EFFECTS OF DEXAMETHASONE, ESTROGEN ADMINISTRATION ON LEPTIN, THYROID, REPRODUCTIVE HORMONE CONCENTRATION AND LIPID PROFILE OF FEMALE RABBITS SERUM.

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ABSTRACT

The aim of this study investigate the effects of long term administration of Dexamethasone (DEX.) 17 β-estradiol (EST.) on body weight, concentration of some hormones (Leptin, thyroid and reproductive hormone) in addition to determination of lipid profile of female rabbits blood serum.

Thirty local rabbits were subdivided randomly and equally into three groups. The first group was used as a control which injected with normal saline . The second group was injected daily (0.5mg /kg B.W) DEX . Intramuscularly. The third group was injected subcutaneously daily with 0.3 mg /kg B.W s/c 17 β-estradiol. All groups in this study were treated for 60 days , and blood collected every 15 days. Serum was tested for leptin, LH, FSH, T3, T4 hormones total Cholesterol(TC), HDL(height density lipo-protein), LDL (low density lipo- protein),TG (triglycerides), Body weight was taken every 15 days from the first day .

The result showed significant ($P \leq 0.05$) decreased in body weight after administration of both dexamethasone (DEX.) and Estrogen (EST.), significant increased in leptin concentration with dexamethasone (DEX.) Treatment while significant decreased with Estrogen (EST.) treatment, in the other hand LH and FSH concentration showed significant decreased in both treatment dexamethasone (DEX.) and Estrogen (EST.) thyroid hormone show significant decreased with dexamethasone (DEX.) Treatment and significant increased T3 & T4 hormone with Estrogen (EST.) treatment as compare with control while the increase in the T4 it was occurred only in the periods (45

and 60)days within treatment groups , lipid profile (TC,TG,LDL, HDL,VLDL) show significant increased with DEX. treatment while Significant decreased with EST. treatment.

INTRODUCTION

Leptin is the adipose tissue peptide hormone which plays an important role in the regulation of body fat and therefore it was called the obesity hormone, since leptin inhibits food intake by its action on Neuropeptide Y (NPY), initially it was believed that reduced leptin levels may be the cause of obesity.

Dexamethasone is potent synthetic member of glucocotricoids class of steroid drugs. It acts as anti inflammatory and immunosuppressant. It is 20 to 30 times more potent than the naturally occurring hormone cortisol (1).

Glucocorticoids have an important influence on the pathogenesis of obesity, Patients with chronic elevated cortisol levels, like patients with Cushing's Syndrome have a significant redistribution of adipose tissue towards the central depots (2).The effects of glucocorticoids on adipose tissue seem to be complex and diverse, *in vitro* studies in rats have shown that glucocorticoids stimulate lipolysis by increasing the activity of hormone sensitive lipase (3). These observations have been confirmed by human *in vivo* studies that showed an increase in fatty acid turnover with hypercortisolaemia (4). Other studies also indicated that glucocorticoids can also stimulate lipoprotein lipase, at least *in vitro*, and therefore have stimulatory effects on lipogenesis (5). Besides effects on lipogenesis and lipolysis, glucocorticoids also have effects on adipogenesis, glucocorticoids promote the differentiation of adipocyte precursor cells in vitro in human, sheep and pig (6, 7, 8).

Estrogens are steroid hormones that are important endocrine effectors of reproduction, cardiovascular physiology, neuronal growth and differentiation, neuroprotection, cognition, sexual differentiation and regulation of mood (9,10).

Adipose tissue produces estrogens through aromatase expression within adipocytes, and this is a major site of estrogen biosynthesis in postmenopausal women and men (11). Estrogen is important in determining body conformation, as demonstrated by ovariectomy, which leads to increased adiposity (12). Another issue may be the type

of fat that predominates in females, as they have greater levels of subcutaneous fat, in comparison to males who have greater levels of visceral fat (13).

Estrogen exerts a wide range of effects on metabolism and weight regulation at various tissues, including the brain. Regarding the neuroendocrine system, estrogens act to reduce feed intake and increase energy expenditure (12). In female mice and rats, discrete silencing of estrogen receptor a (ERα) in the VMH causes hyperphagia and reduces physical activity and thermogenesis, leading to increased adiposity (14).

Aim of study:

Study was aimed to find the effects of administration of DEX or Estrogen on metabolic hormone leptin and some other hormones that have relationship with metabolic function, and some biochemical parameters.

MATERIAL AND METHODS

Thirty female rabbits from local markets weighted 1300-1600 gram were divided equally and randomly into three groups, first group used as control, second group was injected daily with treatment dose of dexamethasone 0.5mg/kg B.W) i/m., the third group was injected daily with 0.3 mg /kg B.W s/c β-17estradiol benzoate (Syva .lab company).

Animal weighed every 15 days till the end of the treatment, after 60 days. Each two experimental animals were kept in one cage, the animals were provided with ration composed of green alfalfa (*Medicago sativa*) and tap water *ad libitum* and were given a prophylaxis drug against coccidiosis (Amprollium 1g/L of drinking water) and these animals maintained in air-conditioned quarters (24 Cº) under standard husbandry condition with alternate 12 hours light /dark period.

Blood sample were collected at directly from the heart (cardiac puncture) in the day 0 and then every 15 days, blood collect in plastic tube without anticoagulant and then refrigeratored for 12 hour as maximum then centrifuged (5000rpm) for 15 min to sprat serum that used in hormonal (Leptin,T3,T4, LH,FSH) and blood biochemical parameters analysis (metabolic enzymes), serum samples stored in -20Cº until used in analysis.

Statistical analysis

All the recorded data were analyzed for ANOVA using a complete Randomized design (CRD) with help of computer packaged program SPSS (Statistical Packages for the Social Science) (V.19). Least significant differences (LSD). Was calculated to compare the variations between the treatments were ANOVA showed significant differences. The data were expressed as mean ± stander deviation (mean ±SD).

RESULTS

The administration of DEX and EST. to female rabbits for 8 weeks caused significant (P≤ 0.05) decrease in the body weight as compared with control group and also within treatment periods. (Table 1)

Table (1) Effect s of DEX. or Estrogen on body weight/g (N=10)

treatment	Periods				
	0 day	15 day	30 day	45 day	60 day
Control	1437.50 ±53.70Aa	1466.00 ±111.06Aa	1469.30 ±96.84Aa	1476.50 ±104.88Aa	1477.00 ±66.84Aa
DEX	1450.50 ±50.71Aa	1336.00 ±47.88 Bb	1271.50 ±33.33 Bb	1193.30 ±31.28 Bc	1066.40 ±30.66 Bd
Est.	1467.00 ±111.06Aa	1332.00 ±46.38 Bb	1307.00 ±71.65 Bb	1225.00 ±76.04 Bc	1177.00 ±83.40 Bc

Capital letters denote differences between groups P≤0.05 Vs control.
Small letters denote differences within groups P≤0.05.

Administration of DEX and to female rabbits for 60 days caused significant (P≤ 0.05) increased in serum leptin hormone concentration while administration of EST. caused significant decreased in serum leptin hormone concentration as compared with control group and also during all periods of experiment (Table 2).

Table (2) Effect s of DEX. and Estrogen on serum leptin(µg/l), concentration

treatment	Periods				
	0 day	15 day	30 day	45 day	60 day
Control	١.٣٣ ±٠.٤٨ Ba	١.٣٤ ±٠.٠٤ Ba	١.٣٤ ±٠.٠٣ Ba	١.٣٤ ±٠.٠١ Ba	١.٣٢ ±٠.٠٣ Ba
DEX	١.٣٣ ±٠.٠٤ Be	١.٨٠ ±٠.٠٦ Ad	٢.٠٣ ±٠.١١ Ac	٢.٣٦ ±٠.٠٤ Ab	٣.٢٠ ±٠.١٧ Aa

Est.	١.٤٠ ±٠.٠٥ Aa	١.٢٩ ±٠.٠٣ Bb	١.٢٢ ±٠.٠٣ Cc	١.١٧ ±٠.٠٤ Cc	١.٠٨ ±٠.١١ Cd

Capital letters denote differences between groups P≤0.05 Vs control.

Small letters denote differences within groups P≤0.05.

Effects of administration of DEX and EST. to female rabbits for 60 days showed significant (P≤ 0.05) decrease in the serum concentration of hormone LH and FSH as compared with control group and also within treatment periods.

Table (3) Effects of DEX. and Estrogen on serum LH and FSH concentration

parameters	treatment	Periods				
		0 day	**15 day**	**30 day**	**45 day**	**60 day**
LH (mIU/ml)	**Control**	٢.٦٨ ±٠.١٢ Ba	٢.٧٠ ±٠.٠٤ Aa	٢.٧٠ ±٠.٠٥ Aa	٢.٦٦ ٠.١٠ Aa	٢.٧١ ±٠.١٢ Aa
	DEX	٢.٥٩ ±٠.٠٦ Ba	٢.٤٢ ±٠.٠٤ Bb	٢.٢٩ ±٠.٠٣ Cc	٢.٢٣ ±٠.٠٣ Cc	٢.٠٩ ±٠.٠٥ Cd
	Est.	٢.٨٠ ±٠.٠٣ Aa	2.65 ±٠.08 Ab	2.58 ±٠.٠7 Bb	2.45 ±٠.١0 Bc	2.32 ±٠.١2 Bd
FSH (mIU/ml)	**Control**	٢.٧٢ ±٠.٠٦ Ba	٢.٧١ ±٠.٠٣ Aa	٢.٧٠ ±٠.٠٦ Aa	٢.٧١ ±٠.٠٥ Aa	٢.٧٤ ±٠.٠٣ Aa
	DEX	٢.٧٠ ±٠.٠٣ Ba	٢.٥١ ±٠.٠٥ Cb	٢.٣٧ ±٠.٠٢ Cc	٢.٢٣ ±٠.٠٢ Cd	٢.٠٣ ±٠.٠٣ Be
	Est.	٢.٧٩ ±٠.٠٣ Aa	2.59 ±٠.11 Bb	2.44 ±٠.07 Bc	2.32 ±٠.٠٩ Bd	2.17 ±٠.10 Ce

Capital letters denote differences between groups P≤0.05 Vs control.

Small letters denote differences within groups P≤0.05 .

Table (4) indicated significant (P<0.05) decrease in concentration of both T3 and T4 in treated group with DEX as compared with control group and in all treatment periods.

While group treated with EST. shows significant increased (P<0.05) as compared with control group and while increased in T4 occurred only in the periods (45 and 60)days as compared within treatment periods.

Table (4) Effects of DEX. and Estrogen on serum T3 and T4 concentration

parameters	treatment	periods				
		0 day	**15 day**	**30 day**	**45 day**	**60 day**
T3 (ng/ ml)	**Control**	1.40 ±0.03 Aa	1.41 ±0.03 Ba	1.43 ±0.01 Ba	1.41 ±0.02 Ba	1.41 ±0.04 Ba

	DEX	1.42 ±0.04 Aa	0.74 ±0.03 Cb	0.64 ±0.03 Cc	0.44 ±0.04 Cd	0.32 ±0.02 Ce
	Est.	1.44 ±0.05 Ae	1.62 ±0.09 Ad	1.90 ±0.16 Ac	2.22 ±0.14 Ab	2.39 ±0.13 Aa
T4 (µg/dl)	**Control**	5.07 ±0.04 Aa	5.03 ±0.09 Aa	5.10 ±0.06 Aa	5.06 ±0.12 Ba	5.08 ±0.11Ba
	DEX	5.10 ±0.08 Aa	4.60 ±0.05 Bb	4.21 ±0.04 Bc	3.97 ±0.12 Cd	3.45 ±0.04 Ce
	Est.	5.02 ±0.08 Ac	5.14 ±0.22 Ac	5.25 ±0.31 Ac	6.00 ±0.18 Ab	6.41 ±0.23 Aa

Capital letters denote differences between groups P≤0.05 Vs control.
Small letters denote differences within groups P≤0.05 .

Concentrations of total cholesterol, TG, LDL and VLDL was significantly (P<0.05) increased in serum of female rabbits treated with DEX respectively compared with control group and within all periods of experiment, On the other hand, there was significantly (P<0.05) decreased of HDL in the group treated with DEX compared with control group and in all treatment periods.

While in group treated with EST. the result shows significant (P<0.05) decrease in the lipid profile (total cholesterol, TG, LDL and VLDL) compared with control group and also during all periods of experiment. (Table 5A and 5B).

Table (5A) Effects of DEX. or Estrogen on serum Total cholesterol and Triglyceride

parameters	**treatment**	**periods**				
		0 day	**15 day**	**30 day**	**45 day**	**60 day**
CHOLESTROL (mg/dl)	**Control**	٨٠.٨٥ ±٠.٣٩ Ba	٨٣.٣٣ ±٢.٦٦ Ba	٨٢.٧٠ ±٠.٩٦ Ba	٨٣.٠٢ ±٣.٨٦ Ba	٨٤.٢٥ ±٣.٢٨ Ba
	DEX	٨١.٢٢ ±٠.٤٥ Be	١٥٢.٠٥ ±٠.٧٦ Ad	١٨٠.٢٠ ±٠.٤٣ Ac	٢٣٢.٦٨ ±١.٠٠ Ab	٢٦٢.١٤ ±٠.٤٤ Aa
	Est.	٨٨.٢٠ ±٣.٨٨ Aa	٨٠.٧٥ ±٠.٩٦ Cb	٧٣.٩٧ ±٣.٢٨ Cc	٦٤.٢٥ ±٣.٧٠ Cd	٥٥.٥٦ ±٢.٧٠ Ce
TRIGLYCERID (mg/dl)	**Control**	٦٥.٧٥ ±0.38 Ba	٦٥.٥١ ±٠.٦٤ Ba	٦٥.١٣ ±١.١٦ Ba	٦٥.٧١ ±٠.٥٧ Ba	٦٥.٤٤ ±٠.٩٨ Ba
	DEX	٦٣.٦٥ ±٣.٤٣ Be	٨٢.١٦ ±٠.٧٣ Ad	١٢١.٦٠ ±٠.٦٣ Ac	١٤٩.٥٩ ±٠.٥٤ Ab	١٨٢.٩٩ ±٠.٣٦ Aa
	Est.	٦٩.٥٧ ±٤.١٢ Aa	٦٠.٨٦ ±٣.١٩ Cb	٥١.٠٣ ±١.١٢ Cc	٤٦.٢٣ ±٢.٧٣ Cd	٤١.٢٠ ±١.٦٣ Ce

Capital letters denote differences between groups P≤0.05 Vs control.
Small letters denote differences within groups P≤0.05 .

Table (5B) Effects of DEX. and Estrogen on serum LDL, HDL, VLDL.

parameters	treatment	periods				
		0 day	15 day	30 day	45 day	60 day
LDL (mg/dl)	Control	١٠.٢٥ ±١.٠٧ Ba	١٤.٣٩ ±٢.٩٣ Ba	١٢.٢٩ ±٣.٧٨ Ca	١٣.١٢ ±٤.٧٠ Ba	١٤.٦٢ ±٤.٤٠ Ba
	DEX	١١.٣٦ ±٠.٩٨ Be	٨٦.٢٨ ±١.١٤ Ad	١١٥.٧٠ ±٠.٣٩ Ac	١٧٠.٥٧ ±١.٣٣ Ab	١٩٧.٦٩ ±٠.٢٧ Aa
	Est.	١٧.٣٩ ±٣.٩٦ Ab	١٥.٨٩ ±١.٢٠ Bb	١٧.٤٩ ±٤.٨٩ Ba	١١.٩٢ ±٣.٧٧ Bc	٧.٣٨ ±٠.٨٣ Cd
HDL (mg/dl)	Control	٥٧.٤٤ ±٠.٧٨ Aa	٥٥.٨٣ ±٠.٨٧ Aa	٥٧.٣٧ ±٢.١١ Aa	٥٦.٧٦ ±١.٠٣ Aa	٥٦.٦٠ ±١.٧٤ Aa
	DEX	٥٩.٤٣ ±٢.٤١ Aa	٤٩.٣٤ ±٠.٥٣ Cb	٤٠.١٤ ±٠.٢٩ Cc	٣١.١٩ ±٠.٦٣ Cd	٢٧.٨٤ ±٠.٣٥ Ce
	Est.	٥٦.٩٠ ±١.٦٣ Aa	٥٢.٦٨ ±١.١٨ Bb	٤٦.٢٧ ±٢.٥٥ Bc	٤٣.٠٧ ±١.٥٠ Bd	٣٩.٩٤ ±٠.٩٨ Be
VLDL (mg/dl)	Control	١٣.١٥ ±٠.٠٧ Ba	١٣.١٠ ±٠.١٢ Ba	١٣.٠٢ ±٠.٢٣ Ba	١٣.١٤ ±٠.١١ Ba	١٣.٦٦ ±٠.٣١ Ba
	DEX	١٢.٦٧ ±١.٣ Be	١٦.٤٣ ±٠.١٤ Ad	٢٤.٣٢ ±٠.١٢ Ac	٢٩.٩٢ ±٠.١٠ Ab	٣٦.٥٩ ±٠.٠٧ Aa
	Est.	١٣.٩١ ±٠.٨٢ Aa	١٢.١٧ ±٠.٦٤ Cb	١٠.٢٠ ±٠.٢٢ Cc	٩.٢٤ ±٠.٥٤ Cd	٨.٢٤ ±٠.٢٣ Ce

Capital letters denote differences between groups P≤0.05 Vs control.
Small letters denote differences within groups P≤0.05 .

DISCUSSION

The results in (Table 1) show significant decrease in body weight of female rabbit after administration of DEX 0.5 mg/kg and EST. 0.3 mg /kg, negative effect of glucocorticoids on body weight was explained by (15, 16) that may be due to its inhibitory effect on feed intake, feed conversion efficiency and increased energy expenditure that influence the growth hormone-insulin like growth factor axis.

Or may be due to DEX caused proteolysis in muscle and reduction in bone mineral mass and increased metabolic catabolism which led to a reduce of growth, (17).

While in EST administration group the decrease may be due to effect of estrogen on the adipose tissue in the body, Estrogen can directly inhibit adipose deposition by decreasing lipogenesis. This action happens principally through decreasing activity of

lipoprotein lipase (LPL), an enzyme that regulates lipid uptake by adipocytes, ovariectomy increases LPL and lipid deposition within the adipocyte and administering physiological doses of estrogen reverses this deposition (18). Recently, work on a 3T3 adipocyte cell line transfected with estrogen receptor showed that the LPL gene has a negatively controlled estrogen response element (19).

(Table 2) show significance increase in leptin hormone after administration of DEX. Glucocorticoids, appear to increase leptin by a transcriptional mechanism, as judged by inhibitor studies (20). A glucocorticoid response element has been identified in the promoter region of the human leptin gene, but there are no reports on its functionality (21).

While appear significant decrease in leptin hormone after administration of EST. estrogen may also regulate the production or response to adipose hormones such as leptin and, through this mechanism, affect processes such as food intake and metabolic energy. Some data have indicated that the increase in adipose stores following estrogen withdrawal leads to increase circulating leptin, indicating that the leptin increase following loss of estrogen is secondary to increased adipose deposition, rather than directly driven by the lack of estrogen (22).

Results of the present study (Table 3) revealed a significant decrease in LH and FSH hormone concentration in animals treated with 0.5 mg / kg DEX. and 0.3 mg / kg estrogen hormone as compared with control group and also within treatment periods.

Illera, (23) Suggested that the treatment with DEX leads to increased estradiol concentration, resulting in reduced pituitary luteinizing hormone (LH) secretion. This was due to the negative feedback action of estrogen or substances with estrogenic activity on LH secretion. (24).

In previous studies performed in ovariectomized pigs, LH concentrations were elevated after ovariectomy, and Estradiol induced suppression in LH and hypothalamic GnRH, The ability of Estradiol to induce a rapid suppression of LH indicates that the sensitivity to the negative feedback effects of estradiol. (24).

Results of the present study (Table 4) revealed a significant decreased in the serum concentrations of (T 4) and (T3) during administration that DEX 0.5 mg/kg BW While the result show that the level of thyroid hormone increase significantly after

administration of EST.0.3 mg/kg as concentration as compare with control group and within treatment periods.

This decrease in the thyroid hormones of female rabbit circulation may be due to DEX action as suppression, of hypothalamic-pituitary-thyroid activity, that's agreed with (25) who found reduced in plasma concentrations of both T3 and T4 in adult male rats, They suggested that there were differences in the sensitivity of the hypothalamic-pituitary-thyroid axis and or the peripheral deiodinases to Glucocorticoids in adult animals and with changes in sex steroid concentrations in the adult.

This result may be due to different causes administration of sex hormones can interfere substantially with the hypothalamic–pituitary–thyroid (HPT) axis, estrogen administration increases thyroid hormone-binding globulin (TBG) concentrations, this glycoprotein is produced in the liver and binds about two-thirds of serum thyroxine (T4), the rise in TBG is paralleled by a T4 increase to maintain a physiological concentration of free T4 (26).

The result in (Table5 A&B) shows that significantly increased in concentration of total cholesterol and triglycerides after treatment with 0.5 mg / Kg DEX.

The increase of serum cholesterol level may be due to that dexamethasone inhibits nitric oxide synthesis which have a role in regulation of lipid levels in blood (27).

Triglyceride levels also increased significantly when used dexamethasone to induce hyperglycemia and hyperlipidemia, (28) reported similar results in rats, and (29) in human. This may be due to that dexamethasone stimulates production and secretion of lipoproteins mainly very low density lipoprotein (LDL) from liver that rich in triglyceride (30), or may dexamethasone cause insulin resistance which decrease effect of insulin on liver and adipose tissue leading to secret triglyceride from liver and prevent ability of tissue to remove lipoproteins from blood (31).

Sex-steroid hormones also have lipolytic activity, estrogen have been shown to increase the insulin levels cause SNS stimulalipolytic activity in women.(32) The actions appeared to be mediated by: (i) estradiol reducing insulin binding capacity; (ii) a direct effect of estradiol on liver lipolytic enzymes, namely acetyl coenzyme- A carboxylase and fatty acid synthetase or (iii) possibly by reducing glucose uptake in muscle.(33).

Recent study (34) showed the effects of administration of 17β-estradiol on some blood parameters and body weight in female rabbits. The treatment with 17β-estradiol decreased the level of cholesterol, TG and lowered significantly HDL and increased significantly LDL.

تاثير اعطاء كل من الديكساميثازون وهرمون الاستروجين في تركيز كل من هرمون اللبيتين وهرمونات الغدة الدرقية والتناسلية ومستوى دهون الدم في مصل دم اناث الارانب

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الخلاصة

استهدفت الدراسة معرفة تاثير اعطاء كل من الديكساميثازون او الاستراديول ١٧ بيتا في وزن الجسم وتركيز هرمون اللبتين ،الهرمون اللوتيني ، الهرمون المحفر للجريبات وهرمونات الغدة الدرقية وتركيز دهون الدم في اناث الارانب.

اجريت الدراسة على ٣٠ انثى ارنب وضعت في اقفاص وقسمت الى ثلاث مجاميع المجموعة الاولى، مجموعة السيطرة حقنت بمحلول normal saline والمجموعة الثانية حقنت بالديكساميثازون ٠.٥ ملغم / كغم ، المجموعة الثالثة حقنت بالاستراديول ١٧ بيتا ٠.٣ ملغم /كغم. لمدة ٦٠ يوم و جمعت العينات الدم كل ١٥ يوم .

اظهرت النتائج انحفاضا معنويا ($P\leq0.05$) في وزن الجسم بعد حقن كل من الديكساميثازون والاستراديول ١٧ بيتا وزيادة معنوية في تركيز هرمون اللبيتين بعد اعطاء الديكساميثازون بينما اظهر انخفاض معنوي بعد حقن الاستراديول ١٧ بيتا، اما بالنسبة الى تركيز الهرمون اللوتيني والهرمون المحفر للجريبات فقد اظهرت النتائج انخفاضا معنويا بعد اعطاء كل من الديكساميثازون والاستراديول ١٧ بيتا، واظهرت نتائج تركيز هرمونات الغدة الدرقية (T3,T4) انخفاضا معنويا عند اعطاء الديكساميثازون بينما كان هناك ارتفاع معنوي عند اعطاء الاستراديول ١٧ بيتا، اما بالنسبة الى دهون الدم (الكولسترول الكلي ، الجليسيرات الثلاثية ، LDL,HDL,VLDL) فقد اظهرت الدراسة انخفاض في تركيز الدهون الدم عند اعطاء الديكساميثازون بينما انخفضت معنويا عند اعطاء الاستراديول ١٧ بيتا

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