Effects of the Anabolic Steroid Nandrolone Decanoate on Plasma Lipids and Coronary Arteries of Female Cynomolgus Macaques

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In this study, we examined the effect of nandrolone decanoate, an anabolic steroid (AS), on plasma lipid concentrations and coronary arteries of female cynomolgus monkeys fed a moderately atherogenic diet. There were four treatment groups: (1) intact, sham-ovariectomized (n = 12); (2) ovariectomized (OVX) + placebo for 2 years (n = 15); (3) OVX + nandrolone decanoate for 2 years (n = 14); and (4) OVX + nandrolone decanoate beginning 1 year after ovariectomy (n = 11). Serial blood samples were analyzed for total plasma cholesterol (TPC), high-density lipoprotein cholesterol (HDL-C), very–low-density lipoprotein (VLDL-C) plus low-density lipoprotein (LDL-C) cholesterol, and estradiol. All animals were necropsied after 2 years, and the coronary arteries were evaluated. There was no difference in plasma lipid concentrations between groups ($P > .05$) at any time. Coronary artery atherosclerosis extent (plaque size) was significantly greater in the group administered nandrolone for 2 years compared with the intact sham-operated group ($P < .05$), but not with the OVX + placebo group. The groups administered nandrolone had significantly larger arteries than the other two groups. Lumen area was significantly larger in the group given nandrolone for 1 year compared with all other groups ($P < .05$). All artery effects remained after controlling the statistical analysis for body weight. Longer-term treatment with nandrolone resulted in increased plaque size, and therefore, the possible benefit of increased lumen area was compromised. The data also suggest that nandrolone was converted to estradiol, and this conversion also may play a role in the arterial and lipid effects observed.

ANABOLIC STEROIDS (AS) are related to androgens but have higher nitrogen-retaining ability, resulting in skeletal muscle–building effects.[1] For this reason, they are widely abused.[1] There have been several reports of sudden cardiac events in otherwise healthy, young (<40 years) male abusers of anabolic steroids.[1-6] Most abusers of anabolic steroids use several anabolic steroids concurrently, and nandrolone decanoate was one of several or the only AS being abused in several reported cases of myocardial infarction and atherosclerosis.[2-4,6,7] AS abusers use much higher doses than those administered for osteoporosis prevention and treatment.[1]

Nandrolone is administered parenterally to prevent or treat osteoporosis in postmenopausal women,[8] and beneficial effects of nandrolone on bone formation and resorption have been shown.[9-13] It is uncertain whether nandrolone is atherogenic when used in doses typically used to treat and prevent osteoporosis.

In this study, we examined the effect of nandrolone decanoate on plasma lipid concentrations and coronary artery atherosclerosis using female nonhuman primates previously found to respond to exogenous hormones in ways similar to women.[14]

MATERIALS AND METHODS

Design

Sixty young adult (5 to 8 years) feral female cynomolgus monkeys (*Macaca fascicularis*) were imported directly from Indonesia (Institut Pertanian Bogor, Bogor, Indonesia) for the study. The study was designed to examine the effects of nandrolone on bone and coronary arteries. Because of prior injury, one animal was found unsuitable for study. Baseline plasma lipid concentrations (total plasma cholesterol [TPC] and high-density lipoprotein cholesterol [HDL-C]), clinical pathologic measurements, and bone densitometry data were obtained following a 90-day quarantine period. Stratified random sampling based on baseline bone density, bone biomarker data, and plasma lipid concentrations was used to place the 59 monkeys into four treatment groups to obtain similar means ± SD in the four groups' baseline bone density and bone biomarker data and plasma lipid concentrations. The four treatment groups were (1) intact, sham-ovariectomized (n = 15); (2) ovariectomized (OVX) + placebo for 2 years (n = 15); (3) OVX + nandrolone decanoate for 2 years (n = 15); and (4) OVX + nandrolone decanoate for 1 year, beginning 1 year after ovariectomy (n = 14). Baseline values for all four groups for all variables were not significantly different ($P > .5$).

Once placed in treatment groups, monkeys in group 1 were sham-ovariectomized and monkeys in groups 2, 3, and 4 underwent bilateral ovariectomies. After 6 months, the almost undetectable estradiol concentrations in groups 1 and 2 indicated successful ovariectomies (Fig 1). In addition, no ovaries were found at necropsy in monkeys in the OVX groups. Animals in the sham-ovariectomized (group 1) and placebo treatment (group 2) groups were anesthetized with ketamine hydrochloride (15 mg/kg body weight) and given intramuscular injections of sterile vehicle every 3 weeks. Animals in the remaining groups were similarly anesthetized and then given intramuscular injections of 25 mg nandrolone decanoate every 3 weeks, for 2 years in animals in group 3 and 1 year in animals in group 4. This dose is approximately half the 3-week–interval dosage used therapeutically to treat postmenopausal women with osteoporosis; after adjusting for caloric intake to correct for differences in body size and metabolic rate, this corresponds to approximately twice the human therapeutic dose. Animals in group 4 received the sterile vehicle in the first year. During the study, seven monkeys died: four of enteritis and three as a result of fight trauma.

The experimental diet is shown in Table 1. This is a moderately atherogenic diet[14] (0.28 mg cholesterol/kcal), and the animals were started on the diet after all baseline data had been collected. The

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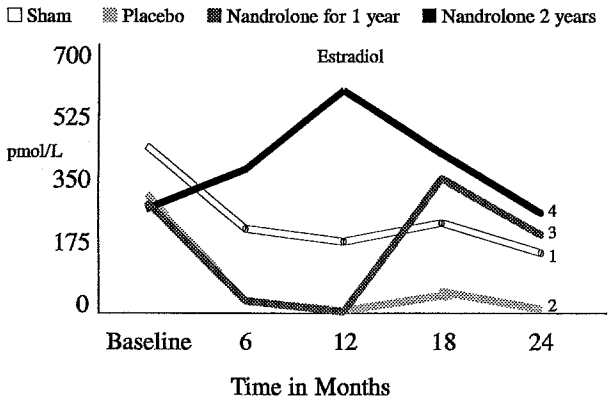

Fig 1. Changes in plasma concentrations of estradiol over time in the 4 treatment groups. By 24 months, concentrations in the 2 nandrolone groups were not significantly different from those in the intact-sham group, but were different from levels in the placebo-OVX group ($P < .05$).

monkeys were housed in groups of four or five in indoor/outdoor pens (2.0 × 3.2 × 2.5 m) that allowed unrestricted mobility and social interaction. Water was provided ad libitum. Guidelines established by our Institutional Animal Care and Use Committee and state and federal laws were followed in all conditions and procedures involving the animals.

Sample Collection and Analyses

Body weights were determined at 2-month intervals. Concentrations of TPC, plasma HDL-C, and triglycerides were determined at 6-month intervals after starting the animals on the various treatments. Blood was collected from the femoral vein of the animals into Vacutainers containing EDTA after overnight fasting. TPC concentrations were measured by enzymatic techniques based on the methods of Allain et al.[15] Plasma triglycerides were determined using methods reported by Fossati and Principe.[16] HDL-C concentrations were measured using the heparin-manganese precipitation procedure described in the Manual of Laboratory Operations of the Lipid Research Clinics Program.[17] Very–low-density lipoprotein cholesterol (VLDL-C) plus low-density lipoprotein cholesterol (LDL-C) was calculated as the difference between TPC and HDL-C. All analyses were performed on a Technicon RA-1000 autoanalyzer (Bayer Diagnostics, Elkhart, IN). Our laboratory subscribes to the Centers for Disease Control ([CDC] Atlanta, GA) Lipid Standardization Program. Methods approved by the CDC Lipid Standardization Program were used for each lipid measurement, as described earlier. The program involves a continuing process in which the laboratory sends results from reference samples to the CDC for assessment of the range of accuracy. Our laboratory is in the final stage, referred to as continuing surveillance, of this program. Plasma estradiol concentrations were determined by radioimmunoassay at the Comparative Endocrinology Laboratory of Yerkes Regional Primate Center of Emory University (Atlanta, GA) using a modification of a commercial kit (Diagnostic Products, Los Angeles, CA).[18] Intraassay and interassay coefficients of variation for this assay were less than 3.0% and 6.8%, respectively.

Table 1. Diet Composition

Ingredient	g/100 g
Casein	8.00
Lactalbumin	8.00
Dextrin	8.00
Sucrose	6.00
Wheat flour	35.50
Applesauce	4.50
Lard	9.50
Beef tallow	7.00
Butter (lightly salted)	3.00
Safflower oil (linoleic)	0.50
Dried egg yolk	3.50
Complete vitamin mix	2.50
Ausman-Hayes mineral mix	5.00
Protein (% cal)	16.70
Carbohydrate (% cal)	38.10
Fat (% cal)	45.10
Saturated	46.00
Monounsaturated	42.90
Polyunsaturated	11.10
Calcium (mg/1,800 cal)	3,145.90
Phosphorus (mg/1,800 cal)	2,629.80

Terminal Procedures and Coronary Artery Measurements

At the end of the study period, the animals were sedated with ketamine hydrochloride (10 mg/kg body weight) and anesthetized with sodium pentobarbital (13 mg/kg body weight) intravenously. Euthanasia was effected with an intravenous injection of sodium pentobarbital (100 mg/kg body weight). The heart and major arteries were dissected out and perfused with 10% neutral buffered Formalin at a pressure of 100 mm Hg for 1 hour. Five adjacent tissue blocks (each ~3 mm in length) were cut perpendicular to the long axis of the left anterior descending, left circumflex, and right coronary arteries. Two 5-μm sections were cut from each block and stained with either hematoxylin and eosin or Verhoeff-van Gieson's stain and evaluated morphometrically. Sections stained with the latter were projected onto a digitizer plate. The component parts of the arteries were traced with a computer-assisted digitizer to obtain the cross-sectional area occupied by the intimal lesion (plaque size) and the area within the internal elastic lamina (IELA). Lumen area was calculated by subtracting the intimal area from the area within the IELA. It has been shown previously using this model that the IELA is highly correlated with the area within the external elastic lamina ($r = .99$),[19] and so the IELA was used here to represent artery size.

Statistical Analysis

Repeated-measures ANOVA was used to determine if there was a significant treatment group × artery block interaction for any of the five measurements per block of plaque size, IELA, and lumen area. There were significant group effects, artery effects, and block effects, but no significant block × group interaction effects; thus, data from 15 sections of the three coronary arteries were converted to a mean to obtain a single value per animal for each measurement.

Repeated-measures ANOVA, ANOVA with Duncan's multiple comparison test, and analysis of covariance (ANCOVA) were performed to compare treatment groups using the GLM procedure in the SAS Package (SAS Institute, Cary, NC).[20] Multivariate analysis was used to determine any significant associations between treatment and coronary artery measurements after controlling for interactive factors (serum lipid concentrations, estradiol concentrations, and body weight). The stepwise regression procedure in SAS was used to determine the best predictive models. The significance level for entry into the model was .5, and if the partial F statistic of a variable in the model was less than a .1 significance level, the variable was removed from the model. The independent variables

used were concentrations of triglycerides, VLDL-C + LDL-C, and plasma estradiol, the TPC:HDL-C ratio, and body weight. The dependent variables were plaque size, IELA, and lumen area. After obtaining the best model for each outcome, the treatment effect, coded as a dummy variable, was forced into the predictive model. If any variable became nonsignificant at the .05 level after inclusion of the treatment effect, it was removed from the model.

RESULTS

Lipid Data

Baseline plasma lipid data are presented in Table 2. No group was significantly different from any other at any sampling time ($P > .05$). During the treatment period, there were no significant time × group interactions for HDL-C, VLDL-C + LDL-C, or TPC concentrations ($P > .05$). There was a significant time effect for all three lipid parameters, with HDL-C concentrations decreasing significantly after treatment (Fig 2) and VLDL-C + LDL-C and TPC concentrations increasing significantly after treatment (Fig 3).

There was a significant time × group interaction for serum triglyceride concentrations ($P < .05$), but no group effect ($P > .05$) (Fig 4).

Estradiol Concentrations

There also was a significant time × group interaction for estradiol (Fig 3). Separate analysis of each period showed that although the groups were not significantly different from each other at baseline, at 6 months of treatment group 3 animals (nandrolone for 2 years) had significantly higher estradiol concentrations than the other groups ($P < .05$). Results at 12 months followed the same pattern. At 18 months, when group 4 had received nandrolone for 6 months, it had the second highest estradiol concentrations after group 3, and these values were significantly greater than in the other two groups. The pattern for 24 months was similar to that for 18 months: although the two nandrolone treatment groups were not significantly different from the sham group, they were still different from the placebo-OVX group. Also, estradiol concentrations for all groups were lower at 24 months.

Body Weights

Body weight measurements at baseline and necropsy and the mean of the treatment body weights are listed in Table 3. Repeated-measures ANOVA revealed a significant group effect of therapy on body weight, with group 3 the heaviest. There also was a significant group × time interaction effect, with group 4 body weights significantly greater than those of the other groups. All groups gained weight over time, although the weight gain was not significant in groups 1 and 2 (Table 3).

Table 2. Baseline Plasma Lipid Concentrations (mmol/L)

Variable	Intact-Sham	OVX + Placebo	OVX + Nandrolone 2 Years	OVX + Nandrolone 1 Year
HDL-C	1.34 ± 0.09	1.32 ± 0.08	1.43 ± 0.10	1.21 ± 0.10
LDL-C	1.86 ± 0.12	1.77 ± 0.16	2.17 ± 0.20	1.83 ± 0.24
Triglycerides	0.53 ± 0.05	0.46 ± 0.05	0.55 ± 0.04	0.54 ± 0.10
TPC	3.45 ± 0.14	3.30 ± 0.18	3.85 ± 0.25	3.30 ± 0.28

NOTE. Values are the mean ± SEM. There were no significant differences between groups.

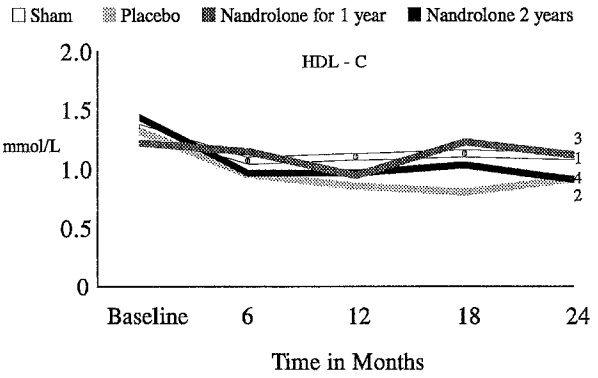

Fig 2. Changes in plasma concentrations of HDL-C over time in the 4 treatment groups.

Artery Measurements

Artery measurements are listed in Table 4. Animals given nandrolone for 2 years (group 3) had significantly larger plaques than the sham group, but these were not different from groups 2 and 4. IELA measurements for both nandrolone treatment groups were larger than those of the sham and placebo-OVX groups. Animals given nandrolone for 1 year had larger lumen areas than all the other groups; however, lumen areas in group 3 were not significantly different from those in the intact sham group, which in turn were not different from those in the placebo-OVX group. These relationships did not change after controlling for body weight.

To determine if the effects on artery size could be explained by increased heart weight, ANCOVA was used to adjust for heart size (weighed at necropsy) while comparing coronary artery size. There was still an overall significant difference in coronary artery size ($P = .01$). In the post hoc analysis of the ANCOVA, IELA measurements for animals given nandrolone for 2 years were significantly larger than for the sham-intact group ($P = .009$) and the placebo-OVX group ($P = .003$). From the stepwise regression analysis, after controlling for treatment effects, the only significant

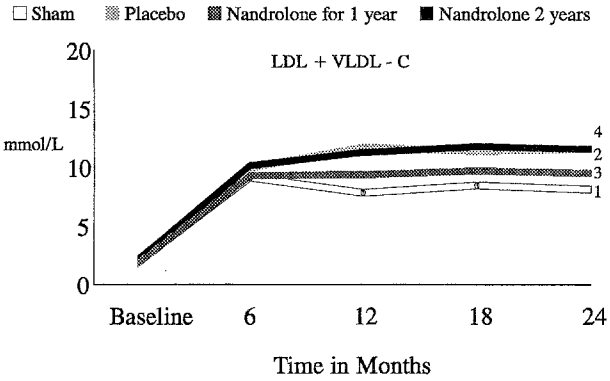

Fig 3. Changes in plasma concentrations of LDL-C + VLDL-C over time in the 4 treatment groups.

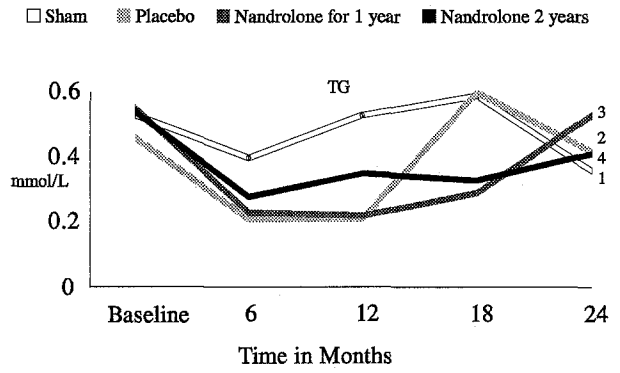

Fig 4. Changes in plasma triglycerides (TG) over time in the 4 treatment groups.

predictor of plaque size was VLDL-C + LDL-C ($P = .0001$, partial $r = .58$). The predictors of lumen area were body weight ($P = .01$, partial $r = .33$) and VLDL-C + LDL-C ($P = .02$, partial $r = .29$), whereas there were no significant predictors of artery size.

DISCUSSION

Some investigators have found that nandrolone treatment decreases HDL-C concentrations in postmenopausal women,[13,21,22] whereas others found no effect on plasma lipid concentrations in postmenopausal women[23] or in male and premenopausal female weight lifters.[24] In our study, nandrolone did not significantly affect plasma lipid concentrations, since lipids increased over time in all groups regardless of treatment.

Route of administration is an important aspect of hormonal effects on plasma lipids. Estrogens administered parenterally are not as potent as orally administered estrogens in producing a cardioprotective lipid profile (lower LDL-C and higher HDL-C concentrations) in people.[25,26] The same kind of process has been suggested for androgens administered parenterally,[27] ie, deleterious effects on plasma lipids may be limited by bypassing first passage through the liver. In women receiving estrogen replacement therapy, it is not known whether the lack of change in plasma lipids eliminates protection against atherosclerosis. However, a study by Adams et al[14] using monkeys suggested that estrogen is cardioprotective even in the absence of changes in lipid concentrations. Protective effects of oral estrogen on coronary artery atherosclerosis are only explained partially by changes in plasma lipids.[28] Most of estrogen's cardioprotective effect is thought to be via direct action on the artery wall. Androgens may act on the artery wall in a manner opposite that of estrogens to cause increased atherosclerosis. Possible ways that androgens may induce this athrogenic effect are through increased platelet aggregation,[5,29-31] increased collagen in arterial vascular wall lesions,[32] or effects on vasomotion.[33] Androgen receptors are present in the cardiovascular system,[34,35] which suggests a role for androgens in atherosclerosis. Since nandrolone inhibits vasodilator responses,[36] it may induce atherosclerosis by acting as a weak androgen.

Table 3. Body Weight (mean ± SEM, kg)

Group	Baseline	Treatment	Necropsy
Intact-sham	2.83 ± 0.11	2.95 ± 0.14	3.04 ± 0.14
OVX + placebo	2.85 ± 0.11	2.84 ± 0.09	2.89 ± 0.10
OVX + nandrolone, 2 years	2.84 ± 0.15	3.39 ± 0.14*	4.96 ± 0.16†
OVX + nandrolone, 1 year	2.85 ± 0.10	3.02 ± 0.12	4.73 ± 0.27†

*$P < .05$, significantly different from all other treatment groups.

†$P < .05$, significantly different from intact-sham and OVX + placebo groups.

Table 4. Coronary Artery Measurements (mm²)

Group	Plaque Size	IELA	Lumen Area
Intact-sham (n = 12)	0.11 ± 0.04	0.73 ± 0.04	0.61 ± 0.03
OVX + placebo (n = 15)	0.20 ± 0.04	0.77 ± 0.03	0.57 ± 0.03
OVX + nandrolone, 2 years (n = 14)	0.32 ± 0.05*	1.05 ± 0.07†	0.73 ± 0.16‡
OVX + nandrolone, 1 year (n = 11)	0.21 ± 0.05	1.07 ± 0.07†	0.86 ± 0.22†

NOTE. Values are the mean ± SEM.

*$P < .05$, significantly different from intact, sham-operated group.

†$P < .05$, significantly different from intact, sham-operated and OVX + placebo groups.

‡$P < .05$, significantly different from OVX + placebo group.

In the present study, the single best predictor of intimal area was VLDL-C + LDL-C concentrations, but they were not significantly different across groups. This could be because of the relatively small number of animals per group in this study. The power to detect differences in bone is higher than for serum lipids because nandrolone causes significant increases in bone mass,[9-12] and fewer animals are needed to detect expected bone effects than to detect effects on plasma lipid concentrations and atherosclerosis. With a larger sample size, significant changes in plasma lipids may have been detected.

The most discernible effect of nandrolone was in increasing the body weight of treated animals. We do not know if this was an increase in lean body weight or fat, but nandrolone increases lean body mass in postmenopausal women[22] and in body builders,[21] which is the main reason the drug is abused by athletes and teenagers.[1]

An unexpected finding was the significantly higher plasma estradiol concentrations resulting from nandrolone treatment. We believe this represents conversion of a significant amount of androgen into 17β-estradiol. Friedl et al[37] found that 17β-androgens administered parenterally in males were differentially converted to estradiol compared with 17α-androgens given orally. In our study, it is not possible to differentiate estrogenic effects on the coronary arteries from those of the anabolic steroid. Because androgens and estrogens are physiologic antagonists and have opposite actions in breast and ovarian tissue, such an antagonist action also might occur in coronary arteries. Considering the high levels of estradiol in the nandrolone-treated animals, we speculate that the two hormones probably interacted to produce their effects on coronary arteries.

We considered the increase in coronary artery size to be the main effect of nandrolone, because it was found to the same extent in both groups treated with nandrolone.

Interestingly, treatment with nandrolone for 1 year did not significantly affect plaque size. However, animals treated with nandrolone for 2 years had the largest plaques and were the only ones with plaques significantly larger than those of the sham-operated group (Table 3). This indicates an association between longer-term nandrolone treatment and increased atherosclerosis. Hence, because of the larger plaques seen in group 3 animals, smaller lumens resulted as compared with animals in group 4, which had the largest lumen areas of all groups. Early on, nandrolone appears to have an anabolic effect on the coronary arteries, resulting in increased artery size. The atherogenic effects may be more gradual, as illustrated in group 3. The proposed atherogenic effects of androgens in females are supported by the findings of Adams et al[38] that testosterone exacerbates atherosclerosis in premenopausal female cynomolgus macaques.

All reported cases of myocardial infarction with atherosclerosis due to anabolic steroid abuse have been in males.[2-7] The cardiac effects of anabolic steroids may differ in men and women, or fewer women may abuse nandrolone. It is noteworthy that women who receive nandrolone for its bone effects take much lower doses than do persons abusing the drug. The lack of any reported cardiovascular complications in women using the drug therapeutically for osteoporosis may indicate that a lower dosage is not atherogenic or thrombogenic in humans, although such effects often progress subtly. Administration of high-dose oral estrogens caused thromboembolic events in men,[39,40] and if the level of conversion of nandrolone to estradiol seen in the current study occurs in men, it could explain the cases of myocardial infarction. Androgens are converted to estradiol in the testis,[41,42] as well as in fat[43] and muscle.[44] Aromatization in fat is the main means by which conversion of androgens to estradiol occurs in postmenopausal women,[43] and obesity has been linked to high concentrations of circulating estrogen.[45,46] As mentioned earlier, we do not know the fat to lean muscle mass ratios of the body weight gained by animals administered nandrolone. Increases in lean body mass have been found with body builders[21] and postmenopausal osteoporotic women[22] given nandrolone. Adams et al[38] found that the weight gain in monkeys administered testosterone was due to both increased adiposity and lean muscle mass. We suspect that such a combination occurred in this study. This degree of conversion of nandrolone to estradiol also may explain why consistent serum lipid effects have not been obtained with nandrolone. If nandrolone acts like orally administered androgens by reducing HDL-C concentrations but then is converted to estradiol (which increases HDL-C concentrations), effects on plasma lipids may be determined by the androgen to estradiol conversion rate, which in turn may depend on the amount of fat or muscle in individuals.

After controlling for body weight in our study, there was still a significant effect of nandrolone on coronary artery size. Hence, the significant increase in body weight associated with treatment does not fully account for the effects on the coronary artery; nandrolone appears to act directly on the coronary artery to increase its size. Increased coronary artery size has been associated with increasing atherosclerosis (compensatory remodeling) in people without clinical signs of coronary heart disease (CHD).[19] In people with CHD, there is failure of this remodeling process. In one experimental study, hamsters with a cardiomyopathy trait treated with nandrolone lived longer than controls and showed induced arterial remodeling.[47] The present data also support a remodeling effect of nandrolone. Whether a coronary angioplasty procedure succeeds in enlarging the lumen area above the increase produced by atherectomy and in alleviating coronary atherosclerosis depends mainly on an increase in artery size.[48] This means that an intervention that is less invasive than angioplasty but accomplishes the increase in artery size may be beneficial therapeutically. Although nandrolone is clearly not the drug of choice for such an intervention because of its possible atherogenic effects, there might be a need to investigate other compounds for effects on coronary artery size for possible therapeutic interventions in CHD.

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