ORIGINAL ARTICLE

Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a)

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Objectives: To investigate the effects of two different regimens of androgenic-anabolic steroid (AAS) administration on serum lipid and lipoproteins, and recovery of these variables after drug cessation, as indicators of the risk for cardiovascular disease in healthy male strength athletes.
Methods: In a non-blinded study (study 1) serum lipoproteins and lipids were assessed in 19 subjects who self administered AASs for eight or 14 weeks, and in 16 non-using volunteers. In a randomised double blind, placebo controlled design, the effects of intramuscular administration of nandrolone decanoate (200 mg/week) for eight weeks on the same variables in 16 bodybuilders were studied (study 2). Fasting serum concentrations of total cholesterol, triglycerides, HDL-cholesterol (HDL-C), HDL2-cholesterol (HDL2-C), HDL3-cholesterol (HDL3-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), and lipoprotein (a) (Lp(a)) were determined.
Results: In study 1 AAS administration led to decreases in serum concentrations of HDL-C (from 1.08 (0.30) to 0.43 (0.22) mmol/l), HDL2-C (from 0.21 (0.18) to 0.05 (0.03) mmol/l), HDL3-C (from 0.87 (0.24) to 0.40 (0.20) mmol/l, and Apo-A1 (from 1.41 (0.27) to 0.71 (0.34) g/l), whereas Apo-B increased from 0.96 (0.13) to 1.32 (0.28) g/l. Serum Lp(a) declined from 189 (315) to 32 (63) U/l. Total cholesterol and triglycerides did not change significantly. Alterations after eight and 14 weeks of AAS administration were comparable. No changes occurred in the controls. Six weeks after AAS cessation, serum HDL-C, HDL2-C, Apo-A1, Apo-B, and Lp(a) had still not returned to baseline concentrations. Administration of AAS for 14 weeks was associated with slower recovery to pretreatment concentrations than administration for eight weeks. In study 2, nandrolone decanoate did not influence serum triglycerides, total cholesterol, HDL-C, HDL2-C, HDL3-C, Apo-A1, and Apo-B concentrations after four and eight weeks of intervention, nor six weeks after withdrawal. However, Lp(a) concentrations decreased significantly from 103 (68) to 65 (44) U/l in the nandrolone decanoate group, and in the placebo group a smaller reduction from 245 (245) to 201 (194) U/l was observed. Six weeks after the intervention period, Lp(a) concentrations had returned to baseline values in both groups.
Conclusions: Self administration of several AASs simultaneously for eight or 14 weeks produces comparable profound unfavourable effects on lipids and lipoproteins, leading to an increased atherogenic lipid profile, despite a beneficial effect on Lp(a) concentration. The changes persist after AAS withdrawal, and normalisation depends on the duration of the drug abuse. Eight weeks of administration of nandrolone decanoate does not affect lipid and lipoprotein concentrations, although it may selectively reduce Lp(a) concentrations. The effect of this on atherogenesis remains to be established.

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The misuse of androgenic-anabolic steroids (AASs) in young, healthy strength athletes has been associated with the occurrence of premature cardiovascular events.[1–3] These events may in part be mediated by the adverse effects on serum lipid variables that have been linked to AAS administration. Previous studies have indicated that the use of AAS results in decreases in high density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo-A1; the major component of the HDL particle), and increases in low density lipoprotein cholesterol (LDL-C).[4–8] A growing number of strength athletes misuse AASs to obtain a well shaped body or increase muscular strength. Most athletes take AASs for periods of 8–12 weeks several times a year.[9–11] Self administration of AASs may result in much higher doses than recommended, with possibly more severe side effects and more profound effects on serum lipids and lipoproteins. In particular, the orally active 17-α-alkyl steroids have been shown to have severe effects on LDL-C and HDL-C.[8 12]

Various studies have suggested that the concentration of lipoprotein (a) (Lp(a)) is an independent risk indicator for the development of vascular disease.[13–15] The fat composition of Lp(a) is comparable to that of LDL-C, but the most important difference is the presence of a specific apoprotein (a).[16 17] This protein is attached to apolipoprotein B (Apo-B) by a disulphide bridge. A close correlation has been reported between the serum concentration of Lp(a) and the accumulation of this particle in the vascular wall.[18 19] The serum concentration of Lp(a) seems to be genetically determined and, when raised, cannot be lowered by alterations in food intake or taking cholesterol lowering drugs.[20–22] Previous reports have suggested that, in contrast with their detrimental effects on lipids, AASs may favourably lower Lp(a) concentrations.[23–26]

The aim of the present studies was to investigate the effects of AASs on lipoproteins and lipids in healthy, young strength athletes. To obtain more insight into the relation between dose of AAS and the response on plasma lipid variables, we performed two prospective studies: one controlled,

Abbreviations: AAS, androgenic-anabolic steroid; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a)

non-blinded investigation and a randomised, double blind, placebo controlled study. The first investigated the effects of self administration of high doses of AASs on these variables. In the second study, the effects of a commonly used single AAS, nandrolone decanoate, on lipoprotein risk factors and Lp(a) were examined. In both studies we also assessed the recovery of the lipoprotein and lipid variables after cessation of drug administration.

SUBJECTS AND METHODS

This study was part of a larger one exploring the effects of AASs on body composition, exercise performance, and health status in male strength athletes.[27] Subjects were recruited by flyers in regional gym clubs. About 90 strength athletes volunteered to participate in one or more of these studies after they had been given detailed informed. All volunteers completed an extensive questionnaire with questions on health status, history, training habits, and the use of AASs, and had a full physical examination to exclude any relevant diseases. Inclusion criteria were: male; bodybuilding training experience of at least three years; at least four strength training workouts a week or eight hours of strength training a week; aged 20–45 years. The following exclusion criteria were set: hypertension, diabetes mellitus, liver disease or abnormal liver enzyme serum concentrations, hereditary hypercholesterolaemia, raised serum cholesterol (>6.5 mmol/l), infertility, and smoking.

The study was approved by the medical ethical review committee of Maastricht University and the University Hospital Maastricht, and all subjects gave their written informed consent before participating.

Study 1

This was a prospective, non-blinded investigation of the effects of AAS self administration. Thirty five male strength athletes participated. Nineteen self administered AASs for eight or 14 weeks in addition to their usual strength training (AAS group). Nine used AASs for eight weeks, and the remaining 10 for on average 14 weeks (range 12–16). Sixteen controls performed strength training without using AASs (CO group). Table 1 presents the physical and training characteristics of the two groups.

The subjects in the CO group had never used AASs. All except one subject in the AAS group had previous experience of AAS self administration. On average, they had started AAS use 4.8 years previously (range 1–14). The mean number of cycles used was 7.1 (range 1–30).

The participants were expected to have been drug free for at least three months before the start of the study. From information supplied by the subjects, the AAS users had been drug free for 8.1 (6.4) months. However, to objectively exclude recent drug use, urine was collected from all subjects for drug analysis.

The subjects in the AAS group purchased the AASs on the black market, although some subjects had received a prescription from a doctor. They designed their AAS courses on the basis of their own experience and beliefs. They administered several steroids (oral and intramuscular) simultaneously. The total amount administered by each participant during the study by far exceeded the recommended therapeutic dose. Table 2 presents a detailed description of the AASs used by each subject. The investigators were not involved in purchasing and administering these compounds nor did they recommend doses.

Table 1 Baseline characteristics of the participants of the androgenic-anabolic steroid (AAS) self administration study (study 1)

	AAS (n = 19)	Controls (n = 16)
Age (years)	31 (7)	33 (5)
Height (cm)	176 (9)	177 (7)
Body weight (kg)	84.0 (9.9)	89.1 (11.4)
Percentage fat (%)	17.0 (5.7)	19.7 (3.5)
Training experience (years)	10.0 (7.3)	8.9 (3.6)
Training (hours/week)	8.8 (2.5)	8.2 (2.3)

At baseline, and after 8 (and after 14, depending on the duration of use) weeks of AAS use, and six weeks after cessation, blood was drawn from the antecubital vein after a 10 hour fast, for the measurement of serum lipids and lipoproteins.

Study 2

This was a randomised, double blind, placebo controlled clinical trial. Sixteen well trained recreational bodybuilders volunteered to participate. None had previously used AASs. Table 3 presents their physical and training data.

All volunteers visited the laboratory weekly for the administration of an intramuscular injection of a high dose (200 mg) of nandrolone decanoate (n = 9) or placebo consisting of arachis oil (n = 7) for eight weeks. At baseline, after the four and eight week intervention periods, and six weeks after cessation, blood was drawn after a 10 hour fast for the measurement of serum lipids and lipoproteins.

Monitoring nutrition, training, and compliance

In both studies, all subjects maintained their regular training and nutritional regimens, and both kept diaries which were monitored. In study 1, before the start of the study and in week 8, all subjects of both groups recorded their training workouts and hours in a seven day training diary and their nutritional habits with the aid of a three day nutritional diary. The AAS users also made similar records in week 6 after drug withdrawal. Volunteers who self administered AASs for 14 weeks also recorded training and nutritional data in the last week of AAS use. In study 2, training and nutritional data were collected at baseline, after the four and eight week intervention period, and six weeks after the administration of nandrolone decanoate or placebo had been stopped.

Weekly training hours were assessed from the training data. The intake of protein, fat (saturated and unsaturated), carbohydrates, cholesterol, linoleic acid, vitamins, and trace elements was calculated from the nutritional diaries using the computer program Becel (version NL04a; Unilever, Rotterdam, the Netherlands).

To objectively monitor compliance in all subjects, urine samples were collected for drug analysis several times. In study 1, urine samples were collected from all volunteers at baseline and after the eight week study period. In addition, samples were collected from the AAS users six weeks after AAS withdrawal, and from the long term users after 14 weeks. In the double blind study, urine samples were collected at baseline, after four and eight weeks, and six weeks after the end of the intervention period. Overall, 163 urine samples were collected, 99 in study 1 and 64 in study 2. About one third of the total were randomly selected for analysis by the Netherlands Institute for Drug and Doping Research (NIDDR), Utrecht, the Netherlands to detect metabolites of anabolic agents. This resulted in 34 samples from study 1 being analysed and 25 from study 2.

Measurements

Serum total cholesterol (CHOD-PAP; Roche, Basel, Switzerland) and triglycerides (Triglycerid Rapid; Roche) were determined by enzymatic methods on a Cobas Bio

Table 2 Total amount of androgenic-anabolic steroids (AASs) and other drugs used by each subject

No	ID	Duration of AAS use (weeks)	AASs used and route of administration	Generic name	Total amount of drug used
1	BC101	16	Stromba (im)	Stanozolol	500 mg
			Deca-Durabolin (i.m.)	Nandrolone decanoate	350 mg
			Primobolan (po)	Metenolone	375 mg
			Primobolan (im)	Metenolone	1400 mg
			Masteron (po)	Drostanolone	14 mg
			Proviron (po)	Mesterolone	350 mg
2	SS102	16	Stromba (im)	Stanozolol	500 mg
			Deca-Durabolin (im)	Nandrolone decanoate	350 mg
			Primobolan (po)	Metenolone	375 mg
			Primobolan (im)	Metenolone	1400 mg
			Masteron (po)	Drostanolone	14 mg
			Proviron (po)	Mesterolone	350 mg
3	MB108	8	Deca-Durabolin (im)	Nandrolone decanoate	1600 mg
			Parabolan (im)	Trenbolone acetate	228 mg
			Dianabol (po)	Methandrostenolone	940 mg
			Pregnyl (im)	Choriongonadotrophin	9000 IU
4	JD111	12	Testoviron (im)	Testosterone enanthate	1250 mg
			Strombaject (im)	Stanozolol	700 mg
			Decadurabolin (im)	Nandrolone decanoate	100 mg
5	ES112	16	Strombaject (im)	Stanozolol	750 mg
			Stromba (po)	Stanozolol	450 mg
			Omnadren (im)	Testosterone propionate	375 mg
			Deca-Durabolin (im)	Nandrolone decanoate	875 mg
			Primobolan (im)	Metenolone	300 mg
6	JN113	8	Dianabol (po)	Methandrostenolone	960 mg
			Deca-Durabolin (im)	Nandrolone decanoate	300 mg
			Masteron (im)	Drostanolone	300 mg
*7	GS115	16	Clenbuterol (po)	Clenbuterol	
			Winstrol (po)	Stanozolol	
			Deca-Durabolin (im)	Nandrolone decanoate	
			Stromba (po)	Stanozolol	
			Stromba (im)	Stanozolol	
			Parabolan (im)	Trenbolone acetate	
			Pregnyl (im)	Choriongonadotrophin	
			Undestor (im)	Testosterone undecanoate	
			Nolvadex (po)	Tamoxiphene	
8	FB121	8	Deca-Durabolin (im)	Nandrolone decanoate	2000 mg
			Strombaject (im)	Stanozolol	750 mg
			Pregnyl (im)	Choriongonadotrophin	13500 IU
9	RT122	16	Stromba (po)	Stanozolol	1080 mg
			Dianabol (po)	Methandrostenolone	1240 mg
			Testosterone (im)	Testosterone heptilate	3000 mg
10	GR124	8	Dianabol (po)	Methandrostenolone	560 mg
			Proviron (po)	Mesterolone	1400 mg
			Primobolan (im)	Metenolone	800 mg
			Deca-Durabolin (im)	Nandrolone decanoate	400 mg
			Sustanon (im)	Testosterone (phenyl) propionate/ isohexanoate	1750 mg
			Parabolan (im)	Trenbolone acetate	602 mg
			Strombaject (im)	Stanozolol	250 mg
			Boldane (im)	Boldenone	300 mg
			Stromba (po)	Stanozolol	420 mg
11	PW125	8	Proviron (po)	Mesterolone	5600 mg
			Primobolan (im)	Metenolone	1600 mg
12	MD139	12	Synasteron (po)	Oxymetenolone	3500 mg
			Deca-Durabolin (im)	Nandrolone decanoate	1625 mg
13	CL148	8	Deca-Durabolin (im)	Nandrolone decanoate	2600 mg
14	FL151	12	Stromba (po)	Stanozolol	1036 mg
			Stromba (im)	Stanozolol	850 mg
			Testoviron (im)	Testosterone enanthate	3750 mg
			Testex Leo (im)	Testosterone cypionate	5000 mg
			Pregnyl (im)	Choriongonadotrophine	4500 IU
15	RD161	8	Dianabol (po)	Methandrostenolone	980 mg
			Testosterone (im)	Testosterone cypionate	750 mg
			Parabolan (im)	Trenbolone acetate	880 mg
			Pregnyl (im)	Choriongonadotrophine	4500 IU
16	HK401	8	Dianabol (po)	Methandrostenolone	1115 mg
			Primobolan (po)	Metenolone	1850 mg
			Proviron (po)	Mesterolone	675 mg
17	GT402	16	Stromba (po)	Stanozolol	2170 mg
			Anapolon (po)	Oxymetholone	1225 mg
18	DV403	8	Deca-Durabolin (im)	Nandrolone decanoate	4400 mg
			Spiropent (po)	Clenbuterol	1.68 mg
			Testoviron (im)	Testosterone enanthate	2500 mg
			Testex Leo (im)	Testosterone cypionate	1000 mg
			Masteron (im)	Drostanolone	300 mg
			Strombaject (im)	Stanozolol	1200 mg

Table 2 (continued)

No	ID	Duration of AAS use (weeks)	AASs used and route of administration	Generic name	Total amount of drug used
19	EK404	12	Strombaject (im)	Stanozolol	1150 mg
			Testosterone (im)	Testosterone	5500 mg
			Spiropent (po)	Clenbuterol	1.00 mg
			Anadrol (po)	Oxymetholone	1900 mg
			Pregnyl (im)	Choriongonadotrophine	1500 IU
			Nolvadex (po)	Tamoxiphene	440 mg

im, Intramuscular; po, oral.
*This subject used the drugs from the start in a stacking way but did not know the exact dose of each drug. The subject himself qualified the doses used as ''high'' for each drug.

analyser. HDL-C was measured enzymatically after precipitation of low density and very low density lipoproteins with poly(ethylene glycol) 6000. Apo-A1 and apo-B were determined by an immunoturbidimetric assay (Roche) on a Cobas MIRA analyser. The within and between assay coefficients of variation were 1.9 and 6.9% respectively for both determinations. Serum apolipoprotein (a) concentration was measured by a solid phase, two site immunoradiometric assay using two monoclonal antibodies to different epitopes of apolipoprotein (a) (Pharmacia Diagnostics, Uppsala, Sweden). The within assay coefficient of variation was 4% at a Lp(a) concentration of 200 mg/l, and the between assay variation was 7%. An apolipoprotein (a) concentration of 1 U/l is equal to 1 mg/l Lp(a).

Statistical analysis

Data are expressed as mean (SD) unless otherwise reported. Results were analysed on the StatView version 4.02 statistical software package (Abacus Concepts, Berkeley, California, USA). Group differences in baseline variables were compared by the Mann-Whitney U test. The same test was applied to compare changes in lipid variables between the treatment groups. Intragroup comparison of lipid variables after drug cessation with baseline data were performed with the Wilcoxon signed rank test, because data from non-using controls were only available for eight weeks. $p<0.05$ was considered significant.

RESULTS

Study 1

Table 1 gives the physical and training characteristics of the 35 participants of the self administration study. At baseline, the AAS and CO group were comparable with respect to age, height, weight, training experience, and weekly training hours. Nutritional intake of AAS users and controls was comparable. No significant differences in lipid and lipoprotein variables between the two groups were observed.

During the study all subjects maintained their regular training regimens. No change in weekly training hours was observed in any subject. The same was true for nutritional intake. AAS use led to no significant changes in serum triglycerides and total cholesterol, but a considerable increase in LDL-C was found, and a significant fall in HDL-C (from 1.08 (0.30) to 0.43 (0.22) mmol/l), HDL2-C (from 0.21 (0.18) to 0.05 (0.03) mmol/l), and HDL3-C (from 0.87 (0.24) to 0.40 (0.20) mmol/l). These changes were paralleled by a 35% increase in Apo-B concentrations (from 0.96 (0.13) to 1.32 (0.28) g/l), and a 50% decrease in Apo-A1 (from 1.41 (0.27) to 0.71 (0.34) g/l). Also a significant reduction in Lp(a) concentration from 189 (315) to 32 (63) U/l was observed (table 4).

After AAS self administration was stopped, the lipoprotein variables only slowly returned to normal; six weeks after AAS withdrawal they had not returned to baseline concentrations. Recovery was significantly slower after 14 weeks of AAS use than after eight weeks. In particular, Lp(a) concentrations remained decreased in the long term users, whereas in the

Table 3 Baseline characteristics of the participants of the double blind, randomised, placebo controlled study (study 2)

	Nandrolone decanoate (n = 9)	Placebo (n = 7)
Age (years)	33 (8)	31 (8)
Height (cm)	175 (10)	177 (7)
Body weight (kg)	76.0 (12.1)	83.8 (9.0)
Percentage fat (%)	15.3 (2.6)	17.6 (2.4)
Training experience (years)	7.3 (5.6)	6.4 (2.8)
Training (hours/week)	7.4 (2.1)	9.1 (2.0)

Table 4 Sequence of changes in serum lipids and lipoproteins induced by eight weeks of anabolic-androgenic steroid self administration and recovery after drug cessation (study 1)

	Baseline	After 8 weeks	6 weeks after drug cessation
Triglycerides (mmol/l)			
CO	1.79 (1.41)	1.70 (1.27)	NA
AAS	1.21 (0.33)	1.23 (0.42)	1.05 (0.32)
Total cholesterol (mmol/l)			
CO	5.02 (0.90)	4.76 (0.71)	NA
AAS	4.57 (0.77)	5.11 (1.41)	4.71 (1.09)
HDL-C (mmol/l)			
CO	1.21 (0.55)	1.20 (0.44)	NA
AAS	1.08 (0.30)	0.43 (0.22)†††	0.89 (0.41)*
HDL2-C (mmol/l)			
CO	0.30 (0.32)	0.27 (0.26)	NA
AAS	0.21 (0.18)	0.05 (0.03)†	0.14 (0.15)**
HDL3-C (mmol/l)			
CO	0.91 (0.29)	0.93 (0.26)	NA
AAS	0.87 (0.24)	0.40 (0.20)†††	0.76 (0.32)
Apo-A1 (g/l)			
CO	1.54 (0.39)	1.48 (0.20)	NA
AAS	1.41 (0.27)	0.71 (0.34)†††	1.15 (0.41)**
Apo-B (g/l)			
CO	1.07 (0.23)	1.02 (0.21)	NA
AAS	0.96 (0.13)	1.32 (0.28)†††	1.08 (0.27)*
Lp(a) (U/l)			
CO	161 (281)	136 (213)	NA
AAS	189 (315)	32 (63)**†††	102 (223)**

Data are mean (SD). NA indicates that data were not available.
For within group changes (compared with baseline values): *$p<0.05$, **$p<0.01$. For interaction effects (change in AAS group compared with change in CO group): †$p<0.05$, ††$p<0.01$, †††$p<0.001$.
AAS, Anabolic-androgenic steroid; Co, control; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a).

Table 5 Influence of duration of anabolic-androgenic steroid self administration on lipoprotein variables and on recovery after cessation of use

	Baseline	End of AAS period	6 weeks after drug cessation
Triglycerides (mmol/l)			
8 weeks	1.22 (0.37)	1.34 (0.38)	1.11 (0.39)
14 weeks	1.20 (0.32)	1.12 (0.36)	1.00 (0.24)
Total cholesterol (mmol/l)			
8 weeks	4.23 (0.59)	4.87 (1.54)	4.41 (0.73)
14 weeks	4.88 (0.81)	5.26 (1.48)	4.98 (1.31)
HDL-C (mmol/l)			
8 weeks	1.01 (0.25)	0.47 (0.20)**	0.89 (0.32)
14 weeks	1.14 (0.35)	0.63 (0.30)**	0.90 (0.49)*
HDL2-C (mmol/l)			
8 weeks	0.23 (0.21)	0.05 (0.04)*	0.14 (0.13)*
14 weeks	0.19 (0.15)	0.05 (0.04)*	0.14 (0.18)
HDL3-C (mmol/l)			
8 weeks	0.78 (0.12)	0.43 (0.18)**	0.74 (0.24)
14 weeks	0.96 (0.29)	0.57 (0.30)**	0.77 (0.38)
Apo-A1 (g/l)			
8 weeks	1.39 (0.22)	0.82 (0.29)**	1.21 (0.34)
14 weeks	1.44 (0.31)	0.91 (0.42)**	1.10 (0.47)**
Apo-B (g/l)			
8 weeks	0.90 (0.10)	1.22 (0.23)*	0.99 (0.09)
14 weeks	1.00 (0.14)	1.32 (0.34)**	1.16 (0.36)
Lp(a) (U/l)			
8 weeks	68 (51)	21 (26)**	58 (68)
14 weeks	299 (410)	42 (84)**	142 (303)**†

Data are mean (SD).
The effects of AAS use for 8 weeks (n = 9) are compared with administration for 14 weeks (n = 10). For within group changes (compared with baseline values): *p<0.05, **p<0.01. For interaction effects (change after 8 weeks of AAS use compared with change by 14 weeks): †p<0.05.
AAS, Anabolic-androgenic steroid; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a).

short term users there was a complete return to baseline values six weeks after drug withdrawal (table 5).

At baseline, all urine samples analysed were free of AASs and metabolites. After the eight week study period, urinanalysis of the CO group was negative. As expected, the urine samples of the AAS group contained a large variety of metabolites of androgenic-anabolic substances after eight and (when applicable) after 14 weeks. In addition, six weeks after AAS withdrawal, in several urine samples of AAS users small amounts of metabolites of various esterified AASs were still detectable.

Study 2

At the start, the physical characteristics, training data, and nutritional habits of the two groups were comparable. Table 6 presents the baseline serum lipoprotein and lipid concentrations of the 16 participants in the double blind nandrolone study. There were no significant differences between the two groups at the start.

Both placebo and nandrolone decanoate had no effect on total cholesterol, HDL-C , HDL2-C , HDL3-C, LDL-C, and triglycerides. Also, no significant changes in Apo-A1 and Apo-B were observed. Lp(a) concentrations in the bodybuilders who received nandrolone decanoate decreased significantly from 103 U/l (range 8–227) to 65 U/l (range 8–130), which is a reduction of about 40%. In the placebo treated subjects, a significant reduction in Lp(a) concentration was also observed. The baseline value was 245 U/l (range 38–756) and after eight weeks it was 201 U/l (range 46–617), a decrement of 19%. However, the changes in Lp(a) were not significantly different between the two groups.

During the study period, training work load and nutritional intake did not change significantly between the two groups. Urinanalysis showed no AASs or metabolites at baseline. After four and eight weeks, the same was true for the placebo group whereas urinalysis of the nandrolone group showed

Table 6 Sequence of serum concentrations of lipids and lipoproteins of the bodybuilders in the randomised, double blind, placebo controlled study (study 2)

	Baseline (week 0)	End of AAS period (week 8)	6 weeks after drug cessation (week 14)
Triglycerides (mmol/l)			
Nandrolone	1.14 (0.37)	1.13 (0.22)	1.37 (0.59)
Placebo	1.29 (0.38)	1.45 (0.58)	1.30 (0.60)
Total cholesterol (mmol/l)			
Nandrolone	4.78 (0.85)	5.06 (0.57)	4.72 (0.67)
Placebo	5.10 (1.01)	5.26 (1.37)	5.16 (0.71)
HDL-C (mmol/l)			
Nandrolone	1.13 (0.32)	1.06 (0.36)	1.08 (0.30)
Placebo	1.16 (0.19)	1.22 (0.41)	1.17 (0.37)
HDL2-C (mmol/l)			
Nandrolone	0.09 (0.06)	0.06 (0.05)	0.07 (0.04)
Placebo	0.10 (0.05)	0.14 (0.20)	0.13 (0.08)
HDL3-C (mmol/l)			
Nandrolone	1.04 (0.30)	1.00 (0.32)	1.00 (0.28)
Placebo	1.05 (0.15)	1.07 (0.28)	1.04 (0.31)
Apo-A1 (g/l)			
Nandrolone	1.37 (0.20)	1.36 (0.29)	1.39 (0.26)
Placebo	1.41 (0.11)	1.50 (0.25)	1.49 (0.33)
Apo-B (g/l)			
Nandrolone	0.98 (0.23)	1.08 (0.18)	0.98 (0.20)
Placebo	1.11 (0.32)	1.13 (0.36)	1.12 (0.27)
Lp(a) (U/l)			
Nandrolone	103 (68) (8–227)	65 (44)** (8–130)	89 (66) (12–185)
Placebo	245 (245) (38–756)	201 (194)** (46–617)	240 (224) (29–657)

Data are mean (SD). For Lp(a), ranges are also given.
For within group changes (compared with baseline values): *p<0.05, **p<0.01. No intervention effects (difference compared with change in placebo group) were observed.
AAS, Anabolic-androgenic steroid; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a).

only metabolites of nandrolone decanoate. Six weeks after the intervention period in some subjects who had received verum, small amounts of metabolites of nandrolone decanoate were still present.

DISCUSSION

AAS induced changes

In experienced strength athletes, the use of polydrug regimens of AASs, which is common practice, resulted in an increase in serum Apo-B concentrations, and a large decrease in serum concentrations of HDL-C, HDL2-C, HDL3-C, and Apo-A1. This leads to an increased risk of cardiovascular disease. The serum concentration of the atherogenic Lp(a) particle was also lowered. Eight weeks of nandrolone decanoate at a high therapeutic dose, however, produced no detrimental effects on serum concentrations of Apo-A1 and Apo-B, triglycerides, total cholesterol, and HDL-C and subfractions. However, a noteworthy, although non-significant, reduction in Lp(a) concentration was observed. A decrease in serum Lp(a) was also found in the placebo group, although this was approximately half of that in the nandrolone treated subjects. However, the net increase in the effect of nandrolone decanoate over placebo on Lp(a) serum concentrations did not reach significance. This lack of significance is probably due to the large differences between individual values of Lp(a) and the small number of subjects in study 2.

Lowering Lp(a) concentrations

The AAS induced effect on serum Lp(a) concentration is of special interest. It is known that Lp(a) is an independent risk indicator for the development of vascular disease.[13 14 28 29] In patients with atherosclerosis due to hyperlipidaemia and raised Lp(a) concentrations, it is recommended that serum cholesterol is reduced as much as possible to prevent new events and achieve regression of atherosclerosis. Serum concentrations of Lp(a), however, seem to be genetically determined and, when raised, cannot be lowered by alterations in food intake or taking cholesterol lowering drugs.[20 21] However, treatment with nicotinic acid and hormone replacement therapy have been shown to beneficially affect serum Lp(a) concentrations.[30] Several studies have found lowered serum Lp(a) concentrations after treatment with testosterone enanthate in eugonadal men,[26] and with nandrolone decanoate in postmenopausal women[24 25] and haemodialysis patients.[31] In a cross sectional study, Cohen and co-workers[23] reported that the proportion of subjects with high serum Lp(a) concentrations was lower in multidrug AAS using strength athletes than in their non-using counterparts, suggesting a suppressive effect of multidrug use of AASs on serum Lp(a) concentrations.

In our study, polydrug regimens of AAS use were found to have a strong lowering effect on Lp(a), and the administration of only nandrolone decanoate induced a strong, although non-significant, reduction in this variable. On the other hand, AAS self administration altered the serum concentrations of apolipoproteins, HDL-C, and its subfractions unfavourably, while nandrolone decanoate did not have any effect on these variables. The effect of the AAS induced reduction in Lp(a) in combination with the detrimentally altered concentrations of apolipoproteins and HDL-C and its subfractions on the risk of cardiovascular disease needs to be established.

Distinction between types and doses of AASs

The most pronounced effects on serum lipids and lipoproteins seem to be exerted by the oral 17-α-alkylated steroids rather than parenterally administered nandrolone decanoate and testosterone esters.[8 12 32] As many of the subjects in study 1 took one or more 17-α-alkylated steroids—that is, methandrostenolone, stanozolol, and oxymetenolone—it seems likely that these agents were responsible for the effects on serum lipids and lipoproteins found in this study. The reduction in serum HDL-C is mediated by hepatic triglyceride lipase, an enzyme that regulates serum lipids.[4] Oral AASs stimulate hepatic triglyceride lipase, resulting in decreased serum HDL-C and its subfractions (especially HDL2-C) as well as apo-A1.[8 12] Parenteral administration of AASs has less profound effects on this enzyme because they enter the circulation without passing through the liver.[33]

The Lp(a) lowering effect may be due to testosterone esters and nandrolone decanoate, as shown previously.[25 26 34] Moreover, LDL-C, a substance very closely related to the atherogenic Lp(a) particle, may also be favourably affected by Lp(a)-lowering AASs. This needs to be firmly established because only a few studies have shown it.[8 33] On the other hand, alterations in Lp(a) and LDL-C concentrations may occur independently of each other.[26] The exact mechanism by which AASs decrease Lp(a) concentrations is still unclear, although it has been suggested that it is mediated by decreasing apo-A synthesis.[26] Further research is needed.

The effects of AASs on serum lipids and lipoproteins are dose dependent.[12 33 35 36] The doses used by the subjects greatly exceeded the maximum therapeutically recommended for all substances used. Therefore all such regimens have high atherogenic risks.

Effect of duration of AAS use

During the last few decades, strength athletes have altered their patterns of AAS self administration. In the early years, long term abuse (continuous administration for many months, even up to several years) was common predominantly orally taken AASs. In the last decade, AAS abusers have reduced the length of administration to reduce the risks. However, they now take more AAS cycles per year, and they use more drugs simultaneously at much higher doses.[10 27 37] There are no previous studies on the effect of the duration of polydrug AAS administration on serum lipids and lipoproteins. We observed that serum concentrations of Apo-A1, Apo-B, and HDL-C and its subfractions were not influenced by the duration of AAS use. After 14 weeks, the serum concentrations of these variables were no different from those after eight weeks. It is known that lipid concentrations change most during the first weeks of AAS administration, although the effects of different substances may vary greatly.[8] However, the suppressive effect of AAS on serum lipoproteins and lipids persisted during long term administration, but no further worsening of these variables was observed over the study period. These findings indicate that a longer period of AAS misuse is not necessarily accompanied by a greater atherogenic risk, but the risk is prolonged.

Recovery after AAS withdrawal

Six weeks after withdrawal of AASs, serum concentrations of HDL-C, Apo-A1, and Lp(a) were not normalised in the long term AAS users, whereas in the short term users lipids and lipoproteins, except HDL2-C, had returned to baseline concentrations. Recovery of the beneficial decrease in Lp(a) concentrations was also prolonged in long term users compared with short term administration. In the nandrolone decanoate study, the decreased Lp(a) concentrations had recovered completely six weeks after the intervention period. As urinalysis after withdrawal showed traces of androgenic-anabolic substances in a few athletes who self administered AAS, the slow elimination of some drugs may contribute to the slow recovery of altered serum lipids and lipoproteins. We therefore conclude that recovery of serum lipid and lipoprotein concentrations depends on the length of AAS use.

Moreover, because of the prolonged deleterious alterations in the lipid profile, long term AAS users have a prolonged increased risk of cardiovascular problems.

Conclusions

In conclusion, self administration of polydrug regimens of AASs in supratherapeutic doses for eight or 14 weeks lowered serum concentrations of HDL-C, HDL2-C, HDL3-C, and Apo-A1, increased the serum concentration of Apo-B, but did not influence serum concentrations of triglycerides and total cholesterol. These alterations were accompanied by an increased atherogenic lipid profile. However, as these regimens also lowered the serum concentration of the atherogenic Lp(a) particle, the effect on the risk of cardiovascular disease remains unclear. Moreover, intramuscular administration of nandrolone decanoate (200 mg a week) for eight weeks did not have any effect on serum concentrations of triglycerides, total cholesterol, HDL-C, HDL2-C, and HDL3-C, although a trend to decreased Lp(a) concentration was found. This may beneficially affect the risk of cardiovascular events.

The effects on serum lipids and lipoproteins were not influenced by the duration of self administration of AASs. However, recovery of the altered serum concentrations of lipids and lipoproteins to baseline values was prolonged in long term (14 weeks) AAS users compared with short term (eight weeks) users. The increased risk of premature disease was therefore prolonged, although the prolonged decrease in serum Lp(a) concentrations may beneficially influence vascular prognosis.

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