Liver Function and Hormone Levels in Kuwait Recreational Bodybuilders Who Abuse Anabolic-Androgenic Steroids

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Abstract: Resistance training is becoming increasing popular in the Middle East, especially in Kuwait. At the same time, the use of anabolic-androgenic steroid (AAS) has been increasing tremendously by Kuwaiti recreational bodybuilders seeking to gain muscle mass and improve their physique. Therefore, the purpose of the present study was to determine the side effects of anabolic-androgenic steroid use on Kuwait recreational bodybuilders who have been using AAS. Blood parameters of male bodybuilders (n=70; age=26±3yr) who have been using AAS were studied. Eighty two percent of bodybuilders showed increased levels of both alanine aminotransferase (ALT; 48±38 U/L) and aspartate aminotransferase (AST; 41±32 U/L) above the upper range of reference. Moreover, in regard to hormones, 69% of participants had estradiol levels above the upper reference limit (57±1.34 pg/ml), but otherwise, all other hormones were within the normal range. Most Kuwaiti bodybuilders use AAS will experience without medical supervision Therefore, the ministry of health in Kuwait should implement strict regulations and increase awareness among recreational bodybuilders of potential health problems associated with AAS use.

[Yousef H, Alkatan M, Alsharji K, Sedky MG, Haiat M. Liver Function and Hormone Levels in Kuwait Recreational Bodybuilders Who Abuse Anabolic-Androgenic Steroids. *J Am Sci* 2018;14(5):1-6]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 1. doi: 1. doi: 10.7537/marsjas140518.01.

Keywords: anabolic-androgenic steroids; bodybuilders; liver function and hormone.

1. Introduction

Drug use to enhance physical performance and muscular development has been practiced for thousands of years. A substantial number of bodybuilders take hormones, vitamins, minerals, and/or other supplements (Karimian & Esfahani, 2011; Ziegenfuss, Landis, & Hofheins, 2008). Anabolic androgenic steroids (AASs) are powerful chemicals whose use can be beneficial to human health, used therapeutically in medicine to stimulate muscle growth and appetite, induce male puberty and treat chronic wasting conditions including HIVwasting, chronic renal failure, chronic obstructive lung disease, muscular disease, alcoholic liver disease, post-operative burn injuries and (Woerdeman & de Ronde, 2011). In addition, AASs are the main drug class of performance-enhancing drugs (PEDs) designed to improve appearance or enhance performance in athletics or other competitive environments. Anabolic steroids are synthetic similar substances to the male hormone testosterone. Frequently, bodybuilders use both oral and parenteral AASs in dosages greater than the recommended therapeutic dosage. Some athletes dietary supplements that include hormones, such as dehydroepiandrosterone (DHEA). This endogenous steroid hormone is converted into other steroid hormones, including testosterone, estrogen, and cortisol. The term 'anabolic' refers to their role of building up organs and tissues, which, in

the case of athletes and especially bodybuilders, tends to be increasing protein synthesis in skeletal muscle. Additional benefits of AASs are to increase bone growth and the stimulation of bone marrow that eventually leads to increased red cell production (Lee, 2006).

There is a wide range of temporary and permanent adverse effects with AASs use that may develop within just a few weeks (i.e. altered reproductive function) or even after several years (i.e. liver carcinoma). Several studies have shown that anabolic steroid intake is associated with glucose intolerance. insulin resistance, increased cardiovascular disease risk profiles, cerebral dangers, musculoskeletal injuries, prostate cancer, psychosis and schizophrenic episodes (Hickson, Ball, & Falduto, 1989; Higgins, Heshmat, & Higgins, 2012; Shahidi, 2001; van Amsterdam, Opperhuizen, & Hartgens, 2010). A frequent side effect of AASs intake is its transformation into estrogen compounds in fat tissue and other body compartments (Buttner & Thieme, 2010).

The resulting increase in blood estradiol level (Friedl, Hannan, Jones, & Plymate, 1990) may also cause gynecomastia (Alen, Rahkila, & Marniemi, 1985; O'Sullivan et al., 2000). A large number of studies have established the ability of natural and synthetic estrogenic steroids to impair hepatic function, especially those associated with bile flow

(Klaassen & Watkins, 1984; Kreek, Weser, Sleisenger, & Jeffries, 1967)

Serum glutamic-oxaloacetic transaminase (SGPT), alanine transaminase (ALT), serum glutamate pyruvate transaminase (SGPT), and aspartate transaminase (AST) are enzymes found in the liver and other tissues. Elevated levels of AST and ALT are clinical indicators for further testing of possible liver damage. Anabolic steroids can cause liver damage when taken inappropriately; however, of anabolic steroid-induced prior reports hepatotoxicity that were based on aminotransferase elevations may have overstated the role of anabolic steroids (Dickerman, Pertusi, Zachariah, Dufour, & 1999; McConathy, Pertusi, Dickerman, McConathy, 2001). Exogenous human growth hormone (hGH) supplementation is a potent anabolic agent known to stimulate linear growth in children who are deficient in endogenous growth hormone (Tanner, Hughes, & Whitehouse, 1977). Further, hGH stimulates protein synthesis and cell growth in vitro and participates in the regulation of body composition in adults, probably through its anabolic and lipolytic actions (Salomon, Cuneo, Hesp, & Sonksen, 1989).

Unfortunately, there is little known data regarding the use, efficacy, and safety of AASs among adolescent and adult bodybuilders in Kuwait (Alsaeed & Alabkal, 2015; KHULLAR, SCULL, DEENY, & HAMDAN, 2016). There are a host of complex health side effects that can originate from the use of these drugs. Unfortunately, a comprehensive examination of all PEDs are beyond our capabilities. Therefore, the aim of this study was to determine the health impacts, specifically liver function, of AASs use by Kuwaiti bodybuilders. Our working hypothesis was that self-administration of AAS in recreational bodybuilders will lead to liver dysfunction that may be associated with increased plasma levels of many liver enzymes such as AST, ALT, ALP, GGT.

2. Material and Methods

Participants: Seventy young Kuwaiti recreational bodybuilders (26±3 years, height 175±7 cm, body mass 85±11 Kg) who self-administered anabolic steroids voluntarily took part in the study. The study was approved by the review committee of the Public Authority for Applied Education and Training. Written informed consent was obtained prior to subject participation. Subjects were guaranteed absolute anonymity.

Body Composition: Height and body mass were measured with a physicians' balance scale. Participants' body mass was measured while barefoot and in light clothing. Body mass index (BMI) was calculated using the equation: mass (kg) / height squared (m²). Percent body fat, lean tissue mass, and

visceral adipose tissue mass were determined noninvasively using a Tanita Body Composition Analyzer (BC-1000 Madison, WI).

Blood Parameters: Venous blood sampling was taken from the right arm after 10 minutes of rest in the supine position between 7:00 pm and 10:00 pm. Complete blood count (CBC) was performed by cell counter ABX MICROSE ES 60 (Horiba). AST and ALT levels were measured using tris- buffer without P5P at 37 °C, gamma glutamyl transferase (GGT) was measured using glutamyl-3-carboxy-4- nitroanilid (IFCC) at 37 °C, and alkaline phosphatase (ALP) was measured using diethanolamin buffer DEA at 37 °C. Urea was measured by urease (GLDH-method, Enzymatic UV-test) and creatinine with enzymatic PAP method. Total cholesterol was measured by cholesterol oxidase and triglycerides were measured by Lipase\GPO-PAP no correction with randox (Dayatona+).

All hormones were measured within the same assay directly after collection of blood samples. Luteinizing hormone (LH), follicle stimulating hormones (FSH), cortisol pm, dehydroepiandrosterone sulfate (DHEA-S), human growth hormone (HGH), testosterone, and estradiol (E2) were measured by immunoassay with COBAS E411 (ROCH).

Spearman correlation coefficients were used for comparison of the dependent sample. The level of statistical significance was set at P<0.05. Results are expressed as means \pm standard deviations (SD), unless otherwise noted.

Table 1. Participants' characteristics.

Variables	Bodybuilding (means \pm SD)
N	70
Age (years)	26 ± 3
Height (cm)	175 ± 7
Body mass (kg)	85 ± 11
Body mass index (kg/m ²)	28 ± 3
Years of training	5.6 ± 1
Exercise sessions per week	6 ± 2
Fat Free Mass (kg)	66 ± 4
Visceral Fat (%)	6.7 ± 1
Muscle Mass (kg)	63 ± 3
Bone Mass (kg)	3.3 ± 0.3

3. Results

The participant characteristics are presented in Table 1. All CBC parameters were within normal ranges, as seen in Table 2.

4. Discussions

Our study was designed to determine whether self-administrations of AASs would lead to liver dysfunction, as assessed by liver enzyme levels, in recreational body builders. Findings were restricted to mild elevation of ALT and AST respectively accompanied with normal level of GGT the more sensitive liver marker, these results suggest that the

AASs usage may not be deleterious to the liver functions.

Table 2. Complete Blood Count (CBC)

Variables	Bodybuilders (means ± SD)	Range of reference
White blood cell (WBC)	$7.7\pm2 \text{ x} 10^3/\text{u}$ l	4.1 - 11.1
Red blood cell (RBC)	$5.2\pm1 \text{ x} 10^6/\text{ul}$	4.3 - 5.9
Hemoglobin	14±3 g/dl	14.0 - 18.0
Hematocrit (HCT)	45 ± 8 %	42 - 54
Mean corpuscle volume (MCV)	$83 \pm 15 \text{ fL}$	76 - 94
Mean corpuscular hemoglobin (MCH)	$27 \pm 5 \text{ pg}$	27 - 37
Mean corpuscular hemoglobin concentration (MCHC)	$31 \pm 5 \text{ g/dl}$	32 - 36
Platelet Count (PLT)	$250 \pm 70 \text{ x} 10^3 / \text{ul}$	150 - 400
Mean platelet volume (MPV)	$8 \pm 1 \text{ fL}$	7.0 - 10.5
Red cell Distribution Width (RDW)	13 ± 3 %	11.5 - 14.5
Lymphocytes	32 ± 10 %	16 – 46
Monocytes	$3.6 \pm 0.4 \%$	2.8 - 10.2
Neutrophils	60 ± 13 %	48.5 - 80.3
Eosinophils	2 ± 0.7 %	1 - 6

Serum chemistry profiles of bodybuilders are presented in Table 3. Eighty two percent of bodybuilders showed levels of both ALT and AST above the upper range of reference.

Table 3. Serum chemistry profile

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Variables	Bodybuilders (means \pm SD)	Reference Range		
Urea	$8.8 \pm 1 \text{ mmol/L}$	1.7 - 8.3		
Creatinine (Crea)	$81 \pm 26 \text{ umol/L}$	63.6 - 110.5		
Cholesterol	$4.6 \pm 1 \text{ mmol/L}$	3.1 - 5.2		
Serum Protein	$72 \pm 6 \text{ g/L}$	63 - 82		
Albumin (ALB)	$46 \pm 3 \text{ g/L}$	32 - 50		
Aspartate aminotransferase (AST)	$41 \pm 32 \text{ U/L}$	0 - 35		
Alanine aminotransferase (ALT)	$48 \pm 38 \text{ U/L}$	0 - 40		
Alkaline phosphatase (ALP)	$190 \pm 64 \text{ U/L}$	98 - 279		
Gamma-glutamyl transferase (GGT)	$20 \pm 13 \text{ U/L}$	11 - 50		

Sixty nine percent of the participants had estradiol levels above the upper reference limit, but otherwise, all other hormones were within the normal range (Table 4). The DHEA/Cortisol ratio was 0.04 ± 0.1 .

Table 4. Hormone concentrations

Variables	Bodybuilders (means ± SD)	Range of reference
Cotisol PM	$230 \pm 135 \text{ nmol/L}$	64 - 327
DHEA-S	$9.2 \pm 3.2 \text{ Umol/L}$	4.34 - 12.2
Estadiol	$57 \pm 1.34 \text{ pg/ml}$	7.63 - 42.6
Total Testosterone	$20 \pm 18 \text{ nmol/L}$	8.64 - 29.0
Growth Hormone	$1 \pm 2 \text{ ng/mL}$	<0.030 - 2.45

Anabolic androgenic steroids (AASs) increase protein synthesis and hypertrophy of skeletal muscle which can enhance athletic performance. However, the adverse side effects associated with AASs can jeopardize health. AASs side effects depend on

several factors including type, dosage, and usage duration, as well as the users sensitivity and physiological response (Kopera, 1993). Frequency and severity of side effects are greatly variable. For example, AASs that contain a 17-alkyl group have

potentially more adverse effects than other forms of AASs, especially in regards to liver function (Wilson & Griffin, 1980; Wright, 1980). Parenterally administered AASs, as well as testosterone and other injectable anabolic steroid, seem to have less serious effects on the liver. Many reports of steroid-induced hepatitis based solely on ALT and AST may be unfounded as these studies had neglected to use GGT, a more sensitive marker for liver damage (25-27). AASs use is often associated with increased plasma levels of many liver enzymes such as AST, ALT, ALP, GGT, and lactate dehydrogenase (LDH) which hepatocellular damage or reflect increased permeability of the hepatocellular membrane (Dickerman et al., 1999; Socas et al., 2005). In some studies, these enzymes were mildly increased, but normalized within weeks after discontinuing AASs use (Alen, 1985; Dickerman et al., 1999; Kiraly, 1988; Lamb, 1984; Mirkin, 1984; O'Connor, Baldini, Skinner, & Einstein, 1990), whereas in others no changes were found (Kuipers, Wijnen, Hartgens, & 1991). In our study, Willems. recreational bodybuilders present with mild elevations in ALT and AST but normal GGT levels. Therefore, we conclude that ALT and AST blood tests have limited ability to determine liver damage.

In the case of athletes and bodybuilders, transaminase elevations may be related to muscle damage (Hartgens, Kuipers, Wijnen, & Keizer, 1996). Anabolic steroids increase muscle cell membrane permeability which results in elevations in creatinine kinase (CK), a marker of muscle damage (Hakkinen & Alen, 1989). To support the theory of muscle damage as an explanation for transaminase elevations, CK enzyme levels were measured and found to be elevated (Dickerman et al., 1999). The bodybuilders who used steroids were larger, stronger, and tended to work out with a greater intensity compared with those who did not use steroids. They also had higher levels of CK, AST and ALT. A positive correlation was found between CK and ALT and AST levels, but not between CK and GGT levels (Dickerman et al., 1999).

To follow this study, we recommend assessing CK and GGT in relation to elevated ALS and AST in order to determine whether elevations are due to liver impairment or muscle damage. Additionally, as we only investigated male bodybuilders, we recommend including female participants for a more representative sample. An additional limitation is that we did not measure CK enzyme level. The increase in mean plasma estradiol is proportional to the intake of AASs in our sample of bodybuilders.

Dehydroepiandrosterone sulfate (DHEA-S) is a naturally occurring, endogenous androstane steroid. Both cortisol and DHEA-S are synthesized within the adrenal cortex. The protective effect of higher DHEA-

S level is interesting, and the anti-glucocorticoid actions of its precursor, DHEA-S, are well documented. The cortisol: DHEAS ratio is a predictor of all-cause mortality and has been found to predict health outcomes better than the level of either hormone alone. Additionally, it also predicts immune function and infectious disease susceptibility better than either hormone alone (Kalimi, Shafagoj, Loria, Padgett, & Regelson, 1994; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999; Quinkler et al., 2004).

In our study there is an increased level of estradiol in self-administrations of AASs bodybuilders. The administration of exogenous estradiol has the ability to cause erectile dysfunction through an inhibitory effect on testosterone production (Srilatha & Adaikan, 2004). Similarly, in humans taking estrogen a reduction is seen in spontaneous erections and nocturnal penile tumescence correlating with a reduction in testosterone levels (Kwan, VanMaasdam, & Davidson, 1985).

Furthermore, the Cortisol: DHEA-S ratio has been found to predict health outcomes better than the level of either hormone alone and all-cause mortality (Phillips et al., 2010). It has been suggested that the ratio of cortisol and DHEA-S may reflect physiological vulnerabilities for psychopathology. In particular. significantly higher cortisol/DHEA-S ratios have been associated with depression (Angold, 2003) and these ratios predict immune function and infectious disease susceptibility better than either hormone alone (Arlt et al., 2006; Butcher et al., 2005). Therefore, it would be worthwhile to examine the cortisol: DHEA-S ratio in the context of other health outcomes (Phillips et al., 2010). Cortisol: DHEA-S ratio in our study is 0.04 ± 0.1 but this finding may have a few limitations. First, the sample was exclusively male and relatively young, so the findings may not be applicable to females and older populations. Secondly, we tested blood levels of the cortisol: DHEA-S which is less accurate than testing saliva. These hormones are often bound to proteins in the blood which prevents them from attaching to cell receptors. Therefore, saliva is preferred over blood and urine because saliva hormone values are more "bio-available" than the other samples.

This study demonstrates the importance of liver enzymes detection in bodybuilders who use AASs. We recommend to accompany AST, ALT and GGT enzymes with CK level assays as the mild elevation in AST may be due to muscle exertion that occurs with resistance exercise. Monitoring Cortisol: DHEA-S ratio is also recommended as it has been found to predict health outcomes, immune function, and infectious disease susceptibility. Therefore, the

ministry of health in Kuwait should implement strict regulations and increase awareness among recreational bodybuilders of the potential health problem associated with AASs use.

Acknowledgements:

Sources of Funding: This work was supported and funded by The Public Authority of Education and Training, Research project No (BE-14-05).

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5/10/2018