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Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids

Nina Gårevik[a], Emmanuel Strahm[a,*], Mats Garle[a], Jonas Lundmark[a], Lars Ståhle[b], Lena Ekström[a], Anders Rane[a]

[a] Karolinska Institutet, Division of Clinical Pharmacology, Karolinska University Hospital, SE-141 86 Stockholm, Sweden
[b] Astra Zeneca AB, Västra Mälarehamnen 9, SE-151 85 Södertälje, Sweden

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ABSTRACT

Aims: To study the long-term impact of anabolic androgenic steroid (AAS) abuse on the cholesterol profile, and the potential to suppress endocrine activity in men working out at gym facilities. To study the relation between urinary biomarkers for testosterone and nandrolone abuse and the UGT2B17 genotype and time profile.
Experimental design: Subjects ($N = 56$) were recruited through Anti-Doping Hot-Line. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), plasma levels of low density lipoprotein (LDL), high density lipoprotein (HDL) and urinary steroid profile were regularly measured for a period of up to one year after cessation of intramuscular AAS abuse.
Results and discussion: A sustained suppression of LH, and FSH was observed for several months. The nandrolone urinary biomarker 19-NA was detectable several months after the last nandrolone intake and was correlated to the levels of LH and FSH. Testosterone abuse on the other hand was detectable only for a few weeks, and some of the testosterone abusers did not test positive due to a genetic deletion polymorphism of the UGT2B17. Significantly increased levels of HDL and decreased levels of LDL were observed for 6-months after cessation of AAS abuse.
Conclusion: Some individuals had a sustained suppression of LH and FSH for a period of 1 year whereas the cholesterol profile was normalized within 6 month. The long term consequences of these findings remain to be established.

1. Introduction

Anabolic androgenic steroids (AAS) including testosterone, other endogenous androgenic hormones and synthetic compounds structurally related to these compounds are the most frequently detected doping agents in sports. They accounted for about 59% of adverse analytical findings in 2008 in accredited doping laboratories around the world (WADA 2008 Adverse Analytical Findings and Atypical Findings reported by accredited laboratories, Montreal, 2009 (http://www.wada-ama.org)). However, the abuse of these agents for cosmetic purposes among non-competitive recreational body-builders and non-athletes is a major societal concern. In fact, AAS abuse has become a growing public health problem [5,11,24].

The current test to detect abuse of testosterone is based on determination of the urinary testosterone glucuronide/epitestosterone glucuronide ratio (T/E). When the T/E is above 4.0, doping in sports is suspected (WADA Technical document TD2004EAAS, reporting and evaluation guidance for testosterone, epitestosterone, T/E ratio and other endogenous steroids, Montreal, 2004 (http://www.wada-ama.org)) and such samples must be subject to further analyses for determination of the origin of testosterone. The major enzyme responsible for testosterone glucuronidation is UGT2B17 [9]. We have shown that the T/E ratio after a single dose of testosterone is highly dependent on the UGT2B17 deletion polymorphism [23] and that there are large inter ethnic differences in the distribution of this trait [9].

In order to detect nandrolone intake, the urinary nandrolone metabolites 19-norandrosterone (19-NA) and 19-noretiocholanolone (19-NE) are used as markers. These metabolites can be endogenously produced at low levels in some cases [15]. When the urine concentration exceeds the threshold of

Abbreviations: AAS, anabolic androgenic steroid; CHD, coronary heart disease; FSH, follicle-stimulating hormone; HDL, high density lipoprotein; T/E, testosterone glucuronide on epitestosterone glucuronide ratio; LDL, low density lipoprotein; LH, luteinizing hormone; 19-NA, 19-norandrosterone; 19-NE, 19-noretiocholanolone.

* Corresponding author. Tel.: +46 8 585 87883; fax: +46 8 585 81070.
E-mail addresses: nina.garevik@ki.se (N. Gårevik), emmanuel.strahm@ki.se (E. Strahm), mats.garle@karolinska.se (M. Garle), jonas.lundmark@ki.se (J. Lundmark), lars.stahle@astrazeneca.com (L. Ståhle), lena.ekstrom@ki.se (L. Ekström), anders.rane@ki.se (A. Rane).

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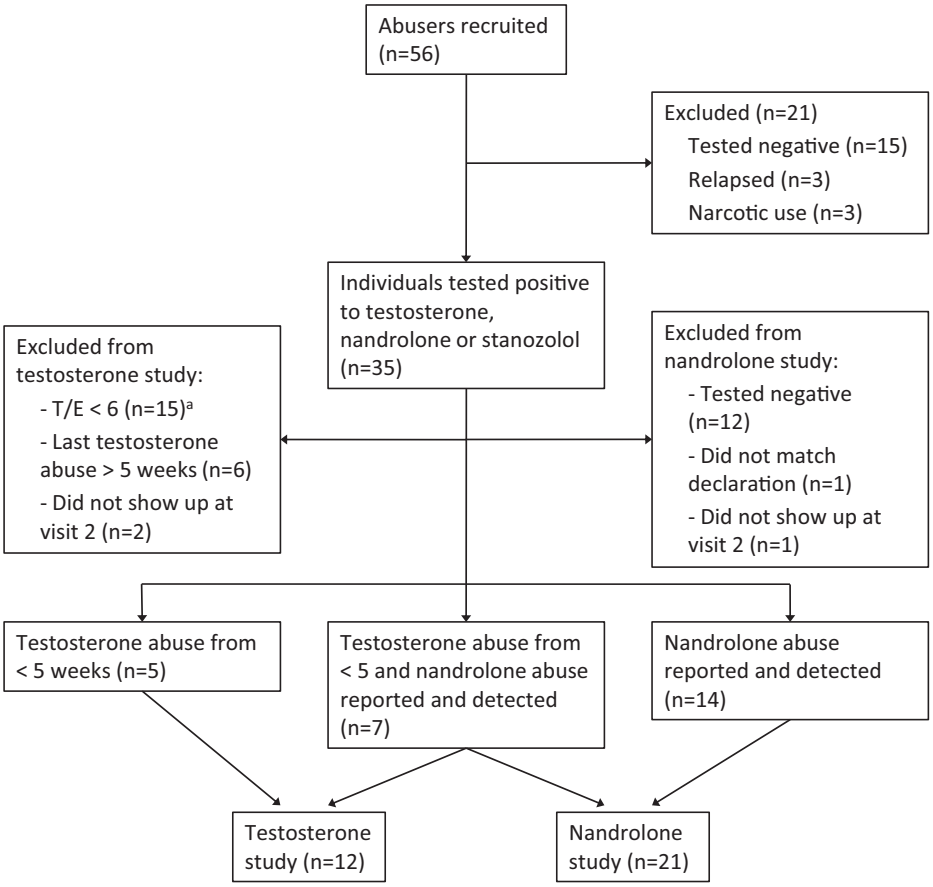

Fig. 1. Flow chart of the volunteers through the study. [a]Only for UGT2B17 inserted volunteers.

2 ng/ml, additional investigations are required to avoid a competitive athlete being wrongly subjected to disciplinary proceedings (WADA Technical document TD2010NA, Harmonization of analysis and reporting of 19-norsteroids related to nandrolone, Montreal, 2010 (http://www.wada-ama.org)).

The side effects related to the abuse of these steroids and other AAS are based on empirical observations, so the potential of serious and persisting health risks associated with the abuse of these steroids is still largely unexplored. Reported endocrine adverse reactions to AAS-abuse include acne, gynecomastia, testicular atrophy and decreased secretion of the pituitary hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [3,17,18,20]. Moreover, cardiovascular side effects such as disturbances in the cholesterol profile, i.e. increased low density lipoproteins (LDL) and decreased high density lipoprotein (HDL) have been reported (reviewed by [1,28]). However, the time course and possible reversibility of these alterations following abuse of AAS is not known. In the present study we addressed these issues in a 12 months follow-up study in AAS abusers that were recruited to the study at cessation of their abuse. We also studied the impact of the UGT2B17 deletion polymorphism on the T/E ratio and the urinary excretion of 19-NA in AAS abusers.

2. Subjects and methods

2.1. Subjects

Fifty-six men between 18 and 57 years old were recruited to the project between 1998 and 2002. A few were referred from colleagues working in emergency medicine, but most were asked to participate when contacting the Anti-Doping Hot-Line, a free telephone counseling service for individuals affected by or people concerned with abuse of anabolic androgenic steroids [5]. A genuine desire to give up using AAS was a prerequisite to be included. Participation was commenced after informed consent, and no economical remuneration was given to participants. The project was approved by the Ethics Committee of the Karolinska Institutet, Stockholm, Sweden. The flow chart of the volunteers through the study is presented in Fig. 1.

Individuals were clinically investigated and a series of endocrine parameters were monitored in blood and urine samples that were collected at different time points. At each time, LH and FSH were quantified in serum and urine samples were screened for metabolites of nandrolone, and testosterone as well as exogenous androgens such as stanozolol. After 6 months, cholesterol profile was analyzed and individuals were examined physically. At each visit they met a research nurse who could answer questions and check their social and psychological condition. If necessary, individuals were referred to qualified medical assessment and treatment at the Psychiatric or Endocrine Departments of hospital.

2.2. UGT2B17genotyping

Of the 56 subjects included in the study, 12 reported a recent use (last abuse time ranged from one day to five weeks) of an intramuscular testosterone depot formulation. Serum DNA was extracted using Qiamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). To genotype for *UGT2B17* polymorphism, 5′ nuclease PCR assays using *UGT2B17* gene exon 1 and exon 6 specific primers [29] and exon 1 and exon 6 specific Taqman probes (VIC-TACATTTTGGTCATATTTTTCACAACTACAAGAATTGT-MGB and VIC-CAGTCTTCTGGATTGAGTTT-MGB, respectively) were performed.

Table 1
Clinical features of 39 abusers that were positive in AAS urine screening.

Characteristics	Mean ± SD	Range
Weight (kg)	93.2 ± 20.1	67–187
Height (cm)	179.8 ± 6.5	166–190
Age	26.4 ± 7.2	18–57
Onset	21 ± 5.01	15–39
Duration	5.2 ± 4.1	0.5–17

The ubiquitously expressed β-actin (β-actin Control Reagents, Applied Biosystems, Carlsbad, CA, USA) and albumin [21] genes were used as internal standards for reaction quality control. Briefly the PCR was carried out in 15 μl volume including 5–10 ng genomic DNA, 2× TaqMan Universal Master Mix (Applied Biosystems), 900 nM of *UGT2B17* specific primers and 200 nM probe. The PCR profile consisted of an initial denaturation step at 95 °C for 10 min followed by 40 cycles at 95 °C for 15 s and 60 °C for 1 min. The fluorescence signal was measured with an ABI 7500 Sequence Detector (Applied Biosystem). Samples in which only β-actin and albumin signal were detected were identified as homozygous for *UGT2B17* deletion allele (*del/del*) whereas samples in which both the control genes and the *UGT2B17* products were amplified were identified as *UGT2B17* allele-carriers (*ins/ins* and *ins/del*). The quality and quantity of serum derived DNA did now allow us to discriminate between *ins/ins* and *ins/del*.

2.3. Urine, serum and plasma analyses

Determination of urinary 19-NA level and T/E ratio were determined using a validated gas chromatography–mass spectrometry (GC–MS) method at our WADA accredited Doping Laboratory within the clinical department of clinical pharmacology. All serum (FSH and LH) and plasma analyses (P-LDL, and P-HDL) were determined by routine methods at the Division of Clinical Chemistry (Karolinska University Hospital, Stockholm, Sweden).

3. Results

3.1. Characteristics of the AAS-abusers

Three individuals were positive for narcotics and were subsequently excluded from the study. Of the 53 individuals that showed up for the first visit, 35 tested positive for nandrolone, testosterone and/or stanozolol (see Fig. 1). Among the volunteers tested positive to 19-NA, two individuals did not claim to have abused nandrolone. This might be due to nandrolone contamination of steroid preparations or memory default in a multiple steroid abuse pattern. Thus, one of these individual was excluded because he relapsed into AAS abuse and the other because the screening test did not match his declaration. Even if all the subjects claimed to use multiple AAS (endogenous or synthetic), only 19 of the abusers were positive for more than one steroid. This is certainly due to the different time periods between the last abuse and the entry into the study. The mean age was 26.4 years and other mean height and weight was 180 cm and 93.2 kg, respectively. They reported to have started the AAS-abuse between 15 and 39 years of age, and the duration varied between 0.5 and 17 years (Table 1). All the AAS substances were reported to have been purchased through black market (internet, gym contact, etc.)

3.2. 19-NA elimination

Twenty-one individuals reported intra-muscular administration of nandrolone decanoate and the administration was confirmed by urinary analysis of 19-NA. The 19-NA elimination kinetics in these individuals are depicted in Fig. 2. At the first visit, all individuals tested positive for nandrolone abuse, i.e. they had 19-NA levels above 2 ng/mL (mean 450 ± 494 ng/mL). Six months later 80% of the individuals had 19-NA levels above 2 ng/mL (mean 35.2 ± 37.0 ng/mL). Interestingly, 58% of the individuals still remaining in the study ($N = 12$) were tested positive 9 months after their last nandrolone administration. After one year only 4 subjects were left in the study and 2 of them were positive for 19-NA (5.5 and 2.0 ng/mL).

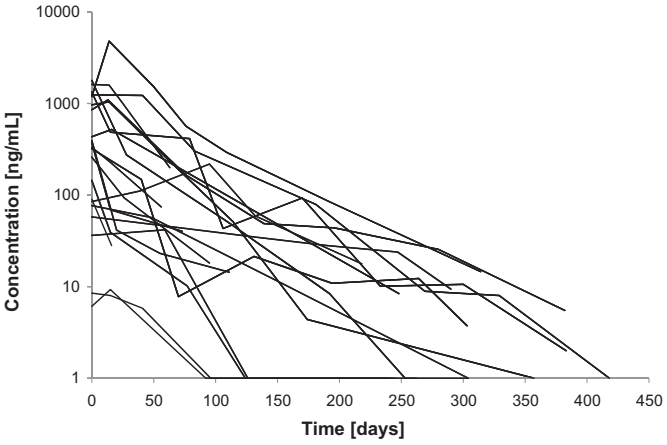

Fig. 2. 19-NA excretion in 21 individuals who tested positive for nandrolone. The 19-NA metabolite could be detected for several months after the last injection. Some individuals still tested positive (>2 ng/mL) one year after their last nandrolone dose.

3.3. Endocrine profile

The 21 individuals positive for nandrolone showed initial signs of compromised endocrine function as revealed by suppressed levels of LH and FSH (Fig. 3). The initial mean concentrations of FSH and LH at the first visit were <0.99 IU/L and <1.17 IU/L, respectively. Fifty % and 70% of the individuals had FSH and LH levels below

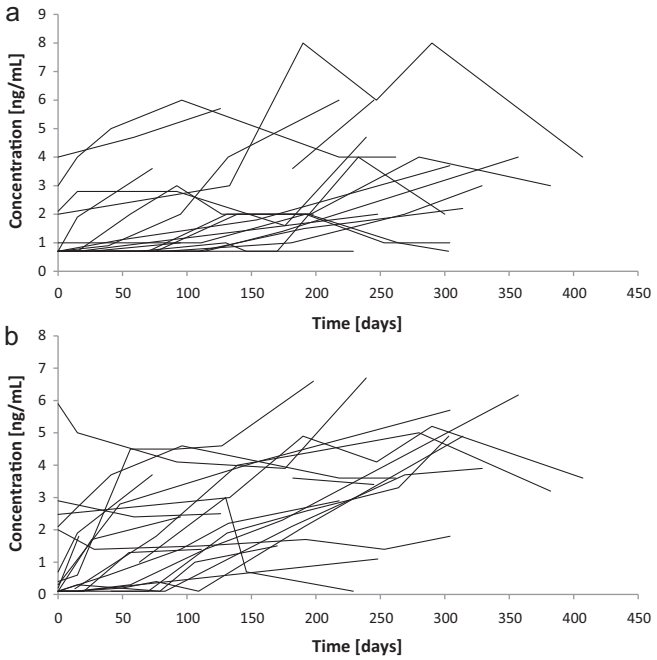

Fig. 3. Recovery of LH and FSH in nandrolone abusers from their first visit (day 0) and the follow up visits.

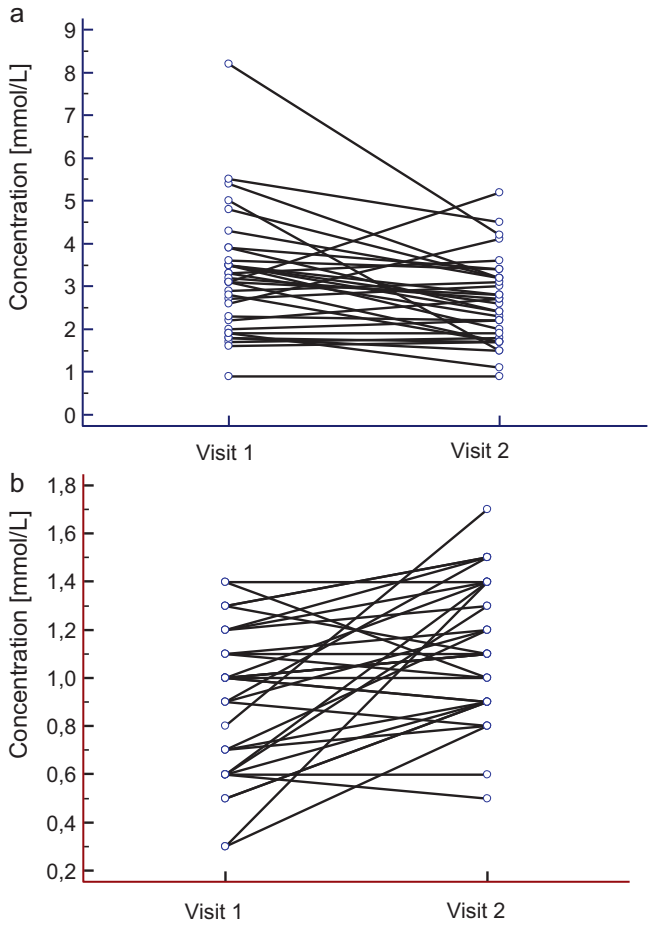

Fig. 4. LDL and HDL levels in 34 individuals at their first visit to the clinic and 6 months later. At visit 1 they were all positive for AAS and at visit 2 they had not relapsed into AAS-abuse. (A) Significantly lower LDL levels were observed at visit 2. (B) Significantly higher levels of HDL were observed at visit 2 (paired *t*-test).

the detection limit of 0.1 IU/L and 0.7 IU/L, respectively. Six months after cessation of AAS abuse, the mean concentration of FSH and LH had increased to 3.31 (±1.5 IU/L, $p = 0.004$) and 2.3 (±1.9 IU/L, $p = 0.04$).

There was a significant correlation between 19-NA and LH and FSH concentration that lasted for 16 weeks. At the first visit, urinary levels of 19-NA were significantly associated with LH and FSH levels ($r = -0.57$, $p = 0.02$ and $r = -0.75$, $p < 0.001$, respectively). There was still a significant correlation 9–16 weeks after the last nandrolone intake, ($r = -0.76$, $p < 0.001$ and $r = -0.72$, $p < 0.001$, for LH and FSH respectively ($N = 15$).

3.4. Lipid profile

Thirty-one of the subjects that were positive on nandrolone, testosterone and/or stanozolol at the first visit did not relapse into AAS abuse and returned at the 6 months re-visit. As seen in Fig. 4a, LDL-C was significantly higher at the first visit (mean 3.24 ± 0.25 mmol/L) than after 6 months without AAS (mean 2.63 ± 0.17 mmol/L; $p = 0.0061$). In contrast the concentration of HDL-C was significantly lower at visit 1 (mean 0.90 ± 0.05 mmol/L) than 6 months after cessation of AAS abuse (mean 1.13 ± 0.05 mmol/L; $p < 0.001$) (Fig. 4b). The level of total cholesterol did not differ between the two visits (data not shown).

3.5. T/E ratio and UGT2B17

Monitoring of the T/E ratios in testosterone abusers was carried out and the results are reported in Table 2. Three of the 12 testosterone abusers were identified as *del/del* (S10, S11 and S12). When tested for testosterone abuse 1–5 weeks after their last testosterone injection, none of the UGT2B17 *del/del* subjects were identified as positive in the doping test using the T/E-ratio as biomarker. As expected, all individuals expressing UGT2B17 displayed a T/E ratio above 4. They remained positive in the test whereas individuals devoid of UGT2B17 were classified as false negatives (Table 1). The T/E ratio was monitored in weeks 2, 4, 6 and 8 after the first visit (week 0). The T/E ratio decreased with time, reaching a T/E below 0.4 in *del/del* subjects in agreement with our previous findings i.e. individuals homozygous for the *UGT2B17* gene deletion have a baseline T/E ratio below 0.4. Two individuals relapsed into testosterone abuse (S6 and S12), but only subject S6 was suspected on the basis of the T/E as a biomarker.

4. Discussion

Interestingly, the urinary nandrolone metabolite 19-NA remained detectable for a long period of time. For some of the individuals, the 19-NA was detected up to one year after their last injection of nandrolone decanoate. This finding is in agreement with a previous study showing that exogenous 19-NA could be detected for 6 months in some individuals after a single dose of 150 mg nandrolone decanoate [4]. In a case report, 19-NA and 19-NE levels in urine were detectable for 8 months [12]. It is not known why these metabolites reside in the body for such as long time since the parent substance nandrolone itself is only detectable in serum for 2–5 weeks [4]. However, it can be assumed that nandrolone is certainly misused as micro-doses in professional sports in order not to reach the threshold of 2 ng/mL of 19-NA in urine established by the WADA.

Our results indicate that 19-NA, or another nandrolone metabolite, may exert a negative feed-back regulation on the hypothalamic–pituitary axis. The marked down-regulation at the start of the study was expected since this was in agreement with several other reports showing that AAS suppresses the LH and FSH secretion [3,19,20]. Several of the individuals had LH and FSH at or below the detection limit. These levels are in the range usually observed in pre-pubertal males and in the lower range for male adults. However, the long persistence of low levels of gonadotropins observed here has not previously been shown in a population study. Two case-reports demonstrate prolonged hypogonadotropic hypogonadism following 2.5 and 4 years intake of supra-physiological doses of mixed AAS [10]. However, in some individuals LH and FSH levels returned to normal 12 weeks following the cessation of testosterone enanthate abuse for 26 weeks [3].

Unfortunately serum testosterone levels were not measured in all of these individuals. But most likely the repression of gonadotropins shown here are associated with hypogonadism. It is commonly known among AAS abusers that AAS induce hypogonadism related side-effects for long period of time after an AAS-cycle (reported to the Anti-Doping Hot-line). There are reasons to believe that the endocrine endpoint following nandrolone abuse would correlate to clinical symptoms such as depression, apathy and impotence. However, our study was not designed to evaluate these possible relationships. Also, possible long-term consequences of these findings need to be addressed in further studies.

We show here for the first time that the long presence and slow elimination of nandrolone metabolites are associated with endocrine consequences. Considering the clinical significance of these findings it is important to further characterize the

Table 2
A follow-up study of the T/E ratio in 12 subjects that reported administration of intra-muscular testosterone preparation in the 5 last weeks. The UGT2B17 genotype is defined as ins (*ins/ins* or *ins/del*) or *del/del*.

Subject	UGT2B17	Last T abuse* [weeks]	T/E ratio				
			Week 0	Week 2	Week 4	Week 6	Week 8
S1	ins	4	36.0	11.8	11.9	5.2	1.7
S2	ins	4	12.9	1.9	1.9	2.0	1.2
S3	ins	2	196.2	26.7	4.1	2.0	2.4
S4	ins	4	79.0	72.1	14.6	1.8	2.4
S5	ins	5	50.6	22.9	1.4		
S6	ins	1	114.0	201.0	23.3	133.9	
S7	ins	4	6.4	4.1	5.0	2.9	
S8	ins	3	14.7	1.0	1.4	–	0.7
S9	ins	4	54.0	7.0			
S10	del/del	3	2.3	1.1	0.2	0.2	0.1
S11	del/del	2	0.8	0.4	0.3	0.3	
S12	del/del	1	0.6	0.5	0.1	1.3	2.0

* Self reported.

metabolism of nandrolone and the 19-NA/19-NE metabolites. The urinary excretion profile of 19-NA showed in our study as well as in healthy volunteers [4,27] disclose an inter-individual variation in the 19-NA excretion kinetics. Nandrolone metabolites are mainly glucuronidated prior to the excretion in urine and 19-NA glucuronide is the metabolite determined in the doping test using GC-MS analysis. So it is possible that genetic variations in UGTs have an impact on the variation observed in 19-NA excretion profile. Since 19-NA is glucuronidated at position 3′, UGT2B17 is probably not involved in this conjugation. Unfortunately, there were no nandrolone abusers homozygote for the UGT2B17 deletion in the cohort to confirm this hypothesis. Five UGTs (UGT2B7, 2B4, 1A1, 1A3 and 1A4) have been identified to catalyze the glucuronidation of 19-NA in vitro [14].

In agreement with several other studies on AAS abusers, we show that AAS induce a deleterious effect on the lipid profile, i.e. high levels of LDL and low levels of HDL. This profile was significantly improved 6 months after cessation of the AAS-abuse. According to other studies the lipoprotein levels are normalized one to three months after AAS cessation [2,13] depending on the duration of AAS course [8]. In our study group the AAS abusers had an HDL level below 1.0 mmol/L at visit 1, whereas six months after AAS cessation they have reached a HDL level of 1.1 mmol/L. According to Framingham data individuals below 1.0 mmol/L had a fourfold increase in risk of coronary heart disease (CHD) compared to those with levels of 1.03–1.27 mmol/L, and in agreement with previous conclusion, the HDL levels could account for an increased risk of CHD in AAS abusers [7]. Unfavorable long-term changes in serum lipid profile increase the risk of CHD, but here we show that after the cessation of AAS-abuse this risk can be decreased.

We have previously described the predictive influence of the *UGT2B17* genotype on the T/E ratio. After administration of a single dose of 360 mg testosterone in healthy volunteers, 60% of the individuals devoid of *UGT2B17* gene did not reach the cut-off T/E ratio of 4 the during 15 days observation [23]. The present study reports for the first time the impact of the *UGT2B17* polymorphism on the T/E ratio in AAS abusers. Our results show that sustained abuse of high doses of testosterone esters, the T/E ratio remains above 4 for up to 3 weeks after the last dose in individuals expressing *UGT2B17*, whereas in agreement with studies in healthy volunteers, *del/del* subjects had a T/E below 4 and did never tested as positive for testosterone. It is obvious that two individuals, i.e. subjects S6 and S12, relapsed into testosterone use at week 6, but only S6 was tested as suspected. We have shown that additional information about *UGT2B17* genotypes in the Bayesian approach [26] increases the sensitivity of the doping test [22]. The combined Bayesian and genotyping approach would certainly have revealed doping in subject S12. However, at the time when the testosterone doping test was conducted (1997–2000) the relation between *UGT2B17* genotype and testosterone excretion had not been described and the longitudinal follow up of the steroid profiling was not employed.

We have collected a unique population, i.e. individuals that are abusing AAS only but not narcotics. The material was collected in 1998–2002, and it would be hard to collect this population today, since abuse of narcotics is common among AAS-abusers in Sweden today [6,16,25]. Of course the study has several limitations. In addition to their mixed intake of AAS, some of them also admit the use of other doping agents (hCG, efedrin, GH, tamoxifen) as well as other drugs (prescribed and/or OTC). We believe that those included were not abusing AAS during the study period. First all individuals were screened continuously during the study period, and excluded if an obvious relapse in to AAS was revealed. Second, all participants contacted the health care facilities voluntarily with a desire to give up there abuse. Moreover, there was no economical compensation or any other advantages from participation. Thus we believe the risk of concealed and continued abuse is negligible. Another disadvantage is that the time since they took their last injection various which must be taken into consideration.

In conclusion we show that AAS-abusers have a disturbed cholesterol and endocrine profile. The lipid levels were recovered after 6 months cessation of AAS whereas the endocrine hormones LH and FSH were repressed for longer periods of time. The recovery of LH and FSH was correlated to the urinary level of the nandrolone metabolite 19-NA. 19-NA was detectable for several months after the last nandrolone administration, and there was a large inter-individual variation in the excretion rate. Moreover, UGT2B17 deletion polymorphism is an important determinant of the T/E ratio even after high doses of testosterone for a long period of time.

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