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# EFFECTS OF SELF-ADMINISTERED, HIGH-DOSE TESTOSTERONE AND ANABOLIC STEROIDS ON SERUM HORMONES, LIPIDS, ENZYMES AND ON SPERMATOGENESIS IN POWER ATHLETES

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Academic dissertation

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Diss.
Eleven top-level power athletes (6 control, 5 experimental subjects) completed the prospective 42 weeks of investigation aimed to elucidate androgenic-anabolic steroid effects on endocrinology and metabolism. During the first 26 weeks of strength training the experimental subjects self-administered testosterone and anabolic steroids in doses which exceeded the therapeutic dose by 5 to 12 times. After 26 weeks serum testosterone had increased 2.3-fold. This was associated with a 7-fold increase in serum estradiol, leading to gynecomastia, and significant decreases in serum FSH and LH. Testicular function was impaired, as seen from both the low serum testosterone (9±8 nmol/l) immediately following drug withdrawal and azoospermia, and decreased testicular volume. Significantly decreased serum HDL and $HDL_2$ -cholesterol were detected, but total cholesterol was not affected. Serum ALAT, AFOS, γ-GT and total bilirubin remained within reference interval. A return towards the initial values was observed in the course of 12-16 weeks following drug withdrawal in the variables affected, indicating long-lasting impairment of testicular function and suggesting increased risk of later development of atherosclerosis. In the control group there were only insignificant fluctuations in the variables registered, except for a significant increase in serum LH after 26 weeks' training.

anabolic steroids, doping, strength training, serum hormones, lipids, enzymes, spermatogenesis.

Markku Alén, Department of Health Sciences, University of Jyväskylä, SF-40100 Jyväskylä.

CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| ACTH | = adrenocorticotrophic hormone |
| AFOS | = alkaline phosphatase |
| ALAT | = alanine aminotransferase |
| ASAT | = aspartate aminotransferase |
| Cortisol | = 11β,17,21-trihydroxy-4-pregnene-3,20-dione |
| CHOD-PAP | = cholesterol oxidase-para-aminophenazone |
| CV% | = intra-assay coefficient of variation (in percentage) |
| Estradiol ($E_2$) | = estradiol-17β:1,3,5,(10)-estratriene-3,17β-diol |
| FSH | = follicle stimulating hormone |
| γ-GT | = gammaglutamyltransferase |
| HDLC | = high density lipoprotein cholesterol |
| $HDL_2C$ | = fraction 2 of high density lipoprotein cholesterol |
| $HDL_3C$ | = fraction 3 of high density lipoprotein cholesterol |
| i.m. | = intramuscularly |
| LDLC | = low density lipoprotein cholesterol |
| LH | = luteinizing hormone |
| p.o. | = perorally |
| PRL | = prolactin |
| RIA | = radioimmunoassay |
| SD | = standard deviation |
| SEM | = standard error of the mean |
| Testosterone | = 17β-hydroxy-4-androsten-3-one |
| TG | = triglycerides |
| TOTBIL | = total bilirubin |
| TOTC | = total cholesterol |

## COMPOUNDS

| | |
|---|---|
| methandienone | = 17α-methyl-17β-hydroxy-1, 4-androstadien-3-one |
| nandrolone | = 17β-hydroxy-4-estren-3-one |
| stanozolol | = 17α-methyl-5α-androstano \|3,2-c\|-pyrazol-17β-ol |
| testosterone | = 17β-hydroxy-4-androsten-3-one |

## DEFINITIONS

| | |
|---|---|
| anabolic steroids | = androgenic-anabolic steroids |
| exogenous androgens | = exogenously administered testosterone and/or anabolic steroids |
| experimental group | = the group in which the athletes self-administered testosterone and anabolic steroids |
| power athletes | = bodybuilders, powerlifters, wrestlers |

# PREFACE

This summary is based on the following papers, which will be referred to in the text by the Roman numerals I-IV:

I ALÉN, M., REINILÄ, M., VIHKO, R. Response of serum hormones to androgen administration in power athletes. Med Sci Sports 17(3), in press 1985.

II ALÉN, M., SUOMINEN, J. Effect of androgenic and anabolic steroids on spermatogenesis in power athletes. Int J Sports Med 5 (Suppl.) 189-192, 1984

III ALÉN, M., RAHKILA, P., MARNIEMI, J. Serum lipids in power athletes self-administering testosterone and anabolic steroids. Int J Sports Med 6(3), in press 1985.

IV ALÉN, M. Androgenic steroid effects on liver and red cells. Br J Sports Med 19(1) 15-20, 1985.

Some hitherto unpublished data from this study are also presented and discussed.

The present study was carried out at the Department of Health Sciences, University of Jyväskylä, in collaboration with the Research Unit for Sport and Physical Fitness, Jyväskylä, with the Department of Clinical Chemistry, University of Oulu, and also with the Department of Anatomy, University of Turku, during the years 1982-1984, and with the collaboration of several individuals to whom I wish to express my sincere thanks.

I wish to thank warmly my supervisors Professor Osmo Hänninen, M.D., Head of the Department of Physiology, University of Kuopio, and Professor Eino Heikkinen, M.D., Head of the Department of Health Sciences, University of Jyväskylä, for the constant encouragement, support and advice I have received during this investigation.

Serum hormone analyses were carried out at the Department of Clinical Chemistry, University of Oulu, and I am grateful to my co-worker, Professor Reijo Vihko, M.D., Head of the Department, for his interest and constructive criticism during the course of this work.

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Markku Alén

# 1. INTRODUCTION

Anabolic steroids and testosterone are compounds commonly used during training periods for competitive sports in order to increase the strength and/or muscle mass of the athletes. Because of the illegality of this procedure in most countries, no reliable figures for the incidence of this practice in various sports are available.

The effect of an anabolic steroid or testosterone in therapeutic doses (5-15 mg/day) on various aspects of physical health and fitness in male athletes has been studied in several investigations (see e.g. the extensive reviews of Wright 1980 and Ryan 1981). It has also been suggested as a summary of those investigations that anabolic steroids or testosterone do not have beneficial effects in sports. Moreover, the possible benefits found are not likely to be worth the health risks involved (Ryan 1981).

However, power athletes do not take therapeutic doses, but doses of anabolic steroids between 10 and 40 times higher (Lamb 1984). Apparent reasons for the excessive use of anabolic hormones in power events are the favourable effects on strength development (Saartok 1983, Alén et al. 1984, Lamb 1984) and peer group pressures (Ryan 1978). Such pressures seem to be so great that anabolic hormones are used in spite of known negative ethical, legal and medical implications (Lamb 1984, Ryan 1984).

In many countries the athletes obtain testosterone and other anabolic hormones on the black market (Alén & Rahkila 1984, Frankle et al. 1984). A recent trend in this illegal use of anabolic hormones is the simultaneous use of parenteral testosterone with oral synthetic anabolic steroids (Strauss et al. 1983, Alén & Rahkila 1984, Frankle et al. 1984). Because all that happens mainly outside medical control, health risks may be intensified. Moreover, nothing is known of the later side-effects, even though there are disturbing

rumors concerning the lethal nature of a high-dose use of exogenous androgens (Rich 1984).

The present study was designed to obtain information about the hormonal and metabolic effects of testosterone and anabolic steroids self-administered in high doses by power athletes in association with heavy resistance strength training.

For ethical and legal reasons and sport regulations involved this phenomenon could not be investigated according to the rules of a strictly controlled clinical trial but within a real life sports environment.

# 2. REVIEW OF LITERATURE

## 2.1. Testosterone and androgenic-anabolic steroids in clinical medicine

Testosterone was isolated from the testes by David et al. (1935) and shortly afterwards, in 1935, methods for its synthesis from cholesterol were developed (see Kochakian 1976).

Most of the androgenic-anabolic steroids are derivates of testosterone, dihydrotestosterone and 19-nortestosterone. For powerful and sustained androgenic or anabolic action it is necessary either to esterify the hydroxyl group at C-17β (e.g. testosterone-propionate, -isocaproate, -decanoate and nandrolone) or to alkylate the molecule, usually at position C-17α (e.g. methandienone and stanozolol). The esterified compounds are usually given intramuscularly and the alkylated compounds are taken orally. Both structural modifications of the testosterone molecule prevent the rapid degradation of the compound in the body and so permit large amounts to reach the target organs. Testosterone propionate produces a steady effect when injected at 2 or 3-day intervals. The other esters are fully effective when given at 2 to 4-week intervals (Brotherton 1976, Murad & Haynes 1980, Wilson & Griffin 1980).

Testosterone and anabolic steroids are used in clinical medicine for such purposes as the replacement of testosterone for hypogonadismus and the stimulation of bone marrow in some forms of anemia (Wilson & Griffin 1980). All the exogenous androgens have potential adverse effects, some as a result of physiological actions of the hormone, and some as a result of the toxic effects of the modified steroid molecules (Brotherton 1976).

## 2.2. Use of exogenous androgens in sport

Four years after the isolation of testosterone Bøje (1939) suggested that it is conceivable that the administration of male sex hormones might increase physical output in sports. Interestingly, 1939 was also the first time in sports when "gland extract treatment" was used by football players of Wolverhampton Wanderers (Bøje 1939).

However, the use of testosterone in sports was very limited until the 1950's, when the first anabolic steroid, 19-nortestosterone, was developed (Hershberger et al. 1953, Wright 1980). It is apparent that athletes in power sports, such as weightlifting, bodybuilding and throwing events began to use anabolic steroids in the late 1950's in an attempt to improve performance (Payne 1975, Beckett 1976, Ryan 1981). Since the 1964 Olympic Games in Tokyo increasing numbers of athletes have used anabolic steroids for training and competition purposes (Ryan 1976, Wright 1980, Frankle et al. 1984).

Because exogenous androgens are used and misused in secrecy, especially since 1975, when anabolic steroids were forbidden for the first time in the sport rules and regulations of the International Olympic Committee (the use of testosterone was prohibited in 1983), it has been impossible to monitor accurately the number of athletes taking exogenous androgens in various sports. However, today their use is known to be wide-spread in those sports events in which success largely depends on maximal strength and/or high body mass or reduced subcutaneous fat (see e.g. Wade 1972, Ljungqvist 1975, Payne 1975, Shephard et al. 1977, Alén & Heikkinen 1982, Sohlberg 1982, Lamb 1984). Quite recently it has been reported that over 90 % of Swedish national team weightlifters in the years 1970-79 had used androgenic-anabolic steroids (Norgren 1984).

A recent trend in the high dose use of such compounds in power events seems to be the incorporation of testosterone conjugates among the anabolic steroids administered (Hill et al. 1983, Strauss et al. 1983, Alén & Rahkila 1984). Moreover, since 1980 the use of injectable androgens has

spread rapidly (Frankle et al. 1984, Alén 1985 unpublished observations).

Apparent reasons for such a use of anabolic hormones in power events are the favourable effects experienced by the athletes (Lamb 1984), peer group pressures (Ryan 1978) and the relatively low risk of receiving a positive result in doping tests (Lantto et al. 1981, Kuoppasalmi & Karjalainen 1984). Moreover, in many countries athletes can buy anabolic hormones at the chemist's without a physician's prescription. In several other countries, including Finland, there are well-organized black markets (Alén & Rahkila 1984, Frankle et al. 1984, Lamb 1984).

## 2.3. Effects of exogenous androgens on healthy men

### 2.3.1. General aspects

The administration of testosterone or anabolic steroids to normal men leads to hormonal and metabolic effects in the body. The presence and magnitude of such androgenic effects depends on the drug used, its dose and treatment time and on the route of administration, as well as on the age of the subject (Simonson et al. 1944, Aakvaag & Strömme 1974, Strömme et al. 1974, Harkness & Kilshaw 1975, Wynn 1975, Brooks 1978). Moreover, the type and duration of physical activity may influence endogenous hormone production and the pharmacokinetic behaviour of the exogenous androgen (Keul et al. 1978, Weiss et al. 1983, Guglielmini et al. 1984).

### 2.3.2. Serum hormones

Testosterone and anabolic steroids have a negative feedback effect on the gonadotropin secretion. The administration of testosterone esters in amounts just sufficient to replace the normal daily testicular secretion (equivalent to 5-10 mg/day)

has no effect on the serum gonadotropins (Vermeulen 1976, Caminos-Torres et al. 1977). When serum testosterone (the sum of the exogenous and endogeneous testosterone) concentration has increased above the normal range, both the basal levels of serum LH, FSH and their response to exogenous gonadotropin-releasing hormone have decreased (Mauss et al. 1975, Cunningham et al. 1979). Administered testosterone also elevates the serum estradiol concentration, because testosterone is converted to estradiol peripherially (Dimick et al. 1961, Wilson & Griffin 1980). The effect of testosterone administration on serum prolactin (PRL) concentration is insignificant (D'Agata 1979).

Methandienone and nandrolone reduce the serum level of LH, FSH and testosterone (Remes et al. 1977, Clerico et al. 1981, Kuhn et al. 1984, Schürmeyer et al. 1984) whereas serum PRL concentrations do not change during treatment (Schürmeyer et al. 1984). Methandienone may retard the rate of adrenocortical cortisol production by inhibiting either the production or the release of ACTH from the pituitary (James et al. 1962, Wynn et al. 1962). On the other hand, it has been reported that nandrolone (Bijlsma et al. 1982) or stanozolol (O'Shea 1974) do not affect the serum cortisol level. The endocrine changes caused by exogeneous androgens are reported to be reversible (Foegh 1983). However, little is known about the long-term consequences of the suppression of the endogenous gonadotropin and testosterone secretion.

### 2.3.3. Spermatogenesis

The endocrine and exocrine function of the testis is controlled by the pituitary through the secretion of LH and FSH. The time needed for the full development of spermatozoa from the spermatogonia, including maturation in the epididymis, is three months. The major determinants which may affect testicular function are diseases (e.g. mumps orchitis, varicocele) and exogenous androgens (see e.g. Schally et al. 1972,

Bardin & Paulsen 1981, Krause 1984). Physical exercise may also transiently influence the testicular endocrine function (Aakvaag et al. 1978).

Testosterone and/or anabolic steroids have long been studied as agents for male contraception (see e.g. Heller et al. 1950, Brenner et al. 1975), but only few studies have been published concerning the androgenic effects on spermatogenesis in athletes during training (Johnson et al. 1972, Holma 1977a,b, Schürmeyer et al. 1984). During anabolic steroid or testosterone treatment sperm production falls and may induce azoospermia (Holma 1977, Steinberger & Smith 1977). Sperm motility seems to remain normal (Holma 1977a,b, Schürmeyer et al. 1984), but sperm morphology changes are remarkable (Holma 1977a,b, Mauss et al. 1975). The seminal fluid volume remains unchanged (Mauss et al. 1978, Schürmeyer et al. 1984), but seminal fluid acid phosphatase activity may decrease (Holma 1977b) during testosterone or anabolic steroid treatment. The seminal fluid fructose concentration remains unchanged during nandrolone treatment (Schürmeyer et al. 1984) but may decrease during testosterone treatment (Börsch et al. 1974).

As a consequence of androgenic effects on the testicular endocrine and exocrine function the size of the testes may decrease markedly (Brotherton 1976, Schürmeyer et al. 1984). It has been suggested that the effects of testosterone or anabolic steroids on the size of the testes and on spermatogenesis is reversible (Bremner & de Kretser 1976, Mauss et al. 1978, Schürmeyer et al. 1984), even though little is known about their long-term effects.

### 2.3.4. Serum lipids

Possible major environmental determinants of serum lipids and lipoproteins include diet, physical exercise, alcohol intake and cigarette smoking. Sex, age and body weight are also reflected in serum lipids (see e.g. Sternby 1980, Miller & Miller 1981).

Serum lipid concentrations are under differential hormonal regulation (see e.g. Eder 1958). Endogenous serum (free and total) testosterone levels are positively correlated with HDL-cholesterol but negatively correlated with VLDL-cholesterol and TG. No correlation between serum concentrations of testosterone and LDL- or total cholesterol (Gutai et al. 1981, Mendozo et al. 1981, Heller et al. 1983) has been detected.

Exogenous testosterone, anabolic steroids and progestational steroids may decrease the serum concentrations of VLDL and HDL and increase LDL levels, whereas the levels of serum TG and total cholesterol may not be affected (Furman et al. 1958, Solyom 1971, Silfverstolpe et al. 1979, Tamai et al. 1979, Hirvonen et al. 1981, Haffner et al. 1983, Hurley et al. 1984). However, little is known about exogenous androgenic steroid effects on HDL subfractions in men. Tikkanen et al. (1983) have recently reported that norgestrel decreases the serum concentration of $HDL_2C$ in women.

It has been suggested that the effects of exogenous androgens on serum lipids and lipoproteins are reversible (Taggart et al. 1982), but little is known about the long-term consequences.

### 2.3.5. Liver function

The liver synthesizes cholesterol, and triglycerides are converted in the liver into lipoproteins by a combination with hepatic apoproteins. The liver also plays a key role in the inactivation of a variety of steroid and peptide hormones (see e.g. Corless & Middleton 1983).

Treatment with exogenous androgens may cause a disturbance of liver function which may be observed by measuring changes in the activities of serum AFOS, ALAT, ASAT and γ-GT and in the concentration of serum bilirubin (Nishino 1975), and also lipids and lipoproteins (see section 2.3.4.).

Infrequent and slight serum aminotransferase elevations owing to the use of exogenous androgens are the most commonly observed aberrations in patients and athletes (O'Shea 1974, Hagerman et al. 1975, Nishino 1975, Hervey et al. 1976, Keul et al. 1976). In some cases the disturbance of liver function has been associated with clinical jaundice, which, however, has been almost always reversible. Every patient in whom jaundice develops after treatment with anabolic steroids has received compounds containing a methyl or ethyl group in the 17α position (e.g. methyltestosterone, methandienone) (Adlercreutz & Tenhunen 1970, Nishino 1975). Some dangerous liver lesions, such as peliosis or tumors have been reported in some patients treated with synthetic anabolic steroids (Westaby & Williams 1981, Turani et al. 1983).

Hepatocellular carcinoma has recently been for the first time reported in an athlete without any previous disease but with prolonged experience in the use of several anabolic steroids (Overly et al. 1984). However, on the basis of one case only it is difficult to make any generalizations concerning causal relationships.

### 2.3.6. Other effects

In mature males androgenic steroid therapy can lead to increased facial and body hair, increased sebaceous secretions, acne and to alopecia (Houssay 1976). Gynecomastia has also been observed in association with the use of testosterone and certain anabolic steroids (Bardin & Paulsen 1981, Lamb 1984).

Fluid retention often accompanies the use of exogenous androgens, owing to sodium and cloride retention induced by those steroids (Landau 1976). In addition, exogenous androgens may induce high blood pressure in some individuals (Freed et al. 1975). A case of Wilm's tumor in the kidney has been reported in an athlete who had a long history of anabolic ste-

roid misuse (Prat et al. 1977). Again, no conclusions as to a possible causal relationship should be made on the basis of one case only.

Psychological changes associated with a high dose use of exogenous androgens include subjective increases or decreases in libido, increased aggressive behaviour, mood elevation or depression and occasional psychotic disorders (Freed et al. 1975, Herrman & Beach 1976, Wright 1980).

Apparently androgenic-anabolic steroids induce an increase in total red cell volume by stimulating the production of erythopoeitin (Gurney 1976). There is, however, no substantial evidence to support the use of anabolic steroids for improving aerobic work capacity (Lamb 1984).

Scientific evidence on the effect of anabolic steroids on muscular development is conflicting. This conflict may in part result from the difficulty in accurately comparing the results obtained because of a lack of uniformity in experimental designs. For example, the experiments differ with respect to the length of the experimental period, the strength training loading used, the pretraining strength level of the subjects/athletes and, expecially, the doses of the androgenic-anabolic steroids used by the subjects (see Haupt & Rovere 1984).

Recent findings suggest that the high-dose use of testosterone and/or anabolic steroids may increase muscle mass and strength more than strength training alone. This is apparent in power athletes with a previous long training experience before the use of steroids but not in athletes still at an initial stage in their sports career (Hervey et al. 1981, Alèn et al. 1984, Haupt & Rovere 1984). The use of anabolic steroids may also increase the training motivation of some athletes, which naturally reflects on the development of performance capacity (see e.g. Freed et al. 1975, Wilson & Griffin 1980, Lamb 1984).

## 2.4. Hormonal and metabolic effects of strength training

The response of the endocrine and metabolic system to exercise stress depends on the type and duration of physical activity (Aakvaag et al. 1978, Remes et al. 1979, Kuoppasalmi et al. 1981). Moreover, physical fitness status may influence endocrine and metabolic responses in the body to exercise stress (see e.g. White et al. 1976).

There are a number of investigations on changes in the endocrine and metabolic system resulting from such sports as sprinting, marathon running, jogging and cross-country skiing etc (see Terjung 1979, Galbo 1983, Kuoppasalmi & Adlercreutz 1984). However, only a few isolated results are available on the effect of strength training on serum hormones, lipids, enzymes or other indicators of physiological responses to such exercise stress.

In a recent study by Häkkinen et al. (1985), it was reported that during a prolonged (six month) strength training period there were increases in serum testosterone, as well as in testosterone to cortisol and testosterone to SHBG (sex hormone binding globulin) ratios. The findings also suggested that the decrease in serum testosterone to cortisol ratio may indicate over-strain. No significant changes were observed in the concentrations of serum estradiol, LH, FSH, prolactin and somatotropin during strength training. In contrast, no changes in testosterone levels were observed during shorter strength training periods in some previous studies (Young et al. 1976, Hetrick & Willmore 1979).

Earlier observations by the present author suggest that weight training with or without testosterone and anabolic steroids does not affect serum total cholesterol (Alén & Rahkila 1984). Furthermore, Farrell et al. (1982) have reported that intensive weight training does not affect serum levels of total cholesterol. Moreover, no significant differences were found by Farrell et al. (1982) in serum levels of total cholesterol or triglycerides between speed skaters, weightlifters and non-athletes. The mean HDLC concentration in serum was

similar in the non-athletes and weight lifters but was significantly higher in the speed skaters. It was concluded that, in contrast to endurance training, intensive weight training does not increase the serum concentration of HDLC (Farrell et al. 1982). Johnson et al. (1983) and Goldberg et al. (1984) have recently reported that middle-aged men who have previously been sedentary can expect an increase in HDLC and a decrease in low density lipoprotein cholesterol from weight training.

Physical exercise may result in an increase in the activity of several serum enzymes originating from the muscle, provided that the exercise is of sufficient intensity and/or of sufficient duration (Tiidus & Ianuzzo 1983). The increases are particularly evident for creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and ASAT enzymes, which are found in high concentrations in muscle cells (Buyze et al. 1976). Moreover, the increase in enzyme activity is the higher the more strenous the physical exercise. Several authors have shown that the increase is greater for untrained than for trained subjects when both groups are subjected to the same physical strain (Buyze et al. 1976, Tiidus & Ianuzzo 1983).

It has been reported that muscle rupture may increase the levels of serum CPK but not LDH, ALAT and ASAT (Thorblad et al. 1983).

## 2.5. Concluding remarks

The use of anabolic drugs by power athletes has spread rapidly. The current regimens used for hormone doping include combinations of injectable and oral preparations of testosterone and anabolic steroids at doses 10 to 40 times greater than dose prescribed therapeutically.

Most of the studies of androgenic-anabolic steroid used by healthy male athletes have been short and/or the steroid doses administerd have been much lower than the doses used by power athletes. The studies on patients treated by androgenic-

anabolic steroids because of some disease are not directly applicable to healthy athletes.

The use of testosterone or anabolic steroids in therapeutic doses by healthy male athletes has led to minor, reversible endocrine and metabolic changes. However, the health risks associated with prolonged self-administration of high-dose testosterone and anabolic steroids are not known.

Intensive strength training of prolonged duration without the use of exogenous androgens has an influence on endogenous steroid production. Decrease in serum testosterone and cortisol ratio during strenuous exercise in some cases may indicate over-strain. On the other hand, strength training as a fitness sport may decrease the risk of atherosclerotic heart disease by increasing serum HDL-cholesterol, and by decreasing serum LDL-cholesterol.

## 3. PURPOSE OF THE PRESENT INVESTIGATION

The aim of the present study was to elucidate the metabolic and hormonal effects to which top-level power athletes were exposed when they self-administered high doses of testosterone and anabolic steroids for several months.

The main focus was on serum hormones and lipids, on spermatogenesis, and on liver function, with an investigation of the effects of self-administered high-dose testosterone and anabolic steroids (methandienone, nandrolone and stanozolol)

- on the concentrations of serum LH, FSH, ACTH, prolactin, testosterone, estradiol and cortisol
- on semen volume, sperm concentration, motility and morphology, on seminal fluid acid phosphatase activity and fructose concentration and on testicular volume
- on the concentrations of serum triglycerides, total cholesterol, LDLC, HDLC, $HDL_2C$ and $HDL_3C$
- on the activities of serum ASAT, ALAT, $\gamma$-GT, AFOS and on the concentration of serum total bilirubin

# 4. MATERIAL AND METHODS

## 4.1. Design of the study

The examinations and measurements for the present investigation were made prospectively over 54 weeks, from 07.07.1982 to 21.07.1983 (Figure 1). Later some semen and blood samples were also studied from 4 experimental subjects after at least 7 months abstinence from the use of androgenic-anabolic hormones.

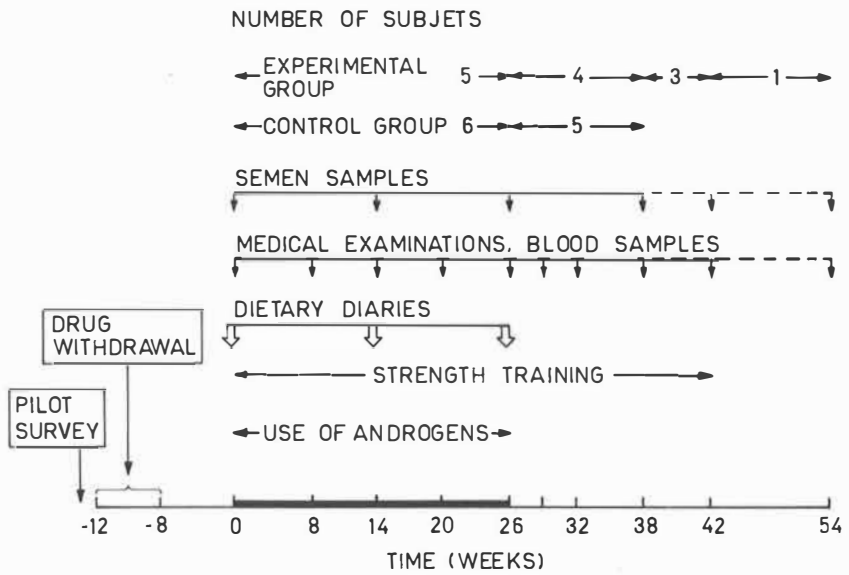


Figure 1. Design of the present study

## 4.2. Subjects

The selection procedure for the subjects for the present investigation is presented in Figure 2.

In the Jyväskylä region there were about 250 power athletes (bodybuilders, powerlifters, weightlifters and wrestlers). Eighty six of them were interviewed by the author after they had, on a voluntary basis, entered as patients the clinic of the Research Unit for Sport and Physical Fitness (Figure 2). Later, during their second visit to the physician, 33 power athletes (experienced in the use of exogenous androgens) filled out a confidential questionnaire in which information was sought concerning their habits of taking testosterone and anabolic steroids, their training and competition background and their future plans for training and hormone use. Seven athletes without experience in the use of androgens also filled out the same questionnaire. A total of twenty-seven of the 40 athletes volunteered for the study. Of them, seven power athletes were selected for the experimental group on the following grounds (see Figure 2):

- they had approximately the same training background and were elite athletes in their respective sport events
- they had all abstained from hormone use for at least eight weeks
- they had individual self-planned programmes for the self-administration of testosterone and the following anabolic steroids: methandienone, nandrolone and stanozolol
- they all planned to train for about six months, continuously, self-administering the above mentioned androgens during the next training period.

Of the androgen users, 11 were excluded from the study because of a substantially lower ranking status in their sport event or because of an abstinence from hormone drugs shorter

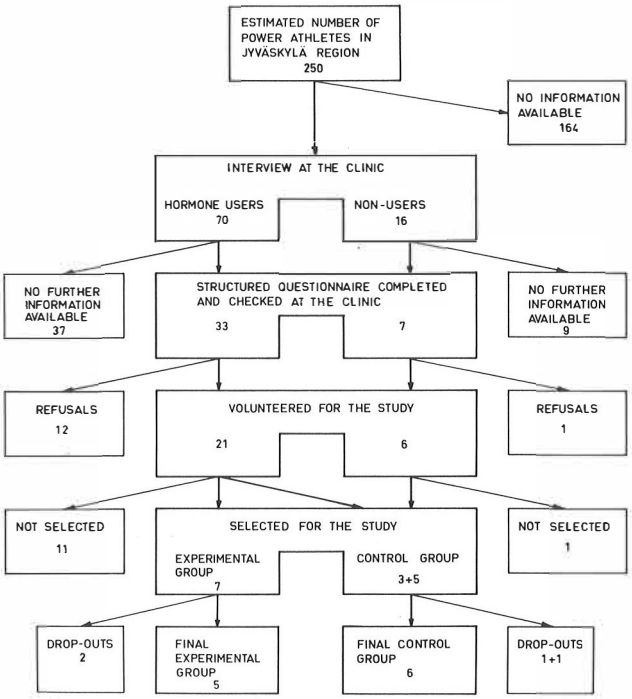


FIGURE 2. Schematic presentation of the subject selection procedure for the prospective investigation.

than eight weeks and/or essentially different regimens in the use of drugs (Figure 2).

For the control group 8 power athletes were selected on the following grounds (see also Figure 2):

- they had the same training background as the athletes in the experimental group (age, number of years of training)
- they had a status in their respective sport events almost equivalent to that of the athletes in the experimental group
- they did not aim at using testosterone or other anabolic hormones during the next training period, and in addition had at least 12 weeks' abstinence from the use of drugs.

From both groups two subjects selected for the present investigation were excluded on the following grounds: The control subjects, because of essential changes in their training programme, and the androgen users, because of their inability to participate in the study after the initial period (Figure 2). However, they were all included in paper II until the time they dropped out of the study except for one control subject because of his unwillingness to deliver a semen sample.

The physical characteristics of the final groups studied are given in Table 1.

Written informed consent was obtained from each subject, and the investigation was approved by the Ethical Committee of the University of Kuopio. To ensure the human rights of the androgen users, the investigation was carried out on strictly confidential basis; alpha-numeric codes instead of the subjects' names were used in documents.

TABLE 1. Physical characteristics of the experimental and control groups before and after 26 weeks of training. The values indicate the mean ± SD. The intergroup values for significance levels are also given.

| Variable | Experimental group (n=5) | Control group (n=6) | 2-tailed t-test |
|---|---|---|---|
| Age (yrs) | 27.0±5.5 | 25.7±5.0 | N.S. |
| Strength training (yrs) | 7.4±5.9 | 5.5±2.0 | N.S. |
| Height (cms) | 177.8±3.3 | 173.1±4.6 | N.S. |
| Caloric intake (MJ/day) | 15.4±2.1 | 14.7±2.9 | N.S. |
| Weight (kg) | | | |
| Before | 86.8±11.4 | 82.8±6.2 | N.S. |
| After | 92.0±9.2 | 82.2±6.1 | $p<0.05$ |
| Fat free weight (kg) | | | |
| Before | 72.8±7.5 | 70.2±5.3 | N.S. |
| After | 80.6±7.4 | 69.8±5.3 | $p<0.05$ |
| Body fat (%) | | | |
| Before | 15.6±6.4 | 15.3±5.3 | N.S. |
| After | 12.1±4.8 | 14.4±5.4 | N.S. |

## 4.3. Diet, use of drugs and training

Diet, the self-administration of testosterone and anabolic steroids and training were followed by means of structured diaries filled in daily for subsequent control. The dietary caloric intake and the composition of the diet was estimated on the basis of one week diaries completed three times during the investigation (Figure 1).

The self-administration of exogenous androgens was checked by means of two random urine analyses with gas chromatography-mass spectrometry, using the Varian MAT 212 instrument (Joki 1982, see also Kuoppasalmi & Karjalainen 1984). On each occasion, in every experimental subject the random urine analyses were positive for the anabolic steroids listed in the personal medication diaries. Random analyses (Varian MAT 212) to identify the constituents of the compounds self-administered (obtained on the black market) proved that the hormones were used as reported by the participants. No urinary hormone analyses were carried out for the control subjects. The results of semen and serum analyses (see Tables 4 and 5) gave credence to the control athletes assurance not to use drugs.

Diet. The reported mean daily caloric intake in the experimental group was 15400 KJ, and that in the control group 14700 KJ, with a protein intake of 2.3 and 2.6 g x $kg^{-1}$, respectively (Table 1). Caloric intake appeared rather low for power athletes but the mean protein intake was probably adequate (see e.g. Laritcheva et al. 1978, Lemon et al. 1984).

Reported use of drugs. During the first 26 weeks of training the experimental group self-administered anabolic steroids and testosterone (obtained from the black market) in a way similar to the one they had previously got used to (Figure 3). Methandienone was taken orally, with slightly increased doses during the course of training. The intramuscularly self-injected anabolic steroids nandrolone and stanozolol (both 50 mg per injection) were initially taken weekly, but the frequency of the injections increased progressively while the doses injected remained the same. Testosterone (250 mg/

injection, consisting of 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate) was self-administered, initially once to twice per month but at the end of the study an average of four times per month (for other details see papers II and IV).

Training. Both the experimental and the control groups had an intensive strength training programme during the 42 weeks of the study (for details see Alén et al. 1984). Both groups trained for special purposes in their chosen power event, which included no aerobic training but heavy resistance strength training for trunk and upper extremities an average of four times per week. Moreover strength training of the leg extensor muscles was performed 2 times a week according to the programme given. This programme consisted of dynamic squat-lift, leg press and leg extension exercises. The back squat-lift was the main exercise and the load used on the barbell was increased progressively during the whole training period according to one maximum repetition. The intensity of the training on the relative scale varied between 80 and 100% and the subjects performed 1-6 reps per set for a total of 18-26 reps for one training session. In the leg press and leg extension exercises the subjects performed 2 sets with 10 reps per set with the intensity between 70 and 80%. Because the subjects were highly motivated power athletes at top national level and had trained for competitive purposes for an average of 6.4 years (Table 1), the exercises were only randomly supervised. The strength training was intensive in both groups and significant increases in the maximal squat lift of 18.2% ($p<0.001$) and 12.9% ($p<0.01$) respectively occurred in both the experimental and control groups (Alén et al. 1984).

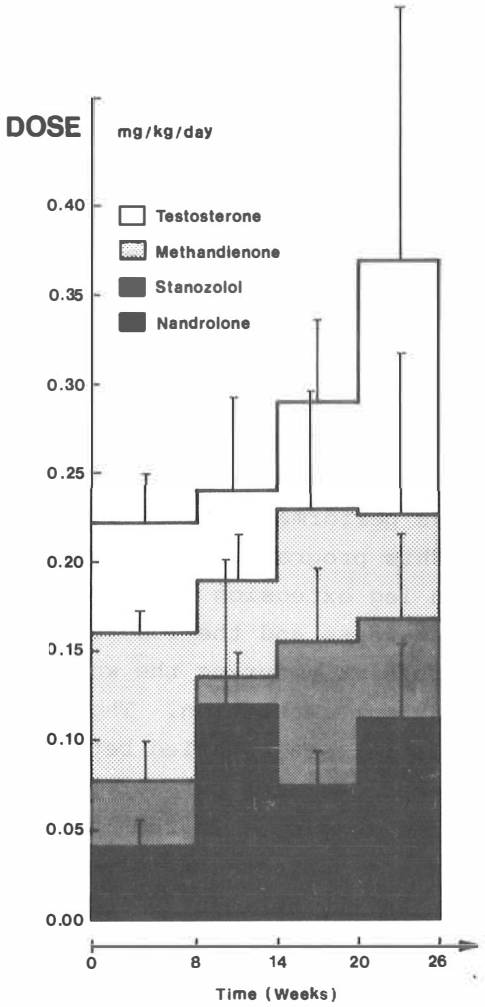


FIGURE 3. Reported mean daily doses (+ SEM) of self-administered testosterone and anabolic steroids (mg/kg/day) of the experimental group (Alén et al. 1985, Paper I)

## 4.4. Clinical examination

The subject's general health status was checked by the author.

For purposes of evaluating the possible contraindications and risks of participation in the study, each subject was examined 9-11 times (see Fig. 1) for blood pressure (mmHg, by sphygmomanometer), the prostate, the liver, the pectoralis major muscles (by manual palpation), and for the testicles (by manual palpation and an orchidometer, Prader 1966). Each subject was also regularly informed by the author about the levels of serum aminotransferases and sperm concentration during the study. However, this information did not lead to any drop-outs or changes in training and drug use.

The height, weight, subscapular, triceps, biceps and crista iliacae skinfold thicknesses of the subjects were measured by the Harpenden instrument. The amount of body fat was estimated according to the method of Durnin & Rahaman (1967). The lean body mass was calculated by subtracting the amount of fat (in kg) from the total body weight (see Table 1). In this study, the same person carried out all skinfold measurements. It has been reported by Katch & Katch (1980) that the test-retest reliability for skinfold measures is above 0.85. In our laboratory the corresponding value has been 0.87.

## 4.5. Collection, handling and storage of blood, semen and urine samples

After one day of reduced training and an overnight fast, the subjects entered the laboratory at 8.00 a.m. for blood sampling. Venous blood samples were drawn from the antecubital vein into clean glass tubes kept on ice. After one hour of clotting the serum was separated by centrifugation at 1500 x g for 15 mins, and the sample was frozen and stored in proper aliquotes at -80 °C for subsequent analyses. These procedures were performed at 0, 8, 14, 20, 26, 32, 38 and 42 weeks of training (see Figure 1).

The semen samples were collected after three to five days of abstinence (excluding two samples from one control athlete in the first and second semen sampling after 1 to 2 days of abstinence) by masturbation (see Figure 1 and Paper II). The handling and analyses of semen samples began within one hour, according to the principles described by Eliasson (1981). For biochemical analyses the semen was centrifuged at 2000 x g for 15 mins, frozen and kept at -20°C until analyzed. The procedures were performed at 0, 14, 26, 38 and 42 weeks of training (see Figure 1).

Random morning urine samples were collected 4 times after the blood samplings, frozen and kept at -20°C for subsequent urine anabolic steroid analyses (as described in detail above).

## 4.6. Serum and semen analyses

All the serum samples were analyzed in duplicate and the analyses for each subject were run in the same series to avoid interassay variation (excluding serum enzyme and total bilirubin analyses used also for health control purposes). Adequate control samples were included in all the series. For other details see Table 2 and the papers I, III and IV and also Jänne et al. (1974), Hammond et al. (1977a,b), Apter et al. (1979), Gidez et al. (1979) and Vihko et al. (1982). The level of serum LDL-cholesterol was calculated according to the formula described by Friedewald et al. (1972).

The semen samples were analyzed according to the principles described by Eliasson (1981) for semen volume, sperm concentration, motility (the percentage of motile spermatozoa and the degree of progressive motility were measured after the incubation of samples for 5-10 mins at 37°C) and agglutination. For the morpohological analyses of spermatozoa and the enumeration of leucocytes, seminal smears were fixed in ethanol-ether (V/V) and stained in Delafield's Haematoxylin-Eosin. To evaluate the secretory function of the prostate, the acid

phosphatase activity of seminal plasma was measured according to Bessey et al. (1946) by using p-nitrophenyl phosphate (Sigma) as a substrate. The fructose concentration, a marker for the seminal vesicles, was determined according to the method described by Mann (1948) (see Table 3).

## 4.7. Calculations and statistical analyses

Means, standard deviations and standard errors were calculated by standard methods. The data were tested for significance by Student's t-test for independent and paired samples. Such calculations were carried out by using the "Statistical Package for the Social Sciences" (SPSS) programme (see Nie et al. 1975).

In the calculations for the mean daily dose/kg the onset body weights for each period between the blood samplings were used.

TABLE 2. Analytical methods for serum parameters measured nine times during the 42 weeks of strength training. Methods, origins of reagents and intra-assay coefficients of variation (CV) are given.

| SERUM PARAMETERS | METHOD | REAGENT | CV% |
|---|---|---|---|
| HORMONES[1] | | | |
| ACTH | RIA | SORIN BIOMEDICA | 9 |
| FSH | RIA | FARMOS DIAGNOSTICA | 8 |
| LH | RIA | AMERSHAM INT. PLC | 5 |
| PROLACTIN | RIA | DIAGNOSTIC PRODUCTS CO | 6 |
| CORTISOL | RIA | FARMOS DIAGNOSTICA | 8 |
| $E_2$ | RIA | FARMOS DIAGNOSTICA | 8 |
| TESTOSTERONE | RIA | FARMOS DIAGNOSTICA | 8 |
| LIPIDS[2] | | | |
| HDLC | HEPARIN $MnCl_2$ PRECIPITATION | SIGMA, MERCK | 3 |
| $HDL_3C$ | DEXTRAN SULPHATE PRECIPITATION | SOCHIBO | 4 |
| TG | ENZYMATIC | BOEHRINGER | 2 |
| TOTC | CHOD-PAP | BOEHRINGER | 2 |
| ENZYMES[2] | | | |
| AFOS | COLORIMETRIC | BOEHRINGER | 6 |
| ALAT | COLORIMETRIC | BOEHRINGER | 4 |
| ASAT | COLORIMETRIC | BOEHRINGER | 4 |
| γ-GT | COLORIMETRIC | BOEHRINGER | 5 |
| OTHER[2] | | | |
| TOTBIL | COLORIMETRIC | BOEHRINGER | 11 |

1) Department of Clinical Chemistry, University of Oulu, Finland

2) Research Unit for Sport and Physical Fitness, Jyväskylä, Finland, except $HDL_3C$ (Rehabilitation Research Center of the Social Insurance Institution, Turku, Finland)

TABLE 3. Analytical methods for semen parameters measured 4-5 times during the 42 weeks of strength training. Methods, origins of reagents, intra-assay coefficient of variation (CV), and references for analytical procedure are given.

| SEMEN PARAMETERS | METHOD | REAGENT | CV%[x)] | REFERENCE |
|---|---|---|---|---|
| Sperm concentration | Microscopic (Bürger-Turk counting chamber) | Hayem (Merck) | 10-15 | Eliasson, 1981 |
| Sperm motility | Microscopic | - | 5-10 | Eliasson 1981 |
| Sperm morphology | Microscopic | Delafield's Haematoxylin-Eosin (Merck) | 2-5 | Eliasson 1981 |
| Acid phosphatase | Colorimetric | p-Nitrophenyl phosphate (Sigma) | 5 | Bessey 1946 Suominen et al. 1983 |
| Fructose | Colorimetric | Resorsinol (Merck) | 2 | Mann 1948 |

x) Department of Anatomy, University of Turku, Finland

# 5. RESULTS

The results are given in detail in the appropriate papers I-IV. They are summarized as follows:

## 5.1. Serum trophic hormones and steroids (Paper I)

The changes in the serum concentrations of FSH, LH, prolactin (PRL), testosterone, estradiol ($E_2$), ACTH and cortisol are shown in Table 4. No significant differences were noticed between the experimental and control groups at the beginning of the investigation.

The concentrations of circulating FSH and LH decreased significantly (see Paper I) during the first eight weeks of drug use and remained at the lowest level of detection during the whole period of hormone use, but returned to the pretreatment level 6-12 weeks after drug withdrawal.

The concentrations of serum testosterone and estradiol had a tendency to increase throughout the period of drug use. The mean concentrations of testosterone and $E_2$ reached at 26 weeks (51 nmol/l and 0.48 nmol/l, respectively) were significantly higher (see Paper I) than at the beginning of the study (22 and 0.07 nmol/l). The peak values were followed by a rapid decrease in those concentrations of testosterone and $E_2$ after drug withdrawal. Serum testosterone levels were significantly lower at 29, 32 and 38 weeks (Paper I) compared with those at the beginning of the study (Table 4).

Four of the androgen users developed gynecomastia, which appeared at 20 weeks and was observed to persist until 12 weeks following drug withdrawal.

The concentrations of the serum trophic hormones and steroids were very stable in the control group, excluding the LH concentrations, which gradually increased in the course of intensive strength training until 26 weeks (Table 4).

TABLE 4. Serum concentrations of ACTH, FSH, LH, prolactin, testosterone, estradiol ($E_2$) and cortisol in the experimental group (EG, n=5) and in the control group (CG, n=6). Mean values, standard deviations and statistical significances of the inter-group differences are given (one-tailed Student's t-test). The experimental group self-administered testosterone and anabolic steroids during the time indicated (0-26 weeks of strength training). (For the number of subjects see also Figure 1).

| | | WEEKS | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | | 0 | 8 | 14 | 20 | 26 | $32_a$ | $38_a$ |
| | | <——— | | | | ———> | | |
| ACTH (ng/l) | EG | 5.0±3.3 | 0.0±0.0 * | 2.4±3.5 * | 1.6±2.9 * | 2.2±1.1 ** | 1.4±1.6 * | 7.3±2.8 |
| | CG | 10.7±6.2 | 9.9±8.0 | 11.5±8.7 | 11.1±5.9 | 10.9±5.9 | 8.8±6.7 | 7.7±4.7 |
| FSH (U/l) | EG | 3.8±3.0 | 0.0±0.0 ** | 0.0±0.0 ** | 0.0±0.0 ** | 0.3±0.4 * | 2.7±4.8 | 2.7±3.3 |
| | CG | 3.0±1.8 | 2.6±1.6 | 2.8±1.8 | 2.3±1.6 | 2.7±2.0 | 2.9±2.2 | 3.2±2.1 |
| LH (U/l) | EG | 3.2±1.1 | 1.2±0.1 ** | 1.4±0.1 ** | 1.2±0.1 ** | 1.5±0.1 *** | 2.3±1.6 | 3.4±3.2 |
| | CG | 4.2±1.6 | 4.0±1.8 | 5.1±1.8 | 5.4±2.5 | 6.7±2.0 | 5.7±1.1 | 5.9±3.0 |
| Prolactin (µg/l) | EG | 17.7±5.5 | 8.5±2.9 | 13.1±5.7 | 17.3±6.2 | 19.7±12.4 | 6.4±2.0 * | 8.2±3.8 |
| | CG | 13.7±5.2 | 11.2±5.4 | 13.3±11.5 | 12.7±7.2 | 14.7±9.7 | 20.6±14.5 | 13.8±10.1 |
| Testosterone (nmol/l) | EG | 22.4±7.7 | 33.2±10.8 | 39.9±22.2 | 35.3±19.3 | 51.2±23.2 * | 8.6±7.5 ** | 10.0±8.5 ** |
| | CG | 27.8±5.6 | 24.4±6.4 | 22.6±4.9 | 23.9±5.2 | 26.0±6.6 | 23.4±3.4 | 24.0±2.6 |
| $E_2$ (nmol/l) | EG | 0.07±.03 | 0.17±.07 ** | 0.27±.14 * | 0.22±.13 * | 0.48±.23 * | 0.06±.03 * | 0.06±.03 |
| | CG | 0.12±.09 | 0.06±.02 | 0.14±.08 | 0.09±.05 | 0.12±.09 | 0.12±.05 | 0.11±.07 |
| Cortisol (µmol/l) | EG | 0.57±.06 | 0.41±.06 | 0.54±.08 | 0.57±.05 | 0.59±.10 | 0.53±.10 | 0.52±.07 |
| | CG | 0.52±.07 | 0.48±.10 | 0.46±.11 | 0.49±.10 | 0.53±.10 | 0.50±.11 | 0.53±.07 |

* $p<0.05$, ** $p<0.01$, ***$p<0.001$, a) EG n=4, CG n=5

## 5.2. Spermatogenesis (Paper II)

The changes in sperm concentration, motility (one hour after ejaculation) and in seminal plasma acid phosphatase activity and fructose concentration as well as in testicular volume are shown in Table 5. At the beginning of the investigation significant differences were noticed between the groups in sperm concentration and in testicular volume (Table 5), but not in sperm motility, morphology (Paper II), acid phosphatase activity, fructose concentration and semen volume (Table 5).

The experienced androgen users were already oligozoospermic at the onset of this investigation and azoospermic at 14 and at 26 weeks. A slow recovery was observed at 38 weeks in the spermatogenesis of the other androgen users, but subject No 3 was azoospermic until 54 weeks (Paper II).

The mean testicular volume decreased in the experimental group by about 25% ($p<0.05$) during the use of drugs, but returned to the initial mean level at 38 weeks.

In the control group the semen parameters were not affected during the intensive strength training, but increases of 20% ($p<0.05$) in mean testicular volumes were observed until 38 weeks (Table 5).

## 5.3. Serum lipids and lipoproteins (Paper III)

The mean concentrations of TG, TOTC, HDLC, $HDL_2C$ and $HDL_3C$ in the course of training are shown in Figure 4 and in Table 6. No significant differences between the groups were noticed at the onset of the present investigation.

Significant changes in serum TG and TOTC concentrations were not seen in either group during the study.

After eight weeks' training the experimental group had a significantly lower HDLC concentration ($p<0.001$) than the control group (Table 6). This difference remained significant from eight to 32 weeks of training. The HDLC serum concentration did not reach the onset value until 12 weeks after the

TABLE 5. Sperm concentration, motility (one hour after ejaculation), semen and testicular volume and seminal plasma acid phosphatase activity and fructose concentration in the experimental group (EG, n=4) and in the control group (CG, n=5). The values indicate the mean ± SD. The intergroup values for significance levels (one-tailed Student's t-test) are also given. The experimental group self-administered testosterone and anabolic steroids during the time indicated (0-26 weeks of strength training).

| Variable | | WEEKS 0 | 14 | 26 | 38[a] |
|---|---|---|---|---|---|
| | | <——— | | ———> | |
| Sperms (x $10^6$/ml) | EG | 5.0±7.3 * | 0.0±0.0 * | 0.0±0.0 ** | 7.0±7.2 ** |
| | CG | 82±72 | 114±91 | 73±39 | 100±59 |
| Motility (%) | EG | 49±2.5 | no | no | 53±2.9 |
| | CG | 47±14 | 46±21 | 49±14 | 54±18 |
| Semen volume (ml) | EG | 3.0±0.7 | 3.5±0.3 | 3.3±1.2 | 3.6±0.8 |
| | CG | 3.0±0.9 | 2.9±1.2 | 2.8±1.2 | 3.7±1.0 |
| Acid phosphatase (x $10^6$/IU/ml) | EG | 30±15 | 32±10 | 31±15 | 16±7 |
| | CG | 33±7 | 38±15 | 41±16 | 28±10 |
| Fructose (mg/ml) | EG | 1.6±0.5 | 2.1±0.9 | 1.5±0.7 | 2.1±0.9 |
| | CG | 2.1±0.5 | 2.0±0.5 | 1.9±0.7 | 2.2±0.2 |
| Testicular volume (ml) | EG | 31±6 ** | 24±4 *** | 23±5 *** | 30±11 ** |
| | CG | 42±6 | 48±5 | 50±3 | 51±1 |

* $p<0.05$, ** $p<0.01$, *** $p<0.001$, a) EG n=4, CG n=4

TABLE 6. Serum concentrations of TG, TOTC, LDLC, HDLC, $HDL_2C$, $HDL_3C$ (mmol/l) and ratios for HDLC to TOTC and $HDL_2C$ to $HDL_3C$ in the groups studied (EG = experimental group, n=5, CG = control group, n=6). The values indicate the mean ± SD. The intergroup values for significance levels (one-tailed Student's t-test) are also given. The experimental group self-administered androgens during the time indicated (0-26 weeks of training). For the number of subjects see also Figure 1 (for empty spaces see Paper III, Table 3).

| Variable | | WEEKS 0 | 8 | 14 | 20 | 26 | $32_a$ | $38_a$ |
|---|---|---|---|---|---|---|---|---|
| | | <——— | | | | ———> | | |
| TG | EG | 1.2±0.3 | 1.6±0.6 | 1.7±0.6 | 1.3±0.4 | 1.3±0.3 | 1.4±0.5 | 1.2±0.2 |
| | CG | 1.1±0.5 | 1.1±0.2 | 1.2±0.5 | 1.3±0.6 | 0.8±0.2 | 0.9±0.2 | 0.9±0.2 |
| TOTC | EG | 5.3±1.6 | 4.6±2.2 | 5.7±3.2 | 5.2±1.7 | 5.4±1.8 | 5.3±1.5 | 5.4±1.2 |
| | CG | 5.2±1.4 | 4.8±1.0 | 5.0±0.9 | 5.2±1.4 | 4.9±0.8 | 4.9±1.1 | 4.9±0.9 |
| LDLC | EG | 3.1±1.5 | 3.3±2.1 | 4.4±3.0 | 3.9±1.7 | 4.2±1.7 | 3.8±1.5 | 3.6±1.2 |
| | CG | 3.3±1.4 | 3.0±1.1 | 3.1±1.0 | 3.2±1.0 | 3.2±0.8 | 3.2±1.2 | 3.0±0.9 |
| HDLC | EG | 1.23±.19 | 0.53±.11 *** | 0.52±.20 *** | 0.59±.24 ** | 0.50±.22 *** | 0.79±.25 * | 1.18±.11 |
| | CG | 1.16±.28 | 1.14±.19 | 1.21±.23 | 1.18±.18 | 1.23±.24 | 1.19±.12 | 1.26±.15 |
| $HDL_2C$ | EG | 0.363±.065 | 0.071±.040 * | 0.099±.128 ** | 0.092±.101 ** | 0.076±.063 ** | | |
| | CG | 0.370±.140 | 0.425±.126 | 0.504±.225 | 0.411±.144 | 0.406±.142 | | |
| $HDL_3C$ | EG | 0.870±.173 | 0.458±.090 ** | 0.476±.131 ** | 0.474±.160 ** | 0.487±.153 ** | | |
| | CG | 0.793±.108 | 0.717±.078 | 0.812±.118 | 0.771±.108 | 0.821±.109 | | |
| HDLC/TOTC | EG | 24±2.5 | 15±5.0 * | 11±3.6 ** | 13±3.7 ** | 11±2.8 ** | 16±2.8 | 22±2.6 |
| | CG | 24±3.8 | 25±3.2 | 25±3.4 | 24±4.9 | 26±3.6 | 25±2.9 | 27±3.6 |
| $HDL_2C/HDL_3C$ | EG | 43±5.2 | 16±4.3 *** | 17±9.5 * | 16±6.3 ** | 14±3.2 ** | | |
| | CG | 46±6.7 | 59±6.3 | 49±7.6 | 54±9.6 | 49±6.2 | | |

* $p<0.05$, ** $p<0.01$, *** $p<0.001$, a) EG n=4, CG n=5

cessation of the self-administration of androgens. No changes were observed in the HDLC concentration of the control group (Figure 4, Table 6).

A reduction in $HDL_2C$ and $HDL_3C$ was also noticed in the experimental group. $HDL_2C$ decreased by about 80% ($p<0.01$) (Figure 4) and $HDL_3C$ by about 55% ($p<0.01$) from the onset values (Paper III). Furthermore, a substantial decrease in the HDLC to TOTC ($p<0.01$) and $HDL_2C$ to $HDL_3C$ ratio ($p<0.01$) was observed (Table 6, Paper III). At the end of the follow-up period the HDLC to TOTC ratio reached the onset value.

Moreover, the circulating LDLC concentrations had a tendency to increase during the use of exogenous androgens (Figure 4).

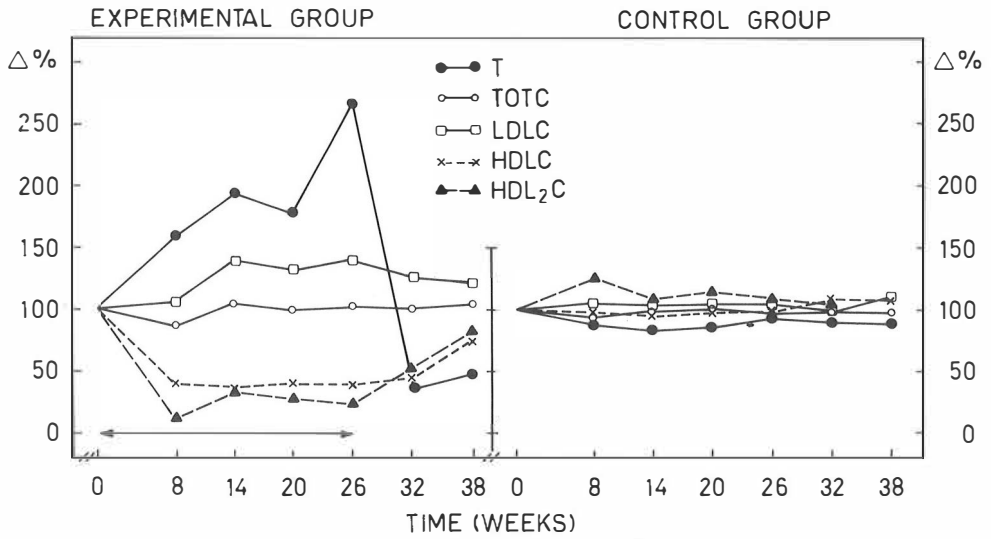


FIGURE 4. Serum concentrations of testosterone (T) TOTC, LDLC, HDLC and $HDL_2C$ of the male power athletes on a relative scale (Δ%) in the course of strength training. The experimental group self-administered androgens during the time indicated (0-26 weeks). Calculations were made using each individual baseline value as 100%.

## 5.4. Serum enzymes and total bilirubin (Paper IV)

The mean values of serum ASAT, ALAT, AFOS, γ-GT and TOTBIL during strength training are shown in Table 7. No significant differences were observed between the experimental and control groups at the beginning of the investigation.

The pattern of serum ASAT activities increased significantly ($p<0.05$) during the first 14 weeks of drug administration and remained at this higher level at 20 and 26 weeks (Paper IV). After drug withdrawal the values returned to the onset level in 12 weeks. There was a statistically significant difference between the groups studied in serum ASAT levels at 26 weeks (Table 7).

The activities of serum ALAT and AFOS were at a higher level in the experimental group than in the control group. However, their mean values remained within the health-associated reference interval in both groups during the investigation. At 20 weeks the intergroup difference was significant for ALAT values (Table 7).

Serum γ-GT activities decreased significantly ($p<0.05$) in the experimental group initially at 14 weeks, and also remained at this lower level during the use of steroids (Table 7).

There were no systematic changes from the initial concentrations of serum total bilirubin in the experimental and control groups (10.7 and 10.5 μmol/l, respectively) (Table 7).

The activities of serum ASAT, ALAT, AFOS, and γ-GT in the control group were stable during strength training (Table 7).

## 5.5. Other findings

The physical well-being and blood pressure of the subjects during strength training and androgen use was not affected. The results of the hematological parameters during the investigation are given in Paper IV.

In the four experimental subjects additionally studied after a minimum of 7 months' abstinence from the use of androgenic-anabolic hormones (see p. 27), all of the above changes were observed to return to initial levels, i.e. did not differ from those of the control group. For example, at the onset of the study, the sperm concentration of the control and experimental groups was 82 mio./ml and 5 mio./ml, respectively. However, at the time the additional measurement was carried out on the four experimental subjects, their mean sperm concentration had reached a level comparable to that of the control subjects, being 84±11 mio/ml. Also, testicular volume in the four experimental subjects was observed to assume normal adult levels of 47±4 ml (see Table 5).

TABLE 7. Serum levels of AFOS, ALAT, ASAT, γ-GT and total bilirubin (TOTBIL) in the groups studied (EG = experimental group, n=5, CG = control group, n=6). The values indicate the mean ± SD. The intergroup significance levels (one-tailed Student's t-test) are also given. The experimental group self-administered androgens during the time indicated (0-26 weeks of strength training). For the number of the subjects see also Figure 1).

| Variable | | WEEKS 0 | 8 | 14 | 20 | 26 | 32[a] | 38[a] |
|---|---|---|---|---|---|---|---|---|
| | | <——— | | | | ———> | | |
| AFOS (U/l) | EG | 191±81 | 207±127 | 174±92 | 187±95 | 167±78 | 192±84 | 170±64 |
| | CG | 156±54 | 161±54 | 166±61 | 153±52 | 146±74 | 149±55 | 144±48 |
| ALAT (U/l) | EG | 34±8 | 37±17 | 30±14 | 34±4* | 33±12 | 24±5 | 24±4 |
| | CG | 24±12 | 24±10 | 22±12 | 22±10 | 22±9 | 25±15 | 24±14 |
| ASAT (U/l) | EG | 34±8 | 42±10* | 57±16** | 48±13** | 55±20* | 42±12 | 32±11 |
| | CG | 28±10 | 26±9 | 27±6 | 24±5 | 29±6 | 27±4 | 33±13 |
| γ-GT | EG | 26±10 | 17±10 | 18±6 | 16±5 | 16±5 | 15±3 | 23±10 |
| | CG | 21±6 | 20±7 | 18±6 | 20±5 | 21±5 | 20±6 | 20±5 |
| TOTBIL (μmol/l) | EG | 11±4 | 7±2 | 8±3 | 13±8 | 13±6 | 7±2 | 7±2 |
| | CG | 11±2 | 9±3 | 12±6 | 11±5 | 14±5 | 15±8 | 12±5 |

* $p<0.05$, ** $p<0.01$, a) EG n=4, CG n=5

# 6. DISCUSSION

## 6.1. General aspects

The present investigation was performed to clarify the consequences of a prolonged high-dose use of testosterone and anabolic steroids (methandienone, stanozol, nandrolone) in adult male power athletes, as it takes place in power sport events. The confidential approach was selected because it is the only possible way of carrying out prospective study under the present regulations concerning doping in sports in Finland. Moreover, in Finland it is illegal to prescribe any anabolic hormone to a healthy person, including athletes. However, the experimental design was ethically acceptable according to the regulations of the University of Kuopio. The double blind design was not considered for adoption in this investigation because athletes can apparently always recognize the effects of androgenic steroids (Freed et al. 1975, Crist et al. 1983).

This investigation involved several problems, including the following: Firstly, the power athletes did not agree with an abstinence time from androgens longer than 8-12 weeks. The time needed for the testicles to recover after prolonged androgen administration may be more than 15 weeks (Mauss et al. 1978, Schürmeyer et al. 1984). This was reflected in low initial sperm concentrations and testicular size in the experimental group, and to some degree also in the control group (Table 5). Furthermore, some other initial measures such as serum ACTH, AFOS, ALAT in the experimental group may have been affected for the same reason.

Secondly, the uncontrolled self-administration of testosterone and anabolic steroids by the athletes could be a major problem as far the reliability of the experimental situation is concerned. For this reason only a small number of athletes could be selected for the prospective part of this study. The amount of drugs used was verified by a diary, which was checked regularly during the investigation.

The frequency of drug taking (methandienone daily, with an average of 12 injections of the other androgens per month) was observed to be high enough not to cause confusing fluctuations in the parameters studied (Paper IV). To insure that data from the medication diaries were correct, urinary anabolic steroid assessments were performed in two random sample series giving expected results. However, it was not possible to estimate the exact dose-effect relations because of the differences in individual drug protocols and the small number of subjects participating in the study.

In healthy males serum levels of hormones, lipids and enzymes and also semen constituents may be affected by several factors, such as age, diet, alcohol, drugs and physical activity (see e.g. Freer & Statland 1977, Burslem et al. 1978, Dufaux et al. 1982, Malkin 1984, White et al. 1984).

In the present investigation the subjects entered the laboratory after a 12 hour fast. Furthermore, the diet of the subjects was controlled by diaries (three times for one week each during the study) and found to involve approximately the same caloric and nutritient content (Table 1). The subjects were non-smokers and only one had taken alcohol regularly; however he was informed that he should not take alcohol for three days before the blood samplings (Papers III, IV). The participants were not taking iron-preparates at all, but were usually taking a combination of B-vitamins on a regular basis. Such factors are unlikely to have had any major effects on the results.

The measured serum parameters may also change with the time of blood collection (Williams 1981), with posture (Felding et al. 1980) and because of physical (King et al. 1976) or psychological (Adlercreutz et al. 1982) stresses during the preceding 24 hours. Therefore, in order to minimize variation in study conditions the athletes entered the laboratory after one day's rest or reduced training and after a normal 7-8 hours night sleep. Blood samples were taken at 8.15-9.00 in the recumbent position.

## 6.2. Findings and conclusions

The present prospective investigation differed from most previous training studies with respect to the large doses, polypharmacy and the long duration of androgen use (see e.g. the reviews of Wright 1980, Ryan 1981, Lamb 1984). The polydrug misuse phenomenon in power athletes has recently been reported by some authors (Hill et al. 1983, Strauss et al. 1983, Frankle et al. 1984, Hurley et al. 1984, Overly et al. 1984).

Recommendations for androgen treatment in clinical practice (see Kochackian 1976, Goodman & Gilman 1980) do not involve figures for doses/kg/day, but for doses per day. However, on the basis of recommendations (see Murad & Haynes 1980) for replacement therapy for androgen deficiency (methandienone 5 mg/day or stanozolol 6 mg/day or nandrolone 50 mg/months or testosterone 250 mg/month) the athletes in the experimental group exceeded the therapeutic dose an average of 5-12 times in the course of strength training (see also Hurley et al. 1984).

It has been suggested (Saartok 1983) that the relatively low receptor affinities characterizing methandienone, stanozolol and nandrolone may explain why high doses are used to obtain more potential anabolic effects. Furthermore, the suppression of endogenous testicular testosterone production because of androgen use (see e.g. Mauss et al. 1975) may be a reason for increasing doses in the course of training.

A prolonged high-dose self-administration of testosterone and anabolic steroids induced profound endocrine changes in the experimental subjects. The rapid decrease in circulating FSH and LH concentrations during self-treatment was most likely caused by hypothalamic and pituitary negative feedback effects of exogenous androgenic steroids (Holma & Adlercreuz 1976, Clerico et al. 1981), testosterone (Mauss et al. 1975) and/or its metabolites, such as 5 α-dihydrotestosterone (Kuhn et al. 1984) and estradiol (D'Agata et al. 1981). Accordingly, testicular endocrine and exocrine functions were impaired during the use of androgens and a very small mean testicular

size was observed in the experimental group. Prolonged androgen treatment may induce testicular atrophy (Foegh 1983, Schürmeyer et al. 1984). Such observations also indicate that 12 weeks abstinence after a prolonged high dosage use of androgens is too short a time for endocrine glands to recover completely. The low level of serum testosterone until 12 weeks after drug withdrawal strengthens the observation of long-lasting testicular impairment, which was also reflected in the slow recovery of testicular sperm production.

Because of the previous use of androgens (case 8 and 10, see Table 2 in Paper II) and too short an abstinence time from sexual activity (1-2 days) before ejaculate sampling (case 10) in the first and second semen samplings (see also Methods), the mean number of spermatozoa and mean testicular size were observed to increase during the training period in the control group. However, in general the semen parameters remained very stable during the intensive training period in the control group.

Gynecomastia was observed in four of those androgen users, most likely because of the high level of serum estradiol (Dimick et al. 1961, Wright 1980). It was slowly reversible, because two out of those four had gynecomastia over 12 weeks.

In line with the recent observations of Costill et al. (1984), Hurley et al. (1984) and Peterson & Fahey (1984), the prolonged use of the androgens by the power athletes also resulted in changes in some serum lipoprotein levels. A remarkable decrease in HDLC, $HDL_2C$ and $HDL_3C$ concentrations already appeared by 8 weeks in the experimental group. The concentrations did not decrease further despite progressively increasing mean daily doses. In the experimental group the concentrations of $HDL_3C$ and especially $HDL_2C$ returned slowly to the initial level following drug withdrawal (in Paper III, Table 3). Furthermore, the HDLC to TOTC and $HDL_2C$ to $HDL_3C$ ratios decreased by 8 weeks to a level not seen in control subjects. These ratios remained low during exposition of the drugs. The HDLC to TOTC ratio did not return to the initial level until 12 weeks after drug withdrawal.

It has been suggested that the incidence of atherosclerotic heart disease is correlated positively with serum LDLC concentrations and negatively with serum HDLC concentration (Miller et al. 1977, Carlson et al. 1979, Kannel et al. 1979). Low serum levels of HDLC and $HDL_2C$ may be risk factors for coronary heart disease, independently of other factors such as TOTC, LDLC, TG, blood pressure, smoking habits and body weight (Kannel et al. 1979, Miller et al. 1977, Wilson et al. 1980).

The studies of stanozolol treatment by Taggart et al. (1982) suggest that intermittent androgen administration in therapeutic doses might not have atherogenic effects on lipoprotein profiles. However, a prolonged high-dose use of androgens with abstinences of no longer than 4 weeks a year, as in the present study (see Paper III, Table 3, subject No 1), induce changes in serum lipoproteins, which may increase the risk of a later development of coronary atherosclerosis. More investigations are needed to elucidate the long term consequences of these lipoprotein changes observed for the cardiovascular health of power athletes using high doses of exogenous androgens. Such investigations are particularly called for in case the misuse of anabolic hormones will continue despite efforts to prevent it.

With regard to the liver function the results of the present investigation are in line with several other studies (Hagerman et al. 1975, Keul et al. 1976, Schürmeyer et al. 1984). The changes in serum enzyme activities and total bilirubin levels were small in the experimental group, indicating an abscence of any serious cholestasis or other serious damage of liver cells.

However, serum ALAT activities tended to be at a higher level in the experimental group than in the control group. After drug withdrawal, the serum ALAT values decreased within 12-16 weeks to a level approximating that of the control group (Paper IV). Despite the minimal difference observed between

the experimental and control groups in serum ALAT activities, the possibility must be taken into consideration that in some cases, serious liver damage may result from the use of anabolic hormones (see e.g. Overly et al. 1984).

A year and half later and after at least 7 months' abstinence from exogenous androgens, serum hormones, lipids, lipoproteins and enzymes and also sperm concentration and motility did not differ from the values of the controls in four of the athletes in the experimental group (one did not agree to an abstinence from drugs longer than six weeks). Furthermore, the mean testicular size returned to a level not different from that of the controls and the gynecomastia disappeared. The hormonal and metabolic indicators of actual health studied here, then, seem to be completely reversed. However, the long-term consequenses of such temporary changes in organs and systems of the body remained obscure.

## 7. SUMMARY

The aim of this study was to elucidate the effects of self-administered testosterone and anabolic steroids in relation to some aspects of endocrinology, and the metabolism in top-level power athletes. The main attention was focused on the effect of a prolonged simultaneous use of high dose testosterone with methandienone, stanozolol and nandrolone on serum LH, FSH, ACTH, prolactin, testosterone, estradiol and cortisol, on triglycerides, total cholesterol, LDL, HDL, $HDL_2$ and $HDL_3$ -cholesterol and on spermatogenesis and liver function.

Altogether 11 national top-level power athletes completed the prospective 38 to 42 weeks of investigation. The experimental group consisted of five subjects, and the control group of six subjects. During the first 26 weeks of strength training the subjects in the experimental group self-administered testosterone and anabolic steroids in doses which exceeded the therapeutic dose, initially by 5 and finally by 12 times.

Because of the illegal nature of drug use (in obtaining supplies and self-administration), standard scientific study protocols could not be adopted. However, individual medication diaries, urinary sample analyses and random analyses to identify the constituents of the compounds obtained all proved that the hormones were used as reported by the participants.

At the beginning of the investigation no significant differences were noticed in the variables studied between the experimental and control groups, with the exception of testicular size and sperm concentrations, which were at a lower level in the experimental group, most likely because of the previous use of exogenous androgens.

In the experimental group, after 26 weeks of testosterone and anabolic steroid use serum testosterone had increased 2.3-fold. This was associated with a 7-fold increase in serum estradiol concentrations, to values typical for females, leading to gynecomastia in four of the androgen users. There was a significant decrease in serum FSH and LH concentrations

to the lowest level of detection. Testicular function was greatly impaired, as seen from the very low serum testosterone concentrations following withdrawal from the drugs and from azoospermia and decreased testicular volume.

In the course of 12-16 weeks following withdrawal from the drugs the observed endocrine phenomena began to return slowly towards the initial values. However, serum testosterone concentrations and sperm concentrations stayed at a subnormal level for at least 12-16 weeks after withdrawal from the drugs, indicating long-lasting impairment of testicular function.

In the experimental group significantly decreased HDL, $HDL_2$ and $HDL_3$ -cholesterol serum concentrations were also detected. A slow return towards the initial values was observed in serum concentrations of HDL-cholesterol and its subfractions after withdrawal from the drugs until 16 weeks. The serum total cholesterol level was not affected. Serum ALAT, AFOS, γ-GT and total bilirubin remained within health-associated reference interval during the use of exogenous androgens.

The additional measurement of four experimental subjects after 7 months' abstinence showed that both the hormonal and metabolic changes observed had assumed normal levels not different from those of the control subjects.

In the control group there were only insignificant fluctuations in the hormone variables measured. One exception was the significant increase in serum LH during the most intensive strength training period. Strength training did not affect serum lipids and lipoproteins or liver function.

Based on the findings of this investigation, it is important to continue efforts against hormone doping in sports because there are real potential health risks if and when, despite more stringent control measures, testosterone and anabolic steroids continue to be used in high doses for prolonged

periods outside of medical control. Therefore, also in physical check-ups on athletes, doctors should continually be cognizant of the possibility of doping substance use by the athlete as the cause of his or her symptoms. Further research is needed, to elucidate the long-term health consequences of androgen misuse which may turn up in subsequent years.

# TIIVISTELMÄ

Tämän tutkimuksen tarkoituksena oli selvittää pitkäaikaisen testosteronin ja anabolisten steroidien yliannostelun vaikutuksia kansallisen huipputason voimailijoiden seerumin hormoni ja lipidi -pitoisuuksiin sekä entsyymiaktiivisuuksiin ja siittiötuotantoon. Tutkituista yhdestätoista vapaaehtoisesta voimaurheilijasta viisi käytti aiemmin omaksumallaan tavalla kuuden kuukauden ajan voimaharjoittelunsa tehostamiseksi testosteronia, metandienonia, nandrolonia ja stanotsololia. Käytetyt annokset olivat aluksi keskimäärin 5 ja lopuksi 12 kertaa suurempia kuin ns. terapeuttiset annokset.

Koska anabolisten hormonivalmisteiden käyttö on kielletty urheilun säännöissä eikä lääkäri ole muutenkaan oikeutettu määräämään niitä terveen henkilön urheilusuoritusten parantamiseksi, standardityyppisiä tieteellisen tutkimuksen asetelmia ei voitu käyttää tutkimusongelman selvittämiseen. Prospektiivinen pitkittäistutkimusasetelma teki kuitenkin mahdolliseksi (strukturoitujen harjoitus-, ravinto- ja lääkepäiväkirjojen avulla) urheilijoiden harjoitusohjelman ja ravintotottumusten ja myös lääkeaineiden käytön yksityiskohtaisen selvittämisen. Lisäksi virtsan hormonianalyysien avulla voitiin todeta lääkepäiväkirjatiedot oikeiksi.

Tutkimuksen alussa ryhmien välillä ei havaittu tilastollisesti merkitseviä eroja tutkituissa muuttujissa lukuun ottamatta koeryhmän urheilijoiden kivesten pienempää kokoa ja siemennesteen pienempää siittiöpitoisuutta kontrolliryhmään verrattuna. Ero johtui mitä todennäköisimmin aiemmasta anabolisten hormonien käytöstä.

Koeryhmässä havaittiin 26 viikon yhtäjaksoisen testosteronin ja anabolisten steroidien käytön seurauksena seerumin testosteronipitoisuuden nousseen 2,3-kertaiseksi lähtöpitoisuuteen nähden. Samanaikaisesti seerumin estradiolipitoisuus oli noussut 7-kertaiseksi (naisille tyypillisiin arvoihin) ja aiheutti gynecomastian neljälle viidestä hormonien käyttäjästä. Täysin odotetusti follikkelia stimuloivan hormonin (FSH)

ja luteinisoivan hormonin (LH) pitoisuudet seerumissa laskivat em. aikana hyvin matalalle tasolle heijastaen aivolisäkkeen eritystoiminnan voimakasta estymistä. Tähän liittyen myös kivesten toiminta heikkeni merkittävällä tavalla. Niiden oma testosteronituotanto oli lähes täysin estynyt, sillä hormonien käytön päätyttyä neljällä koeryhmän urheilijalla voitiin todeta seerumin testosteronipitoisuuden olevan vain hieman naisten viitearvojen yläpuolella. Kivesten toiminnan heikkenemistä kuvasti myös niiden koon pieneneminen 25 %:lla huolimatta poikkeavan pienestä alkutilavuudesta ja siittiöiden täydellinen häviäminen siemennesteestä.

Mainittujen hormonaalisten muutosten lisäksi havaittiin seerumin HDL, $HDL_2$ ja $HDL_3$ -kolesterolin tilastollisesti merkitsevä lasku anabolisten hormonien käytön aikana. Vaikka seerumin kokonaiskolesterolipitoisuus ei muuttunut, saattaa mainittu HDL-kolesterolifraktioiden lasku merkitä lisääntynyttä sepelvaltimotaudin riskiä myöhemmällä iällä.

Hormonien käytön aikana ei maksan toiminnassa todettu seerumin entsyymi- ja kokonaisbilirubiiniarvojen perusteella merkittäviä muutoksia.

Havaitut hormonaaliset ja metaboliset muutokset eivät täysin palautuneet lähtötasolle kolmen kuukauden pituisen hormonien käyttötauon aikana. Neljältä koeryhmän urheilijalta saatiin kuitenkin myöhemmin seitsemän kuukauden tauon jälkeen veri- ja siemennestenäytteet, jotka osoittivat kaikkien havaittujen muutosten palautuneen tutkimuksen ensimmäisten mittaustulosten tasolle. Lisäksi kivesten koko ja siittiöiden määrä olivat jopa ylittäneet lähtötilanteen arvot eivätkä enää poikenneet tilastollisesti merkitsevästi kontrolliurheilijoiden vastaavista arvoista.

Tutkimuksen aikana kontrolliryhmän veri- ja siemennestenäytteissä ei todettu merkitseviä muutoksia lukuun ottamatta luteinisoivan hormonin tilastollisesti merkitsevää nousua kovimman harjoittelujakson loppuvaiheessa.

Tämän tutkimuksen perusteella voidaan todeta, että kuvatunlainen anabolisten hormonien käyttö aiheuttaa huomattavia hormonaalisia ja metabolisia muutoksia elintoiminnoissa ja

elimistössä. Vaikka mainitut muutokset lyhyellä aikavälillä näyttävät olevan palautuvia, ei pitkän aikavälin seurauksista voida vielä tehdä varmoja johtopäätöksiä. Jos hormonidopingia tehostuneesta valvonnasta huolimatta edelleen esiintyy, tulee jatkotutkimuksissa kiinnittää erityisesti huomiota pitkän aikavälin riskien selvittämiseen. Myös käytännön lääkärintyössä olisi urheilijoiden terveystarkastusten yhteydessä edelleen pidettävä mielessä se mahdollisuus, että jotkut urheilijat lisääntyneestä doping-valvonnasta huolimatta saattavat edelleen käyttää doping-aineita. Urheilijoiden seerumin entsyymiaktiivisuuksia (ALAT, AFOS, gamma-GT) ja lipoproteiinipitoisuuksia (HDL) seuraamalla lienee mahdollista ehkäistä potentiaalisten riskien muuttumista joidenkin urheilijoiden kohdalla todelliseksi pysyväksi haitaksi.

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