. The reason of cell damage may be caused by the effect of estrogen and progesterone on liver cells[38].

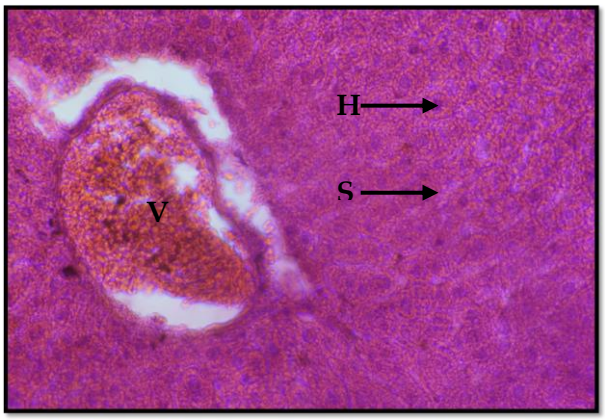
Conclusions: The effect of dexamethasone and contraceptive pills on glucose level and liver enzymes associated with damage of liver.



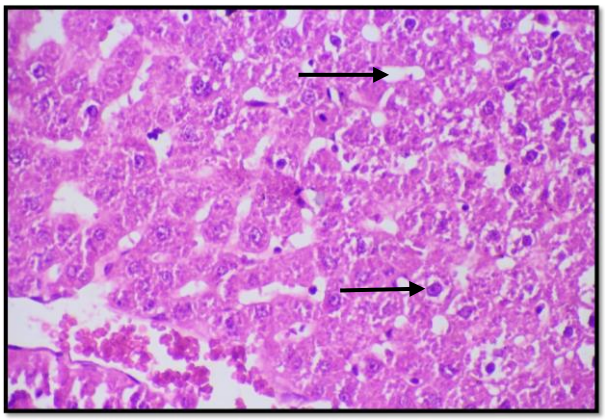
(Fig.1). No morphological damage was served in any o of the rats in the control group. central vein **V**, hhepatocytes **H**, and sinusoids **S** within normal limits. **H&E 100 X**



(Fig.3)Contraceptive dose, Liver, congested sinusoids **S**, central vein **V** and enlargement hepatocytes H. **H&E 200X**



(Fig.2) Dexamethasone dose, Liver, congested sinusoids **S**, central vein **V** and enlargement of hepatocytes H .**H&E 200X**



(Fig.4).Dex and Contraceptive dose, Liver, minimal vaculation of center lobular hepatocytes, enlargement sinusoids **S**, congested central vein **V** and enlargement hepatocytes H. **H&E 200X**

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