

ANOBOLIC ANDROGENIC STREEROLDS IN MALE ADULTS MICE INDUCED : HYPOTHYROIDISM , OXIDATIVE STRESS

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Abstract :

Thyroid function is affected by AAS used in humans, although the mechanisms of the effects of androgenic anabolic steroid (AAS) are unclear. The present study is designed to know the effect of AAS in thyroid function and oxidative stress.

Experimental animals used in the study(30 Swiss mice) were allocated to three groups as general control group, and test groups(N=10). The test groups received (5,10) mg/kg of body weight nandrolone Decanoate by subcutaneous injection each 48 hours , but control groups received the same volume of normal saline . The duration of the experiment was 4-weeks. Blood samples were collected after two days at the end of experimental period from the control and treated groups. The serum samples were assayed for (TSH,T3,T4, total cholesterol , MDH,GSH,) Results revealed that all ND-treated animals exhibited a significant increase of body weight (B.W) and serum TSH hormone, total cholesterol, MDA, a significant decrease was found in GSH level,T3 and T4 hormone, Our data of this study indicate that anabolic steroids at supraphysiological doses exerts direct actions on the thyroid gland and might lead to thyroid dysfunction and increase of oxidative stress of males .Testosterone or its derivatives such as Nandrolone Decanoate are being problem commonly. Athletes, coaches, and physicians should be aware of their harmful side effects.

الستيرويدات الابتنائية الاندروجينية سببت انخفاض الدرقية وزيادة الجهد التأكسدي في ذكور الفئران
البيض

شيماء احمد رحيم

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الخلاصة :

تعد الغدة الدرقية من اكبر الغدد في الجسم والتي تتأثر وظائفها بشكل كبير بالستيرويدات الاندروجينية المستعملة من قبل الانسان، بالرغم من ان ميكانيكية تأثير هذه المركبات في وظيفة الغدة الدرقية لم تتوضح بشكل نهائي. لذا صممت هذه الدراسة لمعرفة تأثير الستيرويدات الابتنائية الاندروجينية في وظيفة الغدة الدرقية والجهد التأكسدي .

استخدم في الدراسة 30 فأراً ابيضاً سويسرياً والتي وضعت في ثلاث مجموعات ،المجموعة الاولى عدت كمجموعة سيطرة والتي عوملت بالمحلول الملحي الفسيولوجي ، فيما عوملت المجموعة الثانية والثالثة بالعقار

عند التركيز (5، 10) ملغم / كغم من وزن الجسم تحت الجلد مدة التجربة استمرت اربعة اسابيع وكان العقار يعطى للحيوانات كل 48 ساعة . بعد نهاية التجربة بيومين وزنت الحيوانات ثم شرحت وجمعت عينات الدم لحساب الهرمون المحفز للدرقية وهرمونات الدرقية فضلاً عن مستوى الكوليسترول الكلي والجهد التأكسدي المتمثل بقياس مستوى الكلوتاثيون والمالونديهايد .

بينت نتائج الدراسة حصول تغيرات معنوية في معايير الدراسة جميعاً في جميع الحيوانات المستلمة للعقار وهذا تمثل بزيادة معنوية في وزن الجسم العام و مستوى الهرمون المحفز للدرقية ومستوى الكوليسترول الكلي والمالونديهايد . فيما سجلت النتائج حصول نقصان معنوي في هرمونات الدرقية ومستوى الكلوتاثيون . اوضحت نتائج الدراسة بان الهرمونات الابتنائية فوق الجرعة الفسيولوجية تمتلك تأثير سيء على الغدة الدرقية ربما يؤدي الى حدوث خلل في عملها فضلاً عن زيادة الجهد التأكسدي في الذكور. ان اساءة استعمال مثل هذه العقاقير اصبحت مشكلة صحية كبيرة مما يعني تنفيذ الخطوات والبرامج الضرورية لارشاد المراهقين والشباب من الاثار السلبية لمثل هذه المركبات للحد من انتشارها .

The thyroid also produces and releases the hormone calcitonin (thyrocalcitonin) which contributes to the regulation of blood calcium levels. calcitonin reduced the concentration of calcium in the blood. Majority of the calcium removed from the blood is stored in the bones.

The Production of T3 and T4 are regulated by thyroid stimulating hormone (TSH), which produced by the pituitary gland. Higher levels of TSH lead to higher rates of hormone production and secretion from the thyroid. TSH in turn is regulated by another hormone secreted from the hypothalamus, thyrotropin-releasing hormone (TRH). TSH levels are also regulated in a negative feedback manner by the levels of circulating thyroid hormone, when T3 and T4 levels are too low TSH Production is increased (2000,Hulbert) . These hormones increase the metabolic activity of the body cells and released throughout the body to direct the body metabolism. They stimulate all body cells to work at a better metabolic rate. Without these hormones the body's

Introduction :

Endocrine system is the second key regulator of various body system functions after nervous system(2013, AbdAlla). One of the largest endocrine glands in the body is The Thyroid gland It is positioned on the neck (2014,Peepre *et al*) just below the Larynx and has two lobes with one on either side of the trachea. The thyroid gland is genetically programmed to be the metabolic regulator in all vertebrates because It is involved in the production of two amino acid-iodine bound hormones known as 3-5-3' triiodothyronine (T3) and 3-5-3'-5' tetraiodothyronine (T4, thyroxine) The thyroid gland secretes the hormone thyroxine (T4) along with small amounts of triiodothyronine (T3). The most of the T3 in the circulation (about 80%) is formed from the conversion of T4 to T3 by the deiodinase enzyme. Most of this transformation takes place in the kidney and liver. T3 is considered the physiologically active hormone; in this sense T4 can be thought as a prohormone(2011,Russell and Joffe) .

variations of thyroid hormone levels can be one of the main physiological modulators of *in vivo* cellular oxidative stress due to their known effects on mitochondrial respiration (1999,Guerrero *et al.*). These conditions determine a higher consumption of cellular antioxidants (1986,Sies; 1988 Fernandez *et al.*; 1998, Huh *et al.*) and inactivation of antioxidant enzymes (1988,Fernandez *et al.*), thus inducing oxidative stress (1986,Sies) with the concomitant increase in lipid peroxidation and protein oxidation (2011,Pasupathi and Latha)., One of the major effects of thyroid hormones is to increase mitochondrial respiration which results in increased generation of reactive oxygen species (ROS) (1978,Nishiki *et al.*).

Material and Methods :

Laboratory animals :

The research was conducted on 30 of Swiss mice 12 weeks old, weight (25-28) g. were brought from the animal house of science collage/Babylon university , Animals had free access to tap water and standard food pellet. and they were housed in metal cages under normal laboratory conditions in a room with an ambient temperature of $21\pm 1^{\circ}\text{C}$ and 12/12 light/dark photoperiod. The animals acclimatized for 2 weeks before the onset of experiment.

Experimental protocol :

The animals were weighed and divided into three groups of 10 animals each:

cells would not be able to regulate the speed at which they performed chemical actions. Their release will be increased under certain situations such as cold temperatures when a higher metabolism is needed to generate heat(1975,Balsam and Sexton).

Anabolic-androgenic steroids (AAS) are a class of compounds that include any drug or hormonal substance, pharmacologically and chemically related to testosterone that stimulates the growth or manufacturing of bone and muscle(anabolic effect) (2008,Salas-Ramirez *et al*) These substances are frequently misused by athletes, bodybuilders and youths in order to increase muscle mass or enhance physical endurance (2004,Bahrke and Yesalis; 2005,Thiblin and Petersson) Of AAS, nandrolone, 19-nortestosterone (C₁₈H₂₆O₂), has a stronger anabolic capacity (about 5 times higher) than testosterone (2006,Chrousos). Nandrolone is either chemically synthesized or naturally found in some mammals, including human and farm animals.

Thyroid gland is one of the non-classical target organs for sex steroids (2006,Bermudez *et al*) . Thus Administration of sex hormones can interfere substantially with the hypothalamic-pituitary-thyroid (HPT) axis (2006,Bisschop *et al.*). Androgen administration in women decreases T4 substitution in patients with primary hypothyroidism (1994,Arafah).

Thyroid hormones regulate oxidative metabolism and thus play an important role in free radical production. Hence

kits is available from Germany Biochek –Inc. Company.

Total cholesterol were determined in serum using commercial kits from Bio Merieux, France.

Fatty acids oxidation was determined by measurement of Malondialdehyde, as a product of polyunsaturated using thiobarbituric acid reactive substances (TBARS) was measured spectrophotometrically, after the reaction with thiobarbituric acid in acidic medium for 30 min with heating. To form chromogen complex reactive product, the absorbance of the resultant pink product can be measured at 532 nm (1979,Moron *et al*) and its concentration was calculated using the extinction coefficient value $1.56 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$ and resus are expressed as mmol MDA/L .

Glutathione was assayed using dithiobis-2-nitrobenzoic acid (DTNB) in alkaline medium (pH=8) . The reaction color was read at 412 nm. (1979,Moron *et al*) (GSH levels were calculated using an extinction coefficient of $13600 \text{ M}^{-1} \text{ cm}^{-1}$. Results are expressed in $\mu\text{mol GSH/L}$. (1979,Moron *et al*).

Statistical Analysis :

The statistical analysis was performed using SPSS statistical program version 17 . All data were expressed as mean \pm SD of number of experiments. The statistical significance was evaluated by t-test. Value of $P < 0.05$ was considered statistically significant.

Group I: Control group which injected with normal saline for 4 weeks .

Group II: test group which injected subcutaneous at 5 mg/kg/b.wt.by nandrolone Decanoate for 4 weeks .

Group II: test group which injected subcutaneous at 10 mg/kg/b.wt. nandrolone Decanoate for 4 weeks.

Tested Materials:

Anabolic androgenic steroid (Nandrolone Decanoate) (produced by Nile Co., Egypt, under license from N.V. Organon, Oss, Holland) was purchased from a local pharmacy in a form of injection. It is an AAS with a chemical formula . (C₂₈ H₄₄ O₃). The drug was diluted to the selected dose in a normal saline .

Collecting of blood sample :

Two days after the final drug administration, body weight was measured and the mice were killed rapidly under ether anesthesia followed by cervical dislocation. The following samples Blood was collected via heart puncture, centrifuged at 2,000 rpm for 10 min and the supernatant (serum) was stored at -20°C. The serum was used to measure level T₃,T₄,TSH, total cholesterol, malondialdehyde (MDA) and glutathione (GSH) level.

Measurements :

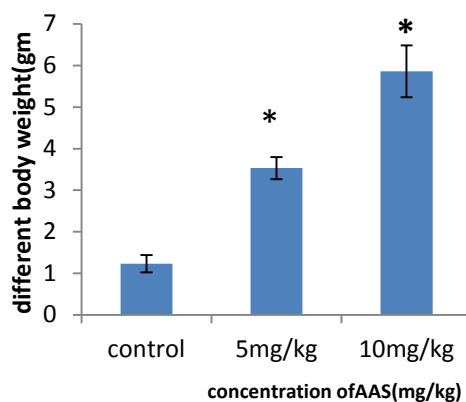
Serum thyroid stimulating hormone (TSH), triiodothyronine (T₃) and thyroxine (T₄) were measured by kits method using enzyme – linked immunosorbent assay (ELISA) .the

after anabolic steroid intake compared to control animals (at $p \leq 0.05$).

Androgenic Anabolic steroids seem to be effective in two ways:

Result and Dissection :

The data in figure (1) showed a prominent significant increase in B .W.



Figure(1)Changes in different of body weight(gm) in treatment groups .values are $M \pm S.E.$,* $P \leq 0.05$ compared to control group.

antiglucocorticoid action (1990, Hickson *et al*).

In our study the anabolic steroid treated animal exerted significant increase of body weight compared to control animal (figure 1) could be a consequence of the increased anabolism and utilization of nitrogen of ingested protein, in tissue building.

Thyroid gland have androgen receptors and the sex steroids might directly influence on thyroid function. (2002, Banu *et al*). showed that testosterone stimulates thyrocyte proliferation in culture, an effect independent of TSH. In rats, testosterone might increase TSH synthesis and secretion.(1998, Borges *et al*).

Nandrolone administration bring significant changes in the TSH ,T3 , T4 levels at the doses used. Figure (2) illustrates the levels of serum thyroid stimulating hormone (TSH) as

the first way was by convert a negative nitrogen balance to positive

one through improving the use of ingested protein and increase protein synthesis in skeletal muscle. Anabolic steroids are believed to exert their effects by binding to androgen receptors, that are present in the reproductive tissue as well as in many non-reproductive tissues, including, skeletal muscle bone, brain, liver, kidney, prostate and adipocytes (2001, Shahidi ; 2010, Attardi *et al*) which then translocate binding sites on chromatin, promoting gene transcription, stimulating production of mRNA and protein synthesis (2009, Li, and Al-Azzawi). The second way was by anabolic Steroids compete glucocorticosteroid receptors, leading to reduce protein catabolism. Thus, the anabolic action of androgens is mediated directly through androgen-receptor binding and also indirectly by

thyroid, the pituitary gland secretes excess TSH. So TSH is HIGH in hypothyroidism. The opposite is observed in hyperthyroidism: the excess thyroid hormone in circulation acts back on the pituitary to suppress TSH production. in hyperthyroidism TSH is LOW.

Figure (5) showed that, nandrolone treatment induced a significant elevation in serum cholesterol levels all over the experimental groups.

When the thyroid hormones level slows down (hypothyroidism), it also slows down the body ability to process cholesterol. This processing lag is largely explained by a decreasing in the activity and number of what are known as (low-density

lipoproteins) LDL_receptors and apolipoprotein B (apo A) in liver LDL receptors help remove bad cholesterol from the body; when the number of receptors decreases, LDL accumulates in the bloodstream, acting to increase both LDL and total cholesterol levels. The high-density lipoprotein (HDL) levels are normal or even elevated in severe hypothyroidism because of decreased activity of cholesteryl-ester transfer protein (CETP) and hepatic lipase (HL), which are enzymes regulated by thyroid hormones. The low activity of CETP and more specifically of hepatic lipase, results in decrease transport of cholesteryl esters from HDL(2) to very low-density lipoproteins (VLDL) and intermediate low-density lipoprotein (IDL), and reduce transport of HDL(2) to HDL(3). Moreover, hypothyroidism

compared to control group was significantly increased . Also figure 3 and 4 is showing The levels of T3, and T4 was significantly decreased as compared to control(at $p \leq 0.05$).

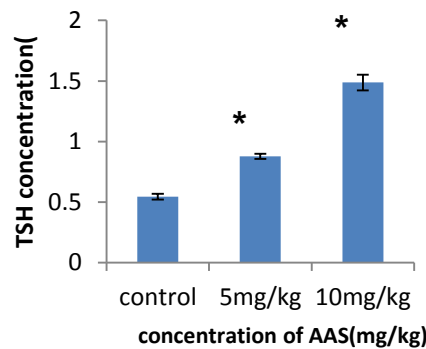
One of the most prominent effects of anabolic steroid is the interfere substantially with the hypothalamic-pituitary-thyroid (HPT) axis(2006,Rodrigo,*et al.*). In a clinical study, Deyssig and Weissel (1993) showed that total T4, total T3, and thyroid hormone-binding globulin (TBG), were significantly decreased, also TRH stimulation was increased in five bodybuilders who used high concentrations of AAS compared with eight control subjects. Thus, the abuse of androgenic anabolic steroid may cause impairment of thyroid

function . In the present study, the anabolic steroid-treated animals had a significant reduction in serum total T3, T4, and significant increase TSH level (figure 2 , 3 and 4) , the reduction in total T3 and T4 level could be explained by reduction a thyroid binding globulin (TBG). The levels of TBG influence the levels of total thyroid hormone in circulation. If TBG level is depressed, total T4 and T3 levels will go down. An increase in TBG due to higher levels of total thyroid hormone. However note that the small ratio of T3 and T4 remain unbound to TBG (0.05% of T4 and 0.5% of T3), the so-called free fraction (1987,Alen *et al*), Thyroid Stimulating Hormone (TSH) levels. Typically increase in hypothyroidism, the thyroid is not secreting adequate concentration of T4, and in an attempt to stimulate the

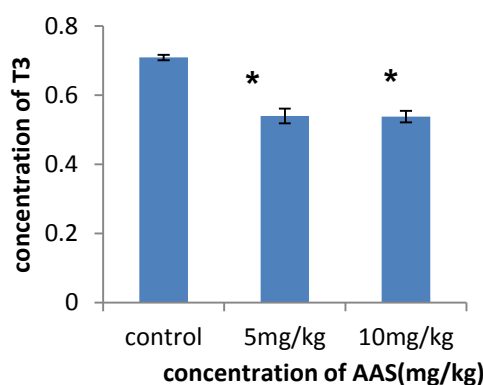
in which nandrolone has an increasing, effect on LDL and reduced effect on HDL levels. It is worth mentioned that, the marked increased levels of total cholesterol (2003,Maron) which presents a substrate for the oxidative stress.

Concerning the effect of nandrolone on serum oxidants/ antioxidants status (figure 6 and 7), statistical analysis revealed a significant increase of MDA and a significant decrease of GSH contents ($p \leq 0.05$) compared to control .

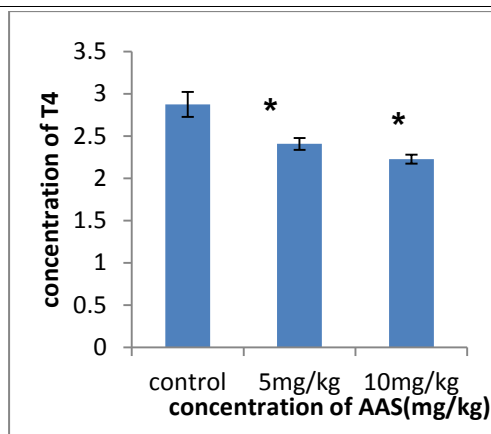
increases the oxidation of plasma cholesterol mainly because of an altered pattern of binding and to the increased levels of total cholesterol, which presents a substrate for the oxidative stress. Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins (LDL)) because of a reduced fractional clearance of LDL by a decrease number of LDL receptors in the liver (2002,Duntase) On the other hand , nandrolone has higher ability to induce hepatic triglyceride lipase(HTGL) which may explain our results



Figure(2)Changes in TSH concentration (ng/L) in treatment groups .values are M± S.E.,* P≤0.05 compared to control group.



Figure(3)Changes in T3(ng/dl) concentration in treatment groups .values are M±S.E., * P≤0.05 compared to control group



Figure(4)Changes in T4 concentration (µg/dl) in treatment groups .values are M± S.E.,* P<0.05 compared to control group.

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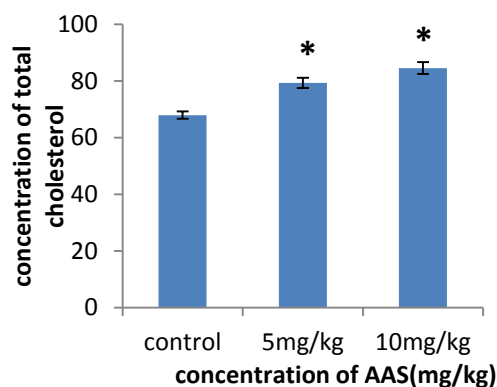
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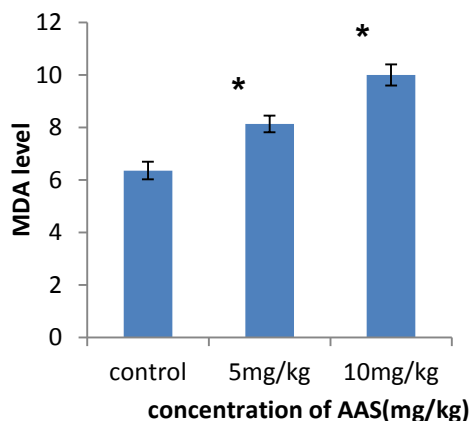
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Figure(5)Changes in total cholesterol level (mg/dl)in treatment groups .values are $M \pm S.E.$,* $P \leq 0.05$ compared to control group.



Figure(6)Changes in MDA concentration(mmol/L) in treatment groups .values are $M \pm S.E.$,* $P \leq 0.05$ compared to control group

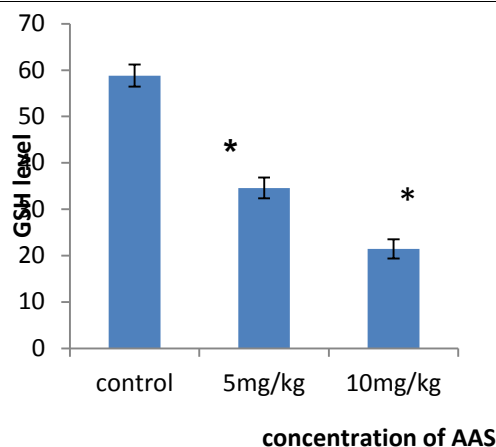
in cellular macromolecules like lipids, proteins, , and DNA and might result in cell death by necrosis or apoptosis.(1999, Gamaley, and Klyubin)

Concerning the effect of treatment with ND our results of the present study revealed hypothyroidism situation induce oxidative stress by increase malondialdehyde (MDA) level as a product of polyunsaturated fatty acids oxidation and decrease glutathione (GSH) level in the serum (figure 6,7) ,this is agreed with data reported by Tugyan *et al.*(2012). Dariyerli *et al.* (2004) showed that there is no statistically significant difference found between hypothyroid and control groups in the lipid peroxidation indicator MDA. The results of Yilmaz *et al.* (2003) reported increased plasma, muscle and liver MDA levels in hypothyroid rats contradict our findings. This conflicting findings are thought to be due to different study materials in several animal models .

The main function of thyroid hormone within physiological ranges is to regulate and enhance metabolic reaction and oxygen consumption of different cells of the body. ROS which are the by-products of tissue metabolism are normally treated by physiological antioxidants.

Previous study showed that both hyper- and hypothyroidism are associated with increased oxidative stress. In the new study with hypothyroid patients it was clearly shown that their antioxidant enzyme systems of their bodies were working overtime trying to keep up with the excessive production of free radicals induced by their hypothyroid situation of metabolic inefficiency (2012,Richards,).

Oxidative stress may result from either over-production of reactive oxygen species (ROS) or from failure of the antioxidant defense systems (2011,Babu, *et al.*). ROS have a high reactivity potential, therefore they are toxic and can due to oxidative damage



Figure(7)Changes in GSH concentration(mmol/L) in treatment groups .values are $M \pm S.E.$,* $P \leq 0.05$ compared to control group.

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Recent stydies have show Hypothyroidism-associated oxidative stress is the consequence of both increased production of free radicals and decrease ability of the antioxidative defense.(2004,Das and Chainy; 2005,Sarandol ,*et al.*) Hypothyroidism-induced dysfunction of the respiratory chain in the mitochondria due to accelerated production of free radicals (i.e., hydrogen peroxide, superoxide anion, and hydroxyl radical as well as lipid peroxides), which consequently dues to oxidative stress (OS). (1997,Venditti *et al*; 2003,Yilmaz *et al*) Metabolic disorder from autoimmune-based hypothyroidism can also increase oxidative stress.(2008,Carmeli *et al*)

In conclusion our data indicate that androgenic anabolic steroid exerts direct actions on the thyroid gland and in the peripheral metabolism of thyroid hormones and might lead to thyroid dysfunction and induced oxidative stress.

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