Lipolytic Effects of Testosterone Hormone Replacement Therapy in A Rat Model of Andropause Versus Normal Controls

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Abstract

Background: Testosterone (T) actions extend beyond the reproductive functions to include diverse metabolic pathways. Lipolytic effect of T is still underinvestigated, especially regarding the involved enzymes.

Aim of Study: This work measures two key lipolysis-enzymes in both normal and orchiectomized rats with/without T administration.

Material and Methods: Forty rats (200-300g) were subdivided into 4 equal groups (n=10/group); (A) Group I: Sham-operated control group. (B) Group II: Sham-operated rats were injected with IM testosterone undecanoate (100mg/kg, for two weeks). (C) Group III: Andropause model was done by orchiectomy, (D) Group IV: Testosterone-replacement therapy in orchiectomized rats. T, Hormone-Sensitive Lipase (HSL), Adipocyte Triglyceride Lipase (ATGL), Free Fatty Acids (FFA), and lipid profile were measured using the commercially available ELISA kits. Food intake was measured manually in addition to body weight changes before during and after treatment. ANOVA with LSD post hoc test and Pearson correlation were used for analysis.

Results: The castrated rats showed lower food intake, lower body weight, and lower weight gain. Regarding adipose tissue lipolytic enzymes, ATGL was significantly decreased while both HSL and FFA were insignificantly changed. T replacement therapy in castrated rats increased blood products of lipolysis due to an increased level of ATGL, HSL, and FFA, in addition to the significant increase in food intake without significant wt changes. Similar effects were demonstrated in normal rats treated with T.

Conclusion: T hormone therapy increased food intake, without significant changes in weight due to stimulation of lipolysis process mainly via stimulation of ATGL and HSL.

Key Words: *Testosterone – Orchiectomy – Food intake – Hormone-sensitive lipase – ATGL.*

Introduction

MALE sex hormones especially testosterone play an important role not only in the regulation and control of the reproductive functions but their

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action extend to include diverse metabolic pathways [1]. Testosterone is a steroid hormone mediates its action by binding to intracellular adrenergic receptors which bind to androgen response elements in the specific promoter regions of target genes which are responsible for the expression of a large number of diverse mediators secreted from different body organs and tissues [2]. Therefore, through its genetic and other rapid-onset non-genetic mechanisms, testosterone supposed to affect protein, carbohydrates and lipid metabolism [3]. At the target, tissues exert testosterone its action either directly or it could be metabolized through 5 a-reductase into Dihydrotestosterone (DHT) or by aromatized to estradiol (E2) which mediate their normal physiological effects through their own receptors [4].

Besides its physiological role as a naturally-occurring hormone, testosterone is used in different dosage forms as a hormonal therapy either a replacement therapy in case of hypogonadism or in pharmacological doses in certain diseases e.g. breast cancer [5].

The changes of serum lipid parameters under the testosterone therapy are variable [6]. Some studies reported a significant reduction in total cholesterol, low-density lipoprotein cholesterol and triglycerides under testosterone therapy either in healthy men or in patients with metabolic syndrome or type-2 diabetes mellitus [7,8]. Other studies report no changes in the lipid profile under the testosterone therapy [9]. The difference between these studies results could be referred to different doses or duration of action of testosterone or different ages of the population [6]. Moreover, the exact mechanisms whereby testosterone regulates the lipid metabolism are uncertain [10]. Therefore, this study tried to investigate the potential role of testosterone therapy on the lipid profile and the possible mechanisms for its effects through study-

ing the potential changes in the key regulatory enzymes in lipid metabolism e.g. Adipocyte Triglyceride Lipase (ATGL) and Hormone-Sensitive Lipase (HSL) beside the changes in the amount of food intake and body changes in both normal and orchiectomized rats with/without testosterone administration.

Material and Methods

Animals and procedures: A total of forty adults, local strain, and male albino rats (240-280g) were obtained from the faculty of Pharmacy-Zagazig University, to be used in this study between June and August 2018. Rats were reared at a clean environment in groups of fives at the animal house (cage dimensions; 40, 30, and 18cm) with 12h light/dark cycle, with free access to food and water. Room temperature was around 25°C and humidity between 20 and 45%. All animals received care in accordance with the guide to the care and use of experimental animals of the Institute of Laboratory Animal Resources [11]. After the habituation period (one week), rats were subdivided into 4 equal groups (n=10/each group). (A) Group I: Which behave as a normal control, in which sham operation was done through a scrotal incision and dissection of testes without excision, in addition to Intramuscular (IM) injection of normal saline (0.3ml). (B) Group II: Sham-operated rats which were injected with IM testosterone undecanoate (100mg/kg [12], for two weeks [13]). (C) Group III: Andropause rat model was done by orchiectomy, and treated with IM 0.3ml of normal saline. (D) Group IV: Testosterone-replacement therapy in orchiectomized rats in which rats induced andropause were managed by Testosterone replacement therapy by daily IM injection of the same dose and duration as Group II. Body weight (g) in all groups was recorded firstly, before treatment, after treatment. Weight gain during the period of treatment was calculated by the difference between weights after and before the treatment period. Food intake measurement was obtained by recording the differences among everyday changes in food intake at 1PM [14].

Surgery: Intraperitoneal injection of thiopental (40mg/kg) [15] was used for general anesthesia of rats. Anesthetized animals were fixed in the dorsal position, then the skin of the scrotum was disinfected with 70% Ethanol alcohol and a Tetracycline eye ointment was applied to the eyes to avoid damage of the cornea during anesthesia. In Groups III and IV, the linear incision and dissection in the ventral aspect of the scrotum to reach and open the tunicae. The main blood vessels were isolated

and ligated by two ligations then cut were done at the lower end of the spermatic cord between these two ligations. Consequently, the testicle and epididymis were removed. The skin was sutured with the application of local antibiotic ointment over the sutures [16]. The sham operation for rats in Groups I and II included midline linear incision in the skin, subcutaneous tissues dissection to explore the testes without removal of any structures, then skin suture. To ensure the metabolic changes, rats were left for two weeks after orchiectomy [17], then the study protocols were applied.

Blood samples: After overnight fasting, approximately 5mL of blood was withdrawn via cardiac puncture under light ether anesthesia. The blood was collected in heparinized tubes to be centrifuged for 15min at 3000rpm, and the plasma was collected and stored at 20°C until time of analysis.

Biochemical analysis: Measurement of lipid panel [Triglyceride (TG), Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C)] were assessed by the biochemistry analyzer [18]. Additionally, Low-Density Lipoprotein Cholesterol (LDL-C), was calculated according to a simple accurate modified Friedewald equation [19]; LDL-C=3/4 (TC HDL-C), while Very Low-Density Lipoproteins (VLDL) were calculated by as 20% of TG [20]. The key lipolytic enzymes i.e. ATGL and HSL, were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kits (catalog numbers; CSB-E14127r and CSB-EL012975RA, respectively, CUSABIO TECHNOLOGY LLC, USA), while Free Fatty Acids (FFA) level was measured by FFA colorimetric assay Kit (catalog number: MB S841629, Mybiosource, USA) [21]. Furthermore, measurement of total testosterone concentration was done by ELISA kits as reported previously [22], (catalog number K7418, BioVion, USA).

Statistical analysis:

The SPSS, Version 23 for Windows (SPSS Inc. Chicago, IL, USA), was used. The study variables were presented as the mean $\pm$ SD. The ANOVA with LSD post hoc test was used to compare means of study groups. The relationships among the study variables were tested by the Pearson correlation coefficient. p-values <0.05 were considered to be significant.

Results

Lipolytic status in the rat model of andropause:

The castrated control rats (Group III) showed a lower food intake, lower body weight and lower weight gain (Table 1). Furthermore, rats with

induced andropause represented with increases in total cholesterol, LDL, VLDL & TG while HDL remained insignificantly changed. Regarding adipose tissue lipolytic enzymes, ATGL was significantly decreased while both HSL and FFA were insignificantly changed (Table 2).

Table (1): Testosterone, food intake and boy weights of all studied groups (n=8).

Parameters	Group I	Group II	GroupIII	GroupIV
Body weight before T (g)	268.67±16.77	264.00±10.53 p=0.733a	256.83±23.58 p=0.391 a	257.00±35.21 p=0.398a p=0.990b
Body weight after T (g)	362.50±20.55	359.50±15.93 p=0.871 a	327.50±29.58 p=0.070a	332.83±49.49 p=0.120a p=0.773b
Weight gain (g)	93.83±6.97	95.50±8.41 p=0.822a	70.67±14.39 p<0.05 a	75.83±17.77 p<0.05 a p=0.488b
Food intake (g)	25.25±10.01	41.63±5.87 p<0.001 a	12.67±3.11 p<0.05 a	31.67±4.07 p=0.094a p<0.001 b
Testosterone (ng/ml)	7.74±1.09	16.24±2.55 p<0.001 a	0.47±0.27 p<0.001 a	5.10±1.47 p<0.05 a p<0.001 b

a= Significance versus Group I.
b= Significance versus Group III.

Table (2):Lipolysis parameters among studied groups (n=8 per each group).

Parameters	Group I	Group II	Group III	Group IV
Cholesterol (mmol/l)	151.20±9.28	145.76±30.55 p>0.05a	310.52±23.97 p<0.001 a	167.60±12.98 p>0.05a p<0.001b
LDL (mmol/l)	88.55±5.41	54.13±23.98 p<0.05a	204.79±23.98 p<0.001 a	78.11±23.3 p>0.05a p<0.001b
HDL (mmol/l)	33.26±3.09	77.72±8.51 p<0.001 a	38.45±6.19 p>0.05a	69.61±10.83 p<0.001 a p<0.001b
VLDL (mmol/l)	25.20±2.32	13.01±5.02 p<0.01a	50.70±0.39 p<0.01a	24.53±3.09 p>0.05a p<0.001b
TG (mmol/l)	127.54±26.57	69.22±6.19 p<0.01a	253.31±56.68 p<0.001 a	120.80±33.66 p>0.05a p<0.001b
HSL (pg/ml)	122.45±4.88	158.71±16.04 p<0.05a	119.33±3.92 p>0.05a	163.11±13.61 p<0.05a p<0.05b
ATGL (ng/ml)	4.96±0.3 8	22.98±1.68 p<0.001 a	6.77±2.06 p<0.05a	25.85±1.44 p<0.001 a p<0.001b
FFA (ng/dl)	493.16±10.94	561.67±6.83 p<0.001 a	496.37±13.62 p>0.05a	573.96±12.61 p<0.001 a p<0.001b

LDL	: Low-Density Lipoprotein.	ATGL	: Adipocyte Triglycerides Lipase.
HDL	: High-Density Lipoprotein.	FFA	: Free Fatty Acids.
VLDL	: Very Low-Density Lipoprotein.	a	: Significance versus Group I.
TG	: Triglycerides.	b	: Significance versus Group III.
HSL	: Hormone-Sensitive Lipase.		

Effect of T therapy on lipolytic enzymes, and substrates' concentrations: The VLDL, LDL, and TG were significantly lower ($p<0.05$), while HDL was significantly higher ($p<0.001$) with insignificant changes in total cholesterol in Group II vs. normal rats in Group I. Additionally, both HSL, and ATGL in addition to FFA concentrations were significantly increased (Table 2). Regarding treated rats with andropause (Group IV), TRT produced a significant increase in HDL level, in addition to significant reductions in levels of total cholesterol, LDL, VLDL, and TG. In adipose tissue, TRT produced a significant increase in ATGL and HSL levels with the subsequent rise of the level FFA.

Changes in food intake and body weight: Regarding food intake and body weight gain, they were significantly decreased by orchiectomy and T treatment fail to increase the weight gain (Group II vs. Group I; $p>0.05$), despite improvement of food intake. Mean worthy, rats in Group IV also showed significant improvement in food intake with insignificant weight changes in comparison with the Group III.

Association of T level with the key lipolytic enzymes:

As shown in figures 1-4, T has a strong positive correlation with ATGL in all groups ($r=0.639$, $r=0.857$, $r=0.710$, $r=0.697$ and $p<0.05$, in Groups I, II, III, and IV, respectively). However, the correlation with HSL was insignificant in all studied androgenic levels.
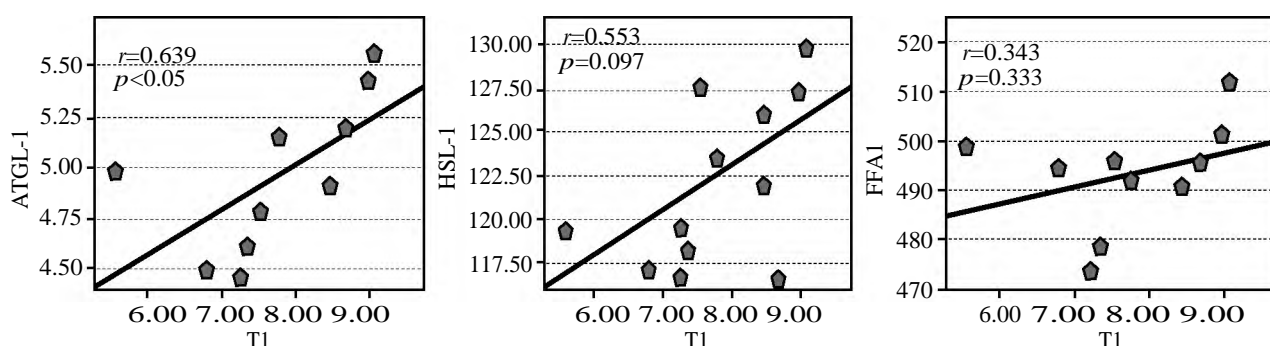

Fig. (1): Correlations of T with the key lipolytic enzymes and free fatty acid levels in Group I.
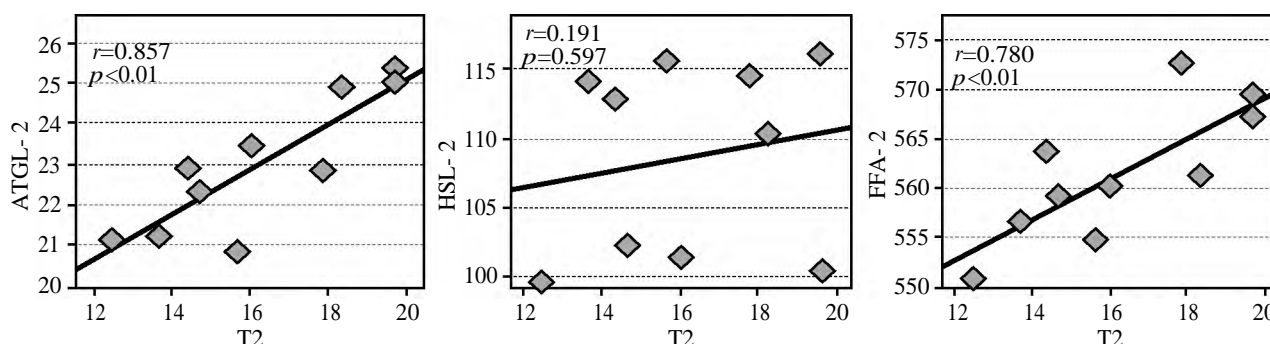

Fig. (2): Correlations of T with the key lipolytic enzymes and free fatty acid levels in Group II.
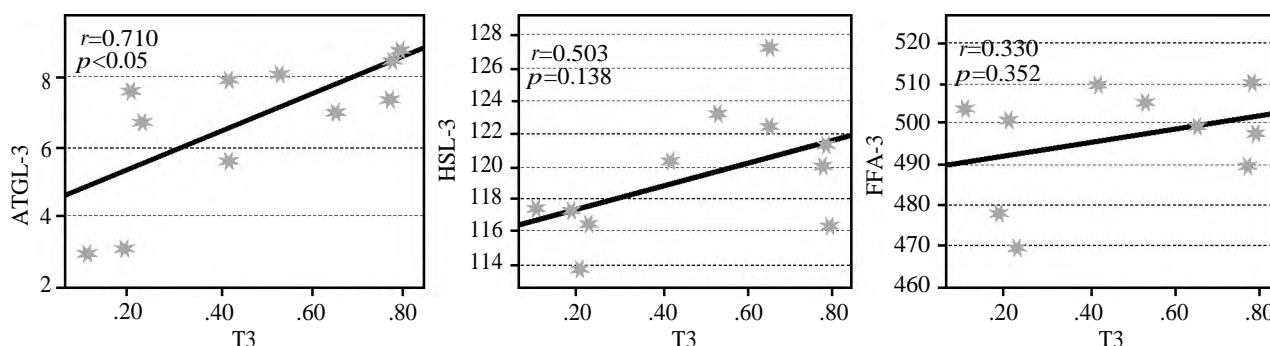

Fig. (3): Correlations of T with the key lipolytic enzymes and free fatty acid levels in Group III.
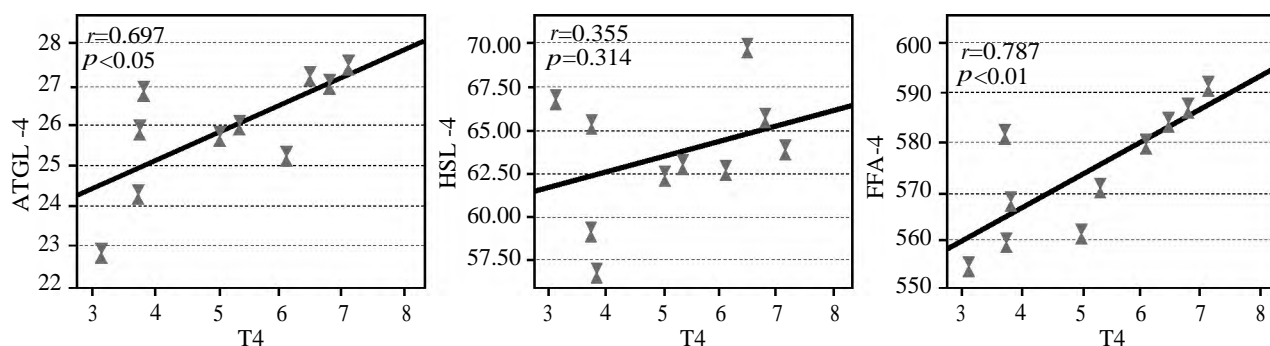
Fig. (4): Correlations of T with the key lipolytic enzymes and free fatty acid levels in Group IV.

Discussion

Several clinical and experimental studies have reported that testosterone plays an important role in the regulation of different metabolic pathways especially lipid metabolism. The ability of testosterone to share in the control of metabolic pathways mediated mainly through different mediators [23].

The results of this study showed a marked reduction in food intake in testosterone-deficient rats in comparison to the control group which is markedly recovered with testosterone replacement therapy. This orexigenic effect could be explained by the action of testosterone and/or its active metabolite estradiol on the genetic regulation of nesfatin-1. Recently, Seon et al., [24] concluded that testosterone plays an essential role in nesfatin-1 regulation whereby the level of expression of nesfatin-1 mRNA in the pituitary gland is reduced significantly after castration with subsequent reduction in the amount of food intake and body weight. On the other hand, testosterone replacement therapy restored the normal level of expressed nesfatin-1 in pituitary gland which enabled the mice to regain their normal eating behavior. Interestingly, Prinz et al., [25] reported that nesfatin-1 which is secreted from the digestive system controls the amount of food intake not only through regulation of gastric motility but through a direct effect in certain brain areas. Furthermore, T regulates the eating behavior through other different mediators such as ghrelin. Through their action at specific receptors in the arcuate nucleus stimulate ghrelin molecules the appetite and increase the amount of food intake [26]. Greenman et al., [27] claimed that a strong positive correlation exists between testosterone and ghrelin not only in men but also in postmenopausal women and the role of testosterone in the regulation of eating behavior is mediated partially through ghrelin.

The metabolic action of testosterone and its effect on the lipid panel is an interesting point in many research activities. Many clinical and experimental studies revealed a strong negative correlation between the serum testosterone level and both total cholesterol and LDL cholesterol levels [23].

Lee et al., [28] showed that the serum cholesterol level is markedly elevated in testosterone-deficient mice moreover testosterone therapy succeeded to decrease the serum level of total and LDL cholesterol. In agreement with these findings Hatch et al., [29] reported that the serum concentrations of cholesterol and triglycerides in castrated mice are markedly elevated with subsequent formation of atherosclerotic lesions in comparison to control group. The results of the current study showed also the significant elevation of LDL cholesterol, VLDL cholesterol and triglycerides levels in testosterone-deficient rats (Group III) in comparison to normal and testosterone-treated groups. However, the exact mechanisms whereby testosterone regulates the cholesterol metabolism still uncertain. Cai et al., [30] studied the potential mechanisms of testosterone effects on cholesterol metabolism in pigs. They have been concluded that testosterone deficiency induces hypercholesterolemia through alteration of gene expression of specific proteins involved in lipoprotein assembly and secretion. The results of their study showed a significant reduction of LDL Receptors (LDLR) expression in the liver of testosterone-deficient pigs. The reduction of LDLR leads to decline in LDL cholesterol uptake and clearance through the liver. The cause of LDLR reduction, in that case, was the overexpression of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), PCSK9 is a proprotein convertase enzyme expressed in different tissues especially in the liver. In the liver bind PCSK9 molecules to LDLR inhibiting its ability to bind to and uptake of LDL molecules [31]. The findings of Cai et al., [30] intensify our assumption that testosterone decreases serum cholesterol level through alteration

of gene expression of LDLR and post-receptor regulatory protein e.g. PCSK9.

As we mentioned above, testosterone increases the appetite through different mediators mainly nesfatin-1 and ghrelin which explained some findings of present study whereby the testosterone-treated groups showed a significant increase in the amount of food intake in comparison to the testosterone-deficient group. Despite this increase in the food intake showed the testosterone-treated group no significant increase in body weight in comparison to the testosterone-deficient group. We assumed a potential effect of testosterone on the lipid metabolizing enzymes as a part of its action on lipid metabolism. According to the best of our knowledge the effect of androgens on the lipases still a matter of controversy. Heemres et al., [32] reported that testosterone deficiency in rats resulted in marked decrease in the mRNA and protein levels of certain genes involved in fatty acids and cholesterol synthesis e.g. fatty acid synthetase and HMG-CoA-reductase. Moreover, the re-administration of testosterone in these rats restored the normal expression of the affected genes increasing the level of lipid synthesis and proving a lipogenic effect of testosterone. Furthermore, Münzker et al., [33] reported that androgen could promote the development of Non-Alcoholic Fatty Liver Diseases (NAFLD) as they facilitate hepatic lipogenesis and the testosterone/Dehydroepiandrosterone ratio is an important determinable factor in the development of NAFLD than the initial concentration of either testosterone or Dehydroepiandrosterone alone.

Therefore this study explored the effect of testosterone on certain key regulatory enzymes in lipid metabolism in order to identify which metabolic pathways could be regulated, even partially, through testosterone. The results in the testosterone-treated groups; either the healthy group (Group II) or the testosterone-substituted group (Group IV) showed a significant increase in the concentration of ATGL, HSL, and FFA in comparison to the testosterone-deficient group (Group III). Furthermore, there were positive correlations between testosterone level and the concentrations of ATGL, HSL, and FFA with different levels of significance. Interestingly the results of the current study showed also an increase in HSL and ATGL concentrations in the Group II in comparison to the control group (Group I), which indicate an effect of testosterone on the tissue lipases even in non-physiological doses. These results are in accordance with the result of Karbowska and Kochan [34] who reported that Dehydroepiandrosterone (DHEA), active metabolite of testosterone, increases lipid mobilization in adipose tissue with subsequent reduction in body fat in rodent and human as a result of enhanced activity and expression of both AGTL and HSL which supposed to be mediated, at least partially, through PPARγ2 which upregulates the genetic expression of both AGTL and HSL. On the other hand, Lee et al., [35] reported that androgen upregulates the adrenergic receptors in adipose tissue which facilitate the action of catecholamines inducing lipolysis. All these findings intensify our assumption that testosterone therapy has not only a negative effect on lipogenesis but it stimulates also lipolysis.

In conclusion, the results of the current study could approve that testosterone-replacement therapy increases the lipolysis through activating some key regulatory enzymes e.g. ATGL and HSL which explained the failure in body gain in spite of excessive food intake. However, his study has some limitation especially absent measurement of energy expenditure and orexigenic mediators such as Nesfatin-1 and ghrelin. Future studies may give proper answers regarding these issues.

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التأثيرات المذيبة للدهون للعلاج الإستعاضى بالتستوستيرون فى نموذج الجرذان المحدث لها إياس الذكور مقبل الضوابط العادية

خلفية البحث: تمتد تأثيرات التستوستيرون إلى ما وراء وظائف التكاثر لتشمل مسارات التمثيل الغذائى المتنوعة. لا يزال تأثير التستوستيرون على إذابة الدهون تحت الأختبار، خاصية فيما يتعلق بالأنزيمات المعنية.

الهدف من الدراسة: يقيس هذا العمل مستويات أثنين من إنزيمات تحلل الدهون الرئيسية فى كل من الفئران الطبيعية والمحدث لها يأس الذكور مع أو بدون إعطاء التستوستيرون.

المواد والأساليب: تم تقسيم أربعين فأر (٢٠٠–٣٠٠جم) إلى مجموعات متساوية (العدد=١٠/مجموعة):

أ– المجموعة الأولى: مجموعة ضابطة أحدث لها عملية غير حقيقية لم يحدث خلالها إزالة الخصية.

ب– المجموعة الثانية: تم حقن الفئران التى لم تستأصل خصيتهم عن طريق العضل بإستخدام دواء الديسستيرون بجرعة ١٠٠ملجرام لكل كيلو جرام من وزن الفئران لمدة أسبوعين.

ج– المجموعة الثالثة: تم إنتاج نموذج الإياس عن طريق إستئصال الخصية.

د– المجموعة الرابعة: العلاج الإستعاضى بالتستوستيرون فى الجرذان المخصية.

ثم تم قياس مستوى التستوستيرون، الإنزيم المذيب للدهون الحساس للهرمونات (HSL)، والإنزيم المذيب للدهون الشحمية فى الخلايا الدهنية (ATGL) مستوى الأحماض الدهنية الحرة (FFA)، ومستوى دهنيات الدم. تم أيضاً قياس كمية تناول الطعام يدوياً بالإضافة إلى تغيرات وزن الجسم قبل وخلال فترة العلاج وبعدها. تم إستخدام سبل التحليل الإحصائى المناسبة.

النتائج: أظهرت الفئران المخصية تناول كمية أقل من الطعام، وإنخفاض فى وزن الجسم، وضعف أكتساب الوزن. فيما يتعلق بالأنزيمات الدهنية للأنسجة الدهنية، إنخفض ATGL بشكل ملحوظ فى حين تم تغيير كل من (HSL وFFA) بشكل ليس ذا دلالة إحصائية. العلاج الإستعاضى بالتستوستيرون للفئران المخصية أدى زيادة منتجات الدم من تحلل الدهون بسبب زيادة مستوى ATGL، HSL وFFA بالإضافة إلى الزيادة الكبيرة فى تناول الطعام دون تغييرات كبيرة بالوزن. وقد أظهرت آثار مماثلة فى الفئران العادية المحقونة بالتستوستيرون.

الخلاصة: أدى العلاج بالتستوستيرون إلى زيادة تناول الطعام، دون تغيرات كبيرة فى الوزن نتيجة لتحفيز عملية تحلل الدهون بشكل رئيسى من خلال زيادة مستوى الإنزيم المذيب للدهون الحساس للهرمونات والإنزيم المذيب للدهون الشحمية الثلاثية فى الخلايا الدهنية.

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