

## Androgenic –Anabolic Steroids Abusing Effect on Liver Enzymes and Lipid Profile in Male and Female Rats

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### Abstract

The present study was conducted at Veterinary Medicine College–University of Basra /Iraq to investigate the effect of testosterone( Sustanon<sup>®</sup> 250) abusing on some physiological and biochemical parameters. Sixty four male and female rats were divided into four groups(each group consisted of 8 males and 8 females). The first group served as control group in which the rats dosed by intramuscular injection with 10 µ l olive oil weekly for 12 weeks, the rest 3 treated groups (G1 . G2 and G3) in which the rats dosed by intramuscular injection with 50 . 100 and 150 mg Sustanon<sup>®</sup> 250 / kg B.W. respectively weekly for 12 weeks , then all rats were terminated for the physiological and biochemical tests . The Sustanon<sup>®</sup> 250 through its effect on liver caused increasing both ALT and AST and decreasing the ALP in treated rats compared with control group . The lipid profile was significantly affected by Sustanon<sup>®</sup> 250 injection through elevation of TG and VLDL , but lowering the HDL ,LDL and AI.

**Keywords: Androgenic –Anabolic Steroids, Liver Enzymes, Lipid Profile**

### الملخص:

أجريت الدراسة الحالية في كلية الطب البيطري / جامعة البصرة لدراسة تأثير فرط استخدام (sustanon<sup>®</sup>250) على مستوى بعض انزيمات الكبد ومستوى الدهون في ذكور و اناث الجرذان المختبرية. قسمت الجرذان المختبرية إلى أربعة مجاميع , المجموعة الأولى اعتبرت مجموعة سيطرة حقنت عضليا ب 10 مايكرو لتر من زيت الزيتون أسبوعيا لمدة ثلاثة شهور . أما المجاميع الثلاثة الباقية فهي مجاميع معاملة بال sustanon<sup>®</sup>250 إذ حقنت المجموعة الأولى ب 50 ملغم / كغم من وزن الجسم والثانية 100 ملغم / كغم من وزن الجسم والثالثة ب 150 ملغم / كغم من وزن الجسم أسبوعيا لمدة ثلاثة شهور ، ثم بعد انتهاء فترة الحقن ضحي بالجرذان لدراسة المعايير الفسلجية والكيموحيوية. أظهرت النتائج زيادة معنوية في إنزيمي ALT و AST ونقصان معنوي لإنزيم ALP في الجرذان المعاملة بمادة ال sustanon<sup>®</sup>25 مقارنة مع مجموعة

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السيطرة. كما تأثر مستوى الدهون معنويا بسبب حقن ال sustanon®250 إذ أظهر زيادة في مستوى الدهون الثلاثية والدهون واطنة الكثافة جدا ونقصان الدهون عالية الكثافة والدهون واطنة الكثافة والدليل التعضدي\*البحث مسئل من اطروحة الدكتوراه للباحث الأول

### Introduction

Clinically testosterone and AASs are used for the treatment of renal failure, anemia, growing deficiency in children, delayed puberty and in case of some chronic weakness such as AIDS and cancer (1). The clinical usage of testosterone for the control of excessive weight loss related to AIDS has increased 400% since 1985 (2). Though AAS usage is more frequently seen in men, it has been reported that the usage among young females is on the increase (3). It has been reported that young people start using testosterone at the age of 16 years and research conducted on the issue show that the reason for using this drug is that they want to have a muscular body and increase their sportive performance (3). Abusing anabolic androgenic drugs by athletes is a serious negative phenomenon which is documented by a number of investigators in many countries around the world including: USA. Canada, UK. Australia and in some Arab countries as well as (4; 5 ; 6 ; 7 and 8). Uncontrolled usage of testosterone derivations may lead to serious side effects such as cardiovascular system disorders, lipid metabolism disorders (9). Sustanon® 250 is one of androgenic – anabolic steroids that usually abused by athletes, young females and males to have a muscular body and increase their sportive performance (3).. The present study aimed to investigate the adverse effects induced by Sustanon abuse on some liver enzymes and lipid profile of male and female rats .

### Materials and Methods

The present study included 112 adult albino rats (*Rattus Rattus*). They were 10 to 12 weeks old , and weight around 200-250 grams. They were left for 2 weeks to acclimatize prior to the experiment. Each animal was housed in an individual cage measured as 15 x 35 x 50 cm and kept under normal temperature ( 22 - 25 °C ) , 12 hours light and 12 hours dark . Animals were daily provided with water and diet .

After the acclimatization period, thirty-two male and thirty-two female rats were randomly divided into four equal groups (each group consisted of 8 adult male rats and 8 adult female rats) as following :-

1-Control group : injected intramuscularly with 10 $\mu$ l of olive oil weekly for 12 weeks.

2-Group 1 ( G1 ), group 2 ( G2 ) and group 3 ( G3 ) : were injected intramuscularly with different doses of (sustanon<sup>®</sup> 250 ) 50, 100 and 150 mg/kg/week respectively, for 12 weeks.

All study rats were sacrificed at the end of the 12 weeks treatment period , blood samples were then collected via cardiac puncture according to the method of Hoff and Rlatg ( 2000 ).(11)

Serum liver enzymes were determined spectrophotometrically by using a special kit for each enzyme( BIOMERIEUX<sup>®</sup> sa Transaminases – kit , France ) for ALT and AST(10 ) and (BIOLABO SA,ALP- Kit ,France) for serum Alkaline phosphatase (ALP) (12).

The estimation of lipid profile includes the total cholesterol (TC),triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), very low density lipoprotein ( VLDL ) and atherogenic index (AI). (13)

Total cholesterol (TC),triglyceride (TG), and high density lipoprotein (HDL-C) were estimated spectrophotometrically by using special kit for each one from Biolabo company, while the very low density lipoprotein ( VLDL ) , low density lipoprotein (LDL-C), and atherogenic index (AI) were determined through different equations as following :-

$$\text{VLDL-C} = \text{TG} / 5 \quad (12)$$

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{VLDL-C}). \quad (12)$$

$$\text{Atherogenic index ( AI )} = \frac{\text{VLDL-C} + \text{LDL-C}}{\text{HDL-C}}$$

## Results

### *Effect of Sustanon<sup>®</sup> 250 on Some Liver Enzymes of rats.*

Table ( 1 ) shows that the ALT and AST activity significantly increased ( $p \leq 0.05$ ) in male rats injected with (sustanon<sup>®</sup> 250 ) 50 ,100 and 150 mg/kg B.W compared with control male rats .While there was no significant differences among treated animals groups.

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**Table ( 1 ) Effect of Sustanon<sup>®</sup> 250 on some liver enzymes of male rats means  $\pm$**

Parameters groups		SD		
		ALT	AST	ALP
		Units/ml	Units/ml	Kind and king units/100ml
Control group (0.1ml olive oil)		44.620 b $\pm$ 1.890	111.373 b $\pm$ 24.437	239.409 a $\pm$ 131.491
Group1 (50mg/kg B.W) Sustanon <sup>®</sup> 250		64.113 a $\pm$ 4.293	276.360 a $\pm$ 88.978	103.168 b $\pm$ 13.110
Group2 (100mg/kg B.W) Sustanon <sup>®</sup> 250		67.515 a $\pm$ 1.265	249.265 a $\pm$ 37.257	100.217 b $\pm$ 13.997
Group3 (150mg/kg B.W) Sustanon <sup>®</sup> 250		65.186 a $\pm$ 2.742	362.300 a $\pm$ 58.767	93.368 b $\pm$ 17.139
LSD		19.493	137.035	136.241

Different letters represent significant difference at ( $p \leq 0.05$ )

Table ( 2 ) revealed that the ALT activity in female rats was increased significantly ( $p \leq 0.05$ ) in treated animals group 100 mg/kg B.W and 150 mg/kg B.W compared with control group and treated animals group 50 mg/kg B.W.

The AST activity increased significantly ( $p \leq 0.05$ ) in treated animals groups 50,100 and 150 mg/kg B.W compared with control female group. It seems that there was not significant differences among treated female groups (table 2).

**Table (2 )Effect of Sustanon<sup>®</sup> 250 on some liver enzymes in female rats (means± SD)**

Parameters Groups	ALT	AST	ALP
	units/ml	units /ml	Kind and king units/100ml
Control group (0.1ml olive oil)	42.90 b ±15.129	78.020 b ±13.618	234.776 a ±42.796
Group1 (50mg/kg B.W.) Sustanon <sup>®</sup> 250	42.572 b ±5.036	304.672 a ±19.222	143.249 b ±64.983
Group2 (100mg/kg B.W.) Sustanon <sup>®</sup> 250	62.060 a ±4.270	247.020 a ±56.831	108.866 b c ±7.725
Group3 (150mg/kg B.W.) Sustanon <sup>®</sup> 250	65.793 a ±5.166	313.413 a ±97.201	81.412 c ±40.614
LSD	19.06	97.201	61.837

Different letters represent significant difference at ( $p \leq 0.05$ )

The activity values of ALP in female rats were observed to be significantly lower ( $p \leq 0.05$ ) in treated animals groups 50, 100 and 150 mg/kg B.W compared with control group also a significant decrease ( $p \leq 0.05$ ) was found in group treated with (150 mg/Kg B.W.) compared with group treated with (50 mg /Kg B.W.) and control group. ,while there were no significant differences between group 1 (50 mg /Kg B.W.) and group 2 (100 mg /Kg B.W.) (table 2).

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### Effect of Sustanon<sup>®</sup>250 on lipid profile of rats

Table ( 3 ) showed a significant decrease ( $p \leq 0.05$  ) in total cholesterol and HDL-C of male rats injected with (sustanon<sup>®</sup>250 ) 50,100 and 150 mg /kg B.W compared with control male rats without significant differences among treated groups

A significant increase ( $p \leq 0.05$  ) is noticed in TG and VLDL level of male rats injected with (sustanon<sup>®</sup>250) 50,100 and 150 mg /kg B.W compared with control male rats .There was non significant differences were observed among treated animals groups with 100 and 50 mg /kg BW , but both of them decreased significantly than the high dose treated group (table 3) .

There was a significant decrease ( $p \leq 0.05$  ) in LDL-C levels observed in all male rats injected with different doses of sustanon<sup>®</sup>250 compared with LDL-C level of control male rats .

**Table ( 3 )The Effect of Sustanon<sup>®</sup>250 on lipid profile of male rats  
(means  $\pm$  SD )**

parameters	Cholesterol mg /dl	TG mg /dl	VLDL mg /dl	HDL mg /dl	LDL mg /dl	AI
Groups						
Control (0.1ml olive oil)	139.757 a $\pm 7.223$	31.372 c $\pm 3.613$	6.227 c $\pm 0.804$	55.22 a $\pm 6.081$	84.058 a $\pm 9.758$	1.632 a $\pm 0.068$
Group1 (50mg/kg B.W) Sustanon <sup>®</sup> 250	107.853 b $\pm 8.167$	39.497 b $\pm 0.828$	7.898 b $\pm 0.167$	48.358 b $\pm 3.382$	45.142 c $\pm 9.33$	1.1 c $\pm 0.249$
Group2 (100mg/kg B.W) Sustanon <sup>®</sup> 250	116.857 b $\pm 8.995$	39.209 b $\pm 1.116$	7.84 b $\pm 0.222$	44.5 b $\pm 0.826$	64.516 b $\pm 9.278$	1.607 a b $\pm 0.214$
Group3 (150mg/kg B.W) Sustanon <sup>®</sup> 250	112.363 b $\pm 5.412$	49.024 a $\pm 3.559$	9.804 a $\pm 0.71$	43.937 b $\pm 0.49$	58.624 b $\pm 5.2$	1.5 a b $\pm 0.111$
LSD	15.004	7.836	1.613	6.862	13.481	0.387

Different letters represent significant difference at ( $p \leq 0.05$  )

The LDL-C level of male rats injected with 50 mg /kg B.W was significantly lower ( $p \leq 0.05$ ) than that of male rats injected with 100 and 150 mg /kg B.W which were not significantly different from each other .

The values of AI were lower significantly ( $p \leq 0.05$ ) in treated male rats compared with control rats . There were no significant differences in AI between male rats injected with 100 and 150 mg /kg B.W and control group.

Table (4) showed a significant decreased ( $p \leq 0.05$ ) in total cholesterol and LDL-C levels of female rats injected with (sustanon<sup>®</sup>250) 50, 100 and 150 mg /kg B.W compared with that of control male rats, without a significant differences among treated groups.

**Table ( 4 )The Effect of Sustanon<sup>®</sup>250 on lipid profile of female rats**

		means $\pm$ SD				
parameters groups	Cholesterol	TG	VLDL	HDL	LDL	AI
	mg /dl	mg /dl	mg /dl	mg /dl	mg /dl	
Control	168.927	24.011	4.80	56.145	115.189	2.166
0.1ml olive oil	a	b	b	a	a	a
Group1	$\pm 24.931$	$\pm 4.081$	$\pm 0.811$	$\pm 6.436$	$\pm 19.442$	$\pm 0.30$
50mg/kg B.W Sustanon <sup>®</sup> 250	110.760	45.980	9.192	53.440	52.370	1.235
Group2	b	a	a	a	b	b
100mg/kg B.W Sustanon <sup>®</sup> 250	$\pm 5.382$	$\pm 1.890$	$\pm 0.375$	$\pm 7.191$	$\pm 2.298$	$\pm 0.082$
Group3	116.720	42.730	8.546	51.328	56.709	1.243
150mg/kg B.W Sustanon <sup>®</sup> 250	b	a	a	a	b	b
LSD	$\pm 10.542$	$\pm 6.829$	$\pm 1.365$	$\pm 1.158$	$\pm 10.599$	$\pm 0.198$
LSD	92.929	41.258	8.250	51.412	33.100	0.807
LSD	b	a	a	a	b	c
LSD	$\pm 8.717$	$\pm 2.342$	$\pm 0.468$	$\pm 0.964$	$\pm 9.387$	$\pm 0.185$
LSD	52.206	17.247	3.450	6.092	23.709	0.427

Different letters represent significant difference at ( $p \leq 0.05$ )

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Although the TG and VLDL levels in female rats injected with (sustanon<sup>®</sup>250) 50,100 and 150 mg /kg B.W were not significantly different from each other , but all of them were significantly ( $p \leq 0.05$  ) higher than the control females . The sustanon<sup>®</sup>250 injection to female rats did not seem to cause significant decrease in HDL levels in all treated groups. The results of AI showed a significant decrease in female rats injected with (sustanon<sup>®</sup>250 ) 50, 100 and 150 mg /kg B.W compared with control females . It seems that the highest dose of sustanon<sup>®</sup>250 led to significant decrease( $p \leq 0.05$ ) in the level of AI compared with other two treated groups .

### Discussion

#### Effect of sustanon<sup>®</sup>250 on some liver enzymes in rats

The significantly higher AST and ALT activities in male and female rats treated 50,100 and 150 mg/kg B.W sustanon compared with control groups was matched with (5 ;14 - 21).On contrary Bhasin *et al.*(1996) reported that the AAS has no effect in AST and ALT plasma levels (9) .

The elevation of AST and ALT levels may be attributed to hepatic disorder in the form of hepatitis and cholestasis induced by testosterone abuse (22 - 25). Dickerman *et al.* (1996) reported that the elevation of hepatic enzymes could be related to the suppression of the hypothalamic – pituitary – testicular axis (26) . Heart damage could be considered as another reason for elevation of AST level in treated rats compared with control rats. A study by Alen *et al*, (1995) reported that ASS may caused AST leak from muscle to serum in athletes ( 27 ) .

The significantly lowered ALP activity in treated male and female rats groups compared with control could be explained through the alteration of bone turnover by supraphysiological dose of testosterone (28). According to Stafford *et al* . (1949) androgen therapy caused hypertrophy of the prostate gland but the acid and alkaline phosphatase active was not increased (29) .

#### Effect of sustanon<sup>®</sup>250 on lipid profile of rats

The treatment of male and female rats with sustanon<sup>®</sup>250 caused a significant reduction in total cholesterol concentration , LDL-C level and AI, whereas the TG and VLDL -C rats were increased significantly. The results



indicated that HDL-C decreased significantly in treated male rats , but it was not affected in treated female rats .

The low cholesterol concentration in treated rats came in agreement with (30) , this reduction could be attributed to upregulation of scavenger receptor B1 ( SR-B1) in hepatocytes and macrophage and thereby stimulates the selective cholesterol uptake and efflux respectively (31).

Decreased HDL-C level in treated males which agree with (9 ; 30 ; 32 -34) could result from up regulated testosterone to the 2 genes involved in catabolism of HDL-C namely hepatic lipase ( HL) and scavenger receptor B1 ( SR-B1) . SR-B1 mediates the selective uptake of HDL-C lipid into hepatocytes and steroidogenic cells (35).

Reduction of LDL -C level in response to testosterone treatment was in agreement with (17 ; 30 ; and 34). The decreased LDL-C level in treated animals may be due to the increase of the oxidation of LDL -C induced by increase the ROS production and increase the lipid peroxidation in response to testosterone injection (17) .

The binding of LDL-C to LDL receptor on the cell membrane initiates a series of events to endocytosis and metabolize the LDL -C (LDL pathway). Because the LDL receptors function is usually highly regulated , the intake relatively large number of LDL-C particles is followed by decreased synthesis of LDL receptors (36) . According to (37), the LDL pathway serve as a mechanism that enables cells to acquire the cholesterol they need for growth and maintenance without need to synthesize their own sterol . This pathway appears to be regulated by the amount of cholesterol ( or related sterol) in certain regions of cells rather than by the concentration of LDL-C . Therefore , it seems that the low level of LDL-C in the treated rats may be caused by the lowering of the cholesterol (by testosterone injection) thus , stimulating the LDL receptor expression on the cell membrane to enhance the LDL-C uptake by the cells resulting in more reduced of LDL -C level in plasma (38).

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Another cause for low LDL-C level in response to testosterone injection may be related to disturbance of the regulatory mechanism of LDL receptors function induced by testosterone as a result of the cell possessing a high number of LDL receptors with high affinity even to oxidized LDL -C as occur in macrophages found in atherosclerotic plaque which may be found in testosterone treated rats .

The results of TG in the present study came in agreement with (39) who reported an elevation in TG level in response to AAS use . Kapoor *et. al.*, (2006) found an increment in the TG level in response to testosterone replacement therapy for hypogonadal men ( 40).

The increase of TG and VLDL-C level in serum of male and female rats injected with 3 doses of sustanon<sup>®</sup>25 may be caused by the inhibition of the testosterone to the hepatic lipoprotein lipase which reduces TG uptake into adipocytes (41) and reduce the degradation of VLDL-C (42, 43).

The lipoprotein lipase ( LPL) is an enzyme found in the inner lining of capillaries in cardiac and skeletal muscles , lactating mammary gland and adipose tissue , converts the TG into fatty acids and glycerol , the TG in VLDL- C also degraded by LPL ( 36 ).The LPL is found to be suppressed by supraphysiological dose of testosterone (33).This suppression of LPL can explain the elevation of TG and VLDL - C in treated rats, and decreased the HDL - C in present study because the LPL participates in the formation of HDL - C (38 , 44) . It can be considered as another cause for decreased LDL -C because LPL is required to degrade the VLDL-C to give intermediate density lipoprotein (IDL-C)and then LDL -C (43 ) .

The reduction of HDL-C and LDL-C in the present study disagrees with (5; 18 ; 45-47 ).

Brooks *et al.* . ( 2005) disagreed with recent results about the increase of TG level (17) but Hartgens and Kuiper (2004) didn't found any changes in TG level in AAS abuser athletes (5).

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