Side-effects of topical androgenic and anabolic substances and steroids. A short review.

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SUMMARY

There is an increasing interest, including androgenic and anabolic substances (AAS). The uncritical use may be associated with severe adverse effects.
We observed five patients with different patterns of adverse reaction to AAS:
two females and three males, they were identified when seeking medical help and advice. The following adverse effects from of AAS have been observed: deepening of the voice due to topical use of AAS in an anti-cellulite cream; circumscribed hypertrichosis and late onset acneiform eruptions due to testosterone replacement therapy after ovariectomy; homolateral gynecomastia and infertility, acne and striae distensae in males using injectable AAS.
Conclusions: ASS can trigger significant adverse effects. An interdisciplinary approach may be necessary for evaluation. The dermatologists should be familiar with the adverse effects.

KEY WORDS

substances, anabolic androgenic steroids, adverse effects

Introduction

Anti-ageing and body building substances became widely accepted in the 21st century due to modified social and –economiconomical attitudes. Such requirements are characteristic of a visually oriented consumer society. The body is considered to be a marker of social prestige. (1). The striving for a nicer appearance is becoming a part of 'peraon's identity (2). Medical and pseudo-medical approaches have been developed to fulfill the above mentioned desires. In the general perception of a modern society such efforts are considered as positive, but some of such procedures are potentially risky, while others seem to be not efficient (3,4). Androgenic anabolic substances (AAS) are popular among power athletes (5) and have also been implicated in life-styling and anti-ageing procedures in males as well in females (6-8). We report five cases of adverse effects due to non-critical and/or unmonitored use of AAS.

Case reports

Case 1

A 44-year-old woman experienced a change in her

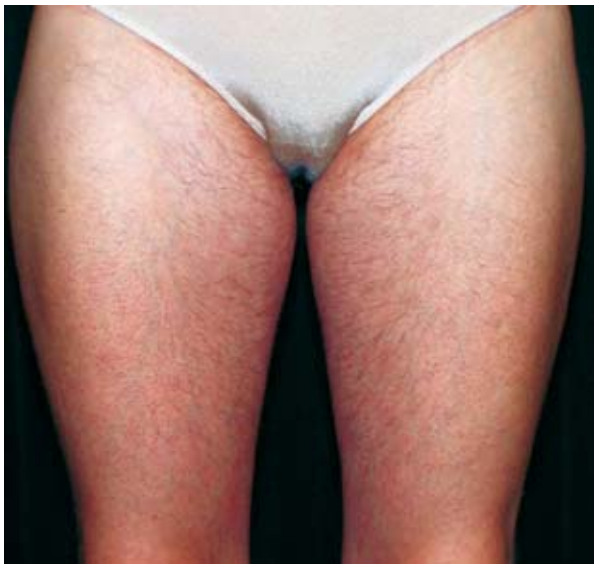

Fig. 1: Hypertrichosis of the inner thighs due to topical testosterone cream (case 2).

voice, half a year before she came to the ENT department of our hospital. She was suffering from cellulite and she had used a topical ointment for 6 months before her voice changes occurred. The prescription contained 2.5 % androstanolone in combination with 0.65 % tamoxifene in gel form. The gel was applied at least twice daily on the buttocks and the upper legs for almost a year.

On examination we found a cellulite grade 2 according to Mirrashed et al. 2004 (9). The voice sounded rough and instable, with permanent changes between modal and falsetto register. Mean speaking level was about 170 Hz (normal range for women 200 to 262 Hz). The voice range profile displayed a markedly extended lower edge at 96 Hz (normal about 130 Hz), thus reflecting acoustic characteristics of a male voice. However, laryngoscopic and stroboscopic examination revealed an anatomically and functionally normal larynx.

Hormonal levels (basal prolactin, follicle stimulating hormone, lutinizing hormone, serum estradiol, serum testosterone, sexual hormone binding globulin, androstendione and 17-OH-progesterone) were within the normal range. Free serum testosterone was 1.4 pmol/L (normal range: 1.4 to 9.4 pmol/L), dehydroepiandrosterone sulfate (DHEA-S) was diminished with 1.7 µmol/L (normal range 2.0 to 8.2 µmol/L). The last use of the "cellulite gel", occurred about 6 months earlier.

Diagnosis: Virility (dysphonia) due to topical androgen use.

The patient was advised to discontinue the use of the anti-cellulite gel and a logopedic therapy was introduced, the outcome of which was promising. The mean speaking level was stabilized at about 185 Hz and the frequency of changes between registers decreased markedly within 8 weeks.

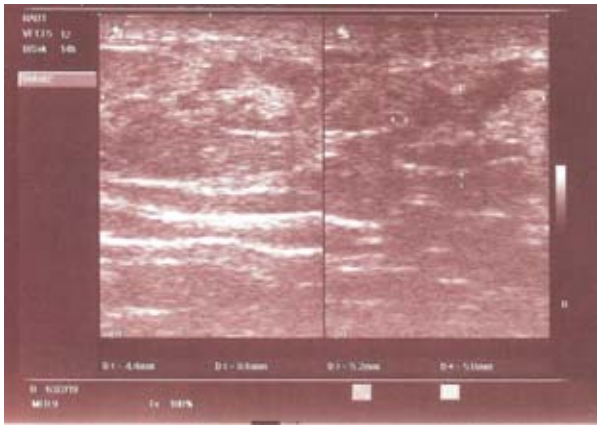

Fig. 2: Male gynecomasty (case 3). Ultrasound.

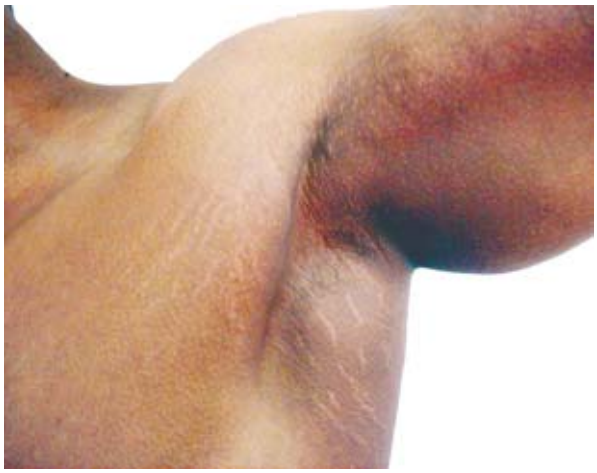

Fig. 3: Striae distensae in a young bodybuilder (case 4).

Case 2

A 52-year-old woman came because of a recent onset of facial acneiform eruption and upper leg hypertrichosis. Her medical history included ovariectomy and chemotherapy. She lost sexual desire and interest, and was set on a low dose estrogen replacement therapy by her gynecologist. The treatment was well tolerated but her sexual satisfaction did not improve. She surfed through the internet and found an internet pharmacy that provided her an androgen cream (Androfeme®), containing 1% testosterone. She used the cream once to twice daily since half a year. No monitoring was performed.

On examination we found a circumscribed dense hypertrichosis of dark terminal hair on the inner thighs

grade 4 according to the modified Ferriman-Gallwey scoring (8) where she used to apply the androgen cream (Fig. 1). In addition there was a mild hypertrichosis of lanugo hair grade 2 on the upper lip. On her face there was a mixture of hypertrophic sebaceous glands in the mid face with some inflammatory papules. She also complained of a muscular pain. The complaints have started after the testosterone treatment.

Diagnosis: Virilism due to topical testosterone.

She was prescribed a topical acne solution containing retinoic acid and erythromycin (Aknemycin plus®; Hermal; Germany) and was advised to stop the androgen therapy. She did not return for a check up..

Case 3

A 31-year-old man was referred to the Dermatology department because of a subcutaneous swelling in the areolar region of the left breast, which was on increase. He was otherwise healthy, of a muscular body, 174 cm high and weighing 75 kg. The testicular volume was 16 ml.

We observed an indolent subcutaneous resistance of 1 cm in diameter not attached to the muscle fascia or the skin. Sonography revealed a subcutaneous nodule of 4.4 mm x 8.6 mm x 5.2 mm (Fig. 2). To exclude a breast carcinoma, surgery was performed with complete removal of the subcutaneous tumor and a primary wound closure.

Histopathologic examination revealed proliferating tubular ducts with epithelial hyperplasia but without dysplasia. The connective tissue showed some degree of myxoid change, but without any signs of malignancy.

Diagnosis: Hemilateral florid tubular gynecomastia.

The patient was a non-professional body builder for several years. He had taken testosterone containing androgens for a couple of months before the tumor developed. He could neither tell the specific compound(s) nor the actual dosage used. He was advised to stop taking the anabolics. No recurrence was noted during the next 3 months.

Case 4

A 35-year old man living in a stable marriage presented with his childless wife since two years, but otherwise healthy. The man suffered from an erectile dysfunction since eight years ago, while his sexual libido was reduced since two years.

After taking a careful history it became evident that he was taking AAS like chlorine-dehydro-methyltestosterone, androstendiole and androstendione, testosterone undecanoate, 17 alpha-methyl testosterone and clenbuterole since 15 years. In addition there was an alcohol abuse which he had stopped half a year before.

On examination we noted a muscular male 173 cm high and weighing 86 kgs. There was no sign of gynecomastia. The testicular volume was on the lower normal limit with 12 ml, while other parts of the outer genitals like penis, epididymis and ductus deferens were within normal limits.

Two independent sperm investigations were performed. The sperm counts were reduced to 1.6 and 7.0 mio/mL respectively, the WHO normal value being 20 mio/mL. The motility was reduced to levels between 0% and 10%, the WHO normal value being 25%. The percentage of spermatozoons with normal morphology was 4% and 16% (WHO normal value 30%).

Laboratory investigations: Lutinizing hormone (LH) 3.0 IU/L (Normal range 1.5-34.6 IU/L), total testosterone 8.34 mol/L (Normal range 8.4-28.7 nmol/L), sexual hormone binding globulin (SHBG) 26.4 nmol/L (Normal range 13-71 nmol/L).

Diagnosis: Infertility due to disturbances of spermatogenesis, total testosterone on the lower limit, and sexually malfunction because of AAS and alcohol misuse. The couple was advised to search for psychological support. The man was strongly advised to stop the use of AAS.

Case 5

A 26-year-old male bodybuilder received several anabolics including testosterone and other AAS, systemic steroids and amino acids during the past 5 years. The patient developed acneiform eruptions, striae distensae and seborrhea that necessitated stopping the intake of all these drugs. While acneiform lesions and seborrhea disappeared the striae persisted as white streaks in the axillae, and in cubital and popliteal fossae (Fig. 3).

Diagnosis: Striae distensae and acne due to AAS.

Discussion

Cellulite is frequently observed in middle aged women and is characterized by furrowed and edematous skin on thighs, hips and buttocks. It seems to be caused by weakened muscular septa and a diffuse pattern of extrusion of underlying adipose tissue into the dermis. An increase of hypodermal adipose tissue and weakened fibrous septa extending perpendicularly from the bones to the skin surface, have been observed. A higher body mass index is associated with an increased r grade of cellulite (9-12).

Androstanolone is an androgen with effects and efficacy comparable to dihydrotestosterone. left breast In Germany it is classified as a doping substance. The German Society of Dermopharmacy expressed serious

concern and demanded caution referring to the topical use of androstanolone. Topical sexual steroid hormones may easily penetrate human skin and cause systemic effects (13-15). Topical androgens like testosterone have been used for decades to treat vulvar lichen sclerosus et atrophicus with a doubtful efficacy. Due to systemic absorption of testosterone virilism expressed as hirsutism may develop (16).

In women androgens may cause a deepening of the voice, acneiform eruptions, androgenic alopecia, excess body hair. Topical application of testosterone causes systemic effects. Indeed, sexual steroids including androgens may show a significant percutaneous absorption leading to changes in the serum levels. Precursors like pregneolone or androstendione fail to alter serum levels because of rapid metabolisation (17).

In controlled trials carefully monitored low-dose testosterone therapy in women efficiently increased female sexual interest and desire in the postmenopausal period. An up to two years administration in clinical trials did not cause serious side effects (18). Topical testosterone therapy has been approved by Western Australian authorities for women after surgical ovarian removal, for loss of libido, diminished sexual responsiveness, impaired well-being and loss of energy. It is, however, recommended that testosterone levels should be carefully monitored (19, 20).

The severe circumscribed hypertrichosis in case 2 and the absence of hypertrichosis in case 1 was attributed to different concentrations of AAS in the topical creams and possibly due to endogenous differences in androgen receptor affinity and density of the hair follicles.

The male cases were non-professional bodybuilders. Among power athletes and bodybuilders the use of AAS seems to be common (21, 22). In a study from gymnasia in Great Britain 9.1% of men and 2.1% of women had used AAS on a regular basis (5).

AAS are used to increase strength and lean body mass, but adverse effects are common, some of them even life threatening, like liver toxicity and increased cardiovascular risks due to increased blood pressure and depression of serum high-density lipoprotein (HDL-), HDL2- and HDL3-cholesterol levels (23). In males, tumor induction of prostate and breast has also been discussed (24).

Ductal proliferations without atypia are benign lesions of the breast. In adult female Wistar rats testosterone administration can induce ductal proliferation and acino-tubular differentiation. After 90 days of exposure there was a progressive reduction in secretory differentiation and an increase in intralobular collagen fibres (25). The authors suggested a direct testosterone-mediated activity but transformation of testosterone to estrogens by mammary gland aromatase was not excluded in these experiments.

From clinical studies in women there is evidence for a genetic predisposition to *multiple* benign breast lesions (26). In postmenopausal women there is an increased risk of breast cancer in association with high plasma levels of free estradiol and testosterone (27). In our male patient the use of AAS was probably responsible for induction benign duct proliferations appearing as a unilateral tumor mass. The administration of methyl testosterone and testosterone to males is known to result in gynecomastia (28). The steroid-dependent male gynecomastia in athletes gains further support from presence of adequate receptors in breast tissue. In a recent study, 85% of gynecomastia tissue contained hormone receptors, while 40% contained both estradiol and androgen receptors (29). The treatment of choice is surgical removal, eventually combined with liposuction (30). The occurrence of unilateral gynecomastia by AAS, as in case 2, is less common than the bilateral type considering the published cases (31).

In a number of patients ASS may be consumed with other (addictive) substances like alcohol and illegal drugs (32). The long term use, especially an overdosage of AAS can affect sexual desire and capability of erection, induce suppression of spermatogenesis, testicular atrophy and prostatic hypertrophy. In case 3 a combined negative effect of ASS and alcohol. might have been a responsible In case 4 we saw striae distensae as a result of rapid muscular hypertrophy. The latter can also be seen in body builders and power athletes without AAS misuse.

Life-style drugs may bear a significant risk of adverse effects, some irreversible or fatal. The uncritical usage of AAS is a challenge. The dermatologist should be aware of these potential side effects.

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