International Journal of Sport Nutrition and Exercise Metabolism, 2007, 17, 92-108
© 2007 Human Kinetics, Inc.

Eight Weeks of Aromatase Inhibition Using the Nutritional Supplement Novedex XT: Effects in Young, Eugonadal Men

Darryn S. Willoughby, Colin Wilborn, Lemuel Taylor, and William Campbell

This study examined the effects of an aromatase-inhibiting nutritional supplement on serum steroid hormones, body composition, and clinical safety markers. Seventeen eugonadal young men ingested either Novedex XT™ or a placebo daily for 8 wk, followed by a 3-wk washout period. Body composition was assessed and blood and urine samples obtained at weeks 0, 4, 8, and 11. Data were analyzed by 2-way repeated-measures ANOVA. Novedex XT resulted in average increases of 283%, 625%, 566%, and 438% for total testosterone ($P = 0.001$), free testosterone ($P = 0.001$), dihydrotestosterone ($P = 0.001$), and the testosterone:estrogen ratio ($P = 0.001$), respectively, whereas fat mass decreased 3.5% ($P = 0.026$) during supplementation. No significant differences were observed in blood and urinary clinical safety markers or for any of the other serum hormones ($P > 0.05$). This study indicates that Novedex XT significantly increases serum androgen levels and decreases fat mass.

Key Words: testosterone, estrogen, body composition, dihydrotestosterone

Many interested in improving muscle mass and strength typically use anabolic steroids. Anabolic steroids are testosterone derivatives that are used based on their ability to increase serum testosterone levels, thereby stimulating protein synthesis and/or decreasing protein breakdown and increasing muscle mass and strength. The exogenous administration of testosterone in healthy, young eugonadal men increases net protein synthesis and reutilization of intracellular amino acids in skeletal muscle (4). In addition, testosterone increases fat-free mass and decreases fat mass in young men (2, 8). Because of the legal and ethical ramifications associated with anabolic steroid use, however, over the last decade nutritional-supplement companies have tried to create prohormone- and testosterone-derivative compounds such as androstenedione, with the hope of increasing serum testosterone and its subsequent anabolic effects, but have had limited success. The newest type of these nutritional supplements is alleged to be aromatase inhibitors (AIs), which are available on the market with promises of suppressing estrogen levels and subsequently increasing endogenous free-testosterone

The authors are with the Dept. of Health, Human Performance, and Recreation, Waco, TX 76798-7313.

levels (increased free-testosterone:estrogen [T:E] ratio), thereby increasing muscle strength and fat-free mass. Although the effects of various pharmacologic AIs (e.g., anastrozole, exemestane) on the T:E in both young and old men are well characterized (15, 16, 21), none of the claims made by companies marketing AI nutritional supplements appear to be substantiated by any research.

In males, the biosynthesis of estrogens from C_{19} steroids is regulated by the aromatase cytochrome p450 (CYP19), a product of a single CYP19 gene. This enzyme regulates the T:E (an estimate of aromatase activity), irreversibly catalyzes the conversion of androstenedione to estrone (E1) and testosterone to estradiol (E2), and is widely expressed in numerous tissues (19). In men, approximately 80% of circulating estrogens are produced in extraglandular tissues (e.g., adipose, muscle, skin, bone) (11). Because E2 is a crucial mediator of hormonal feedback at the pituitary and hypothalamus in men (7), aromatase inhibition would be expected to promote endogenous pituitary stimulation of testicular testosterone production (13). An attenuation in the T:E, such as with aging, is known to increase fat mass and decrease fat-free mass and muscle strength in men (3), and longer term studies with androgen replacement in men with low or borderline testosterone levels have shown beneficial effects on body composition with no effects on muscle strength (20).

In young men receiving daily 1.0-mg doses of the irreversible AI anastrozole for 10 wk, contrary to the effects of testosterone withdrawal there were significant decreases in E2 with concomitant increases in serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). There were, however, no significant estrogen-suppressive changes in fat mass, fat-free mass, muscle strength, or rates of protein synthesis or degradation (16). The use of AI nutritional supplements in the sports and fitness community is a new approach, and even in light of the fact that there appear to have been no studies conducted using any of these AI sport supplements, nutritional-supplement companies continue to market these products on the premise that they will inhibit aromatase activity, with the supposed result being an increased T:E and a subsequent increase in muscle mass and strength.

Because there currently appear to be no published data on the effects of alleged AI nutritional supplements, we used a commercially available AI nutritional supplement (Novedex XT™) and designed this study with the purpose of determining the effects of 8 wk of AI supplementation on serum steroid hormones, clinical safety markers, and body composition. We also sought to determine the effects of a 3-wk washout period on the same variables assessed during the supplementation period. We hypothesized that this AI nutritional supplement would have no effect on serum steroid-hormone profiles, clinical safety markers, or body composition during the course of the 11-wk study.

Methods

Participants

Sixteen resistance-trained (regular resistance training for at least 3 y), eugonadal men with a mean ± SD age of 26.11 ± 4.42 y, height of 182.88 ± 6.83 cm, total body mass of 91.48 ± 14.42 kg, fat-free mass of 75.59 ± 9.50 kg, and body fat of 17.20% ± 5.94% participated in this placebo-controlled, double-blind study.

All were cleared for participation by passing a mandatory medical screening. Participants with contraindications to exercise as outlined by the American College of Sports Medicine or who had consumed any nutritional supplements (excluding multivitamins) such as creatine monohydrate or various androstenedione derivatives or pharmacologic agents such as anabolic steroids 2 mo before the study were not allowed to participate. All eligible subjects signed a university-approved informed-consent document. In addition, all experimental procedures involved in this study conformed to the ethical considerations of the Helsinki Code.

Testing Sessions

Total body mass and body composition were determined at week 0 and after weeks 4, 8, and 11. Total body mass (kg) was determined on a standard dual-beam balance scale (Detecto, Bridgeview, IL). Percentage body fat, fat mass, and fat-free mass were determined using DEXA (Hologic 4200W, Waltham, MA). Total body water was determined by bioelectric-impedance analysis (Xitron Technologies Inc., San Diego, CA). Venous-blood samples were obtained from the antecubital vein into a 10-mL collection tube. Blood samples were allowed to stand at room temperature for 10 min and then centrifuged. The serum was removed and frozen at –20 °C for later analysis. Urine samples were obtained in midstream in a collection container using a standard collection protocol. Urine samples were frozen at –20 °C for later analysis. Blood and urine samples were obtained at week 0 and after weeks 4, 8, and 11 (3-wk washout period) after a 12-h fast and standardized to the same time of day for each sample. On completing the 8-wk supplementation protocol, all participants underwent a 3-wk washout period. At the end of the washout period, all testing and assessment procedures were performed in the identical fashion as at weeks 0, 4, and 8.

Supplementation Protocol

Participants were equally divided, matched by age and body mass, and then randomly assigned in double-blind fashion to an 8-wk supplementation protocol consisting of oral ingestion of either Novedex or placebo. The Novedex group (n = 8; total body mass = 95.83 ± 17.61 kg, fat-free mass = 80.10 ± 13.21 kg, body fat = 18.40% ± 6.32%) ingested 4 capsules/d (72 mg/d) of AI Novedex XT™ (hydroxyandrost-4-ene-6,17-dioxo-3-THP ether and 3,17-diketo-androst-1,4,6-triene; Gaspari Nutrition, Neptune, NJ) at bedtime, whereas the placebo group (n = 8; total body mass = 87.62 ± 10.44 kg, fat-free mass = 71.07 ± 5.80 kg, body fat = 16.01% ± 5.57%) ingested 4 capsules/d of 72-mg maltodextrin at bedtime. After the supplementation period, a 3-wk washout period was required in which neither supplement was ingested. During both the supplementation and washout periods, the participants' resistance-training sessions and dietary intake were not supervised; however, it was required that all participants keep detailed training and dietary records and not change their routine dietary habits or level of physical activity. On analysis of serum testosterone from the baseline blood samples at week 0, it was confirmed that all participants completing the study were eugonadal (10–30 nmol/L [27–107 ng/mL]) (13) and also had a normal T:E and free-estrogen index (FEI; estrogen/sex-hormone-binding globulin [SHBG]) (21).

Physical Activity and Dietary Records

The participants' diets and physical activity levels were not standardized, and participants were asked to not change their dietary habits during the course of the study. Participants were required to keep weekly physical activity records and 4-d dietary records during weeks 0, 8, and 11 and turn them in during each testing session. Each participant returned all of their dietary and physical activity evaluations at the required time points for a 100% compliance rate. The 4-d dietary recalls were evaluated with the Food Processor dietary-assessment software program (Salem, OR) to determine the average daily macronutrient consumption of fat, carbohydrate, and protein.

Serum Hormone Analyses

Serum samples were assayed for the hormones total and free testosterone, dihydrotestosterone (DHT), total prostate specific antigen (PSA), E1, E2, estriol (E3), SHBG, LH, growth hormone (GH), cortisol (Diagnostics Systems Laboratories, Webster, TX), and FSH (Alpco Diagnostics, Windham, NH), using enzyme-linked immunoabsorbent assays (ELISA) and enzyme-immunoabsorbent assays (EIA) with a Wallac Victor-1420 microplate reader (Perkin-Elmer Life Sciences, Boston, MA), and the assays were performed at a wavelength or either 450 or 405 nm, respectively.

Blood and Urinary Clinical Safety Marker Analyses

The serum clinical-chemistry variables glucose, total protein, blood urea nitrogen, creatinine, BUN:creatinine ratio, uric acid, AST, ALT, CK, LDH, GGT■, albumin, globulin, sodium, chloride, calcium, carbon dioxide, total bilirubin, alkaline phosphatase, triglycerides, cholesterol, high-density lipids, and low-density lipids were determined with a Dade Dimension clinical-chemistry analyzer (Dade-Behring, Inc., Newark, DE). The whole blood, hematological variables, hemoglobin, hematocrit, red-blood-cell counts, MCV, MCH, MCHC, RDW■, neutrophils, lymphocytes, monocytes, eosinophils, and basophils were determined with an Abbott Cell Dyne 3500 hematology analyzer (Abbott Laboratories, Chicago, IL). The urinary variables glucose, ketones, blood, protein, nitrite, bilirubin, leukocyctes, specific gravity, pH, and urobilinogen were analyzed with a Bayer Clinitek 200 Plus urine analyzer (Bayer Diagnostics, Tarrytown, NY).

Statistical Analyses

Statistical analyses were via separate 2×4 (group [Novedex, placebo] $\times$ test [weeks 0, 4, 8, 11]) factorial analyses of variance (ANOVA) with repeated measures for each criterion variable. Further analysis of the main effects for group and test were performed by separate 1-way ANOVAs. Significant between-groups differences at each testing session were then determined with the Tukey post hoc test. Bivariate correlations were performed on selected variables using the Pearson product–moment correlation coefficient. All statistical procedures were performed using SPSS 11.0 software, and a probability level of <0.05 was adopted throughout.

Power analysis of the design indicates that a sample size of 8 per group yields a power greater than 0.80, with delta values between 0.80 and 1.25.

Results

Dietary and Physical Activity Analysis

There were no significant differences between groups in total daily caloric or macronutrient intake of carbohydrates, protein, and fats over the course of the 11 wk (Table 1; $P > 0.05$). In addition, subjective analysis of the physical activity evaluations revealed that none of the participants had any noticeable changes in their level of physical activity over the course of the 11 wk.

Hormones

Significant group × time interactions were observed for total testosterone ($P = 0.001$; Figure 1), free testosterone ($P = 0.001$; Figure 2), DHT ($P = 0.001$; Figure 3), and T:E ($P = 0.002$; Figure 4), indicating increases in these variables for the Novedex group compared with placebo at the 4- and 8-wk sampling periods. No significant interactions or main effects ($P > 0.05$) were observed, however, for PSA, E1, E2, E3, SHBG, FEI, LH, FSH, GH, and cortisol (Table 2).

Table 1 Four-Day Dietary Analyses for the Placebo and Novedex Groups During Weeks 0, 8, and 11, Mean ± SD

	Placebo			Novedex		
	Week 0	Week 8	Week 11	Week 0	Week 8	Week 11
Protein (g/kg)	1.9 ± 1.0	2.4 ± 1.6	2.4 ± 1.4	2.5 ± 0.8	2.7 ± 1.1	2.6 ± 0.9
Fat (g/kg)	1.7 ± 0.5	1.5 ± 0.5	1.3 ± 0.8	1.7 ± 1.6	1.3 ± 0.6	1.2 ± 0.5
Carbohydrates (g/kg)	2.3 ± 0.6	2.2 ± 0.6	2.3 ± 0.7	2.6 ± 1.3	2.8 ± 1.3	2.8 ± 1.5
Total calories (kcal/kg)	26 ± 6.0	28 ± 8.0	28 ± 6.0	31 ± 10.0	31 ± 8.0	31 ± 9.0

No significant differences were observed between groups throughout the 11-wk study for total calories or macronutrient intakes ($P > 0.05$).

Body Composition

No significant group × time interactions were observed for any of the body-composition variables. For fat mass, however, there was a significant main effect for group ($P = 0.038$) and test ($P = 0.009$), indicating decreases in fat mass for the Novedex group compared with placebo occurring at the 8-wk sampling period (Figure 5). No significant changes ($P > 0.05$) were observed, however, for total body mass, total body water, or fat-free mass (Table 3).

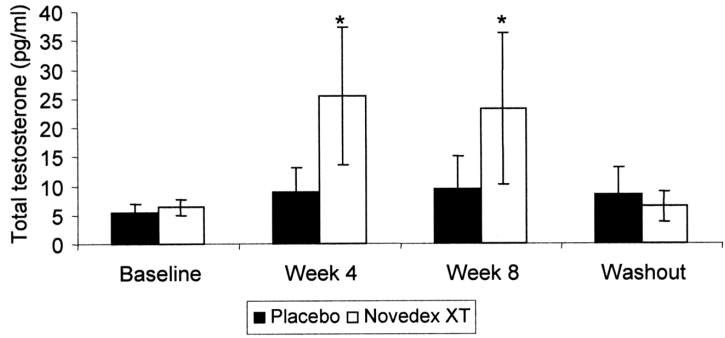

Figure 1 — Serum total testosterone levels over the course of the 11 wk. A group × time interaction was observed ($P = 0.001$). *Significant increase for the Novedex group compared with placebo at the 4- and 8-wk sampling period.

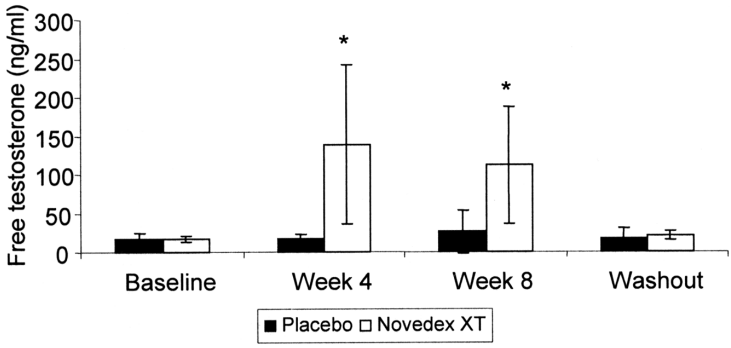

Figure 2 — Serum free-testosterone levels over the course of the 11 wk. A group × time interaction was observed ($P = 0.001$). *Significant increase for the Novedex group compared with placebo at the 4- and 8-wk sampling period.

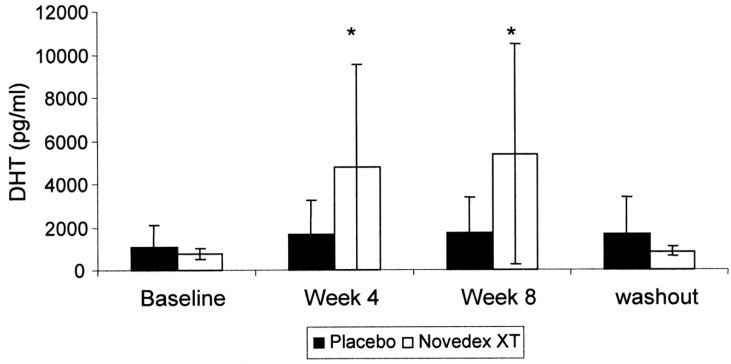

Figure 3 — Serum dihydrotestosterone levels over the course of the 11 wk. A group × time interaction was observed ($P = 0.001$). *Significant increase for the Novedex group compared with placebo at the 4- and 8-wk sampling period.

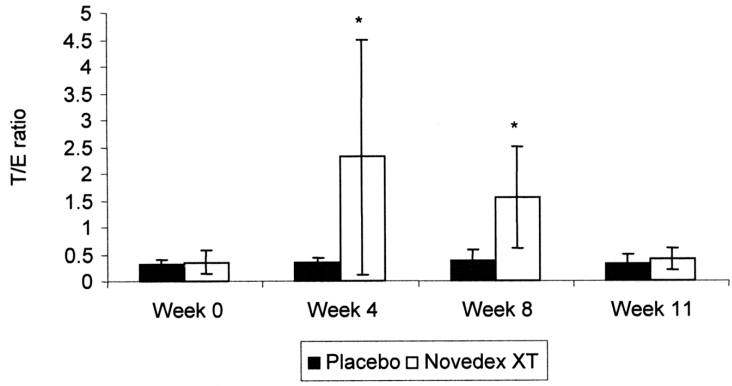

Figure 4 — Serum free-testosterone:estradiol ratio (T:E) levels over the course of the 11 wk. A group × time interaction was observed ($P = 0.002$). *Significant increase for the Novedex group compared with placebo at the 4- and 8-wk sampling period.

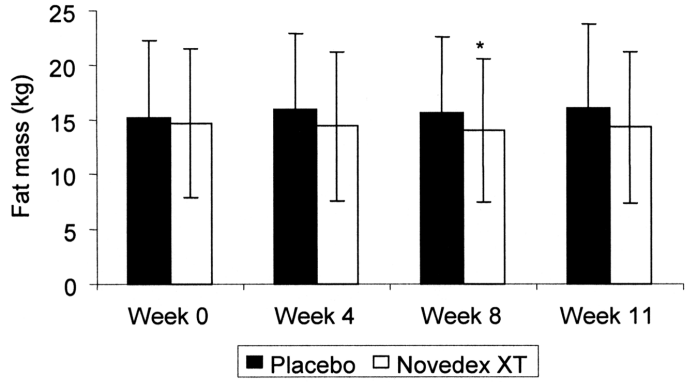

Figure 5 — Fat mass over the course of the 11 wk. A significant main effect for group ($P = 0.038$) and test ($P = 0.009$) was observed. *Significant decreases in fat mass for the Novedex group compared with placebo occurring at the 8-wk sampling period.

Clinical Safety Data

No significant group × time interactions or main effects ($P > 0.05$) were observed for any of the whole-blood, serum, and urinary clinical safety markers (Tables 4, 5, and 6).

Discussion

The purpose of this study was to evaluate the effects of an alleged AI nutritional supplement on serum hormone levels, body composition, and clinical safety markers. Our hypothesis was not supported because this study demonstrated 8 wk of

Table 2 Serum-Hormone Values for the Placebo and Novedex Groups at Weeks 0, 4, 8, and 11, Mean ± SD

	Placebo				Novedex			
	Week 0	Week 4	Week 8	Week 11	Week 0	Week 4	Week 8	Week 11
PSA (ng/mL)	3.4 ± 0.5	3.5 ± 0.6	3.7 ± 0.6	3.4 ± 0.5	3.3 ± 0.6	3.5 ± 0.6	3.4 ± 0.6	3.1 ± 0.3
Estrone (pg/ml)	361.2 ± 63.7	395.1 ± 124.3	392.0 ± 173.8	410.3 ± 150.6	405.1 ± 167.1	43057 ± 85.4	433.89 ± 11.5	431.0 ± 153.0
Estradiol (pg/mL)	63.0 ± 50.3	54.3 ± 38.2	58.3 ± 37.2	56.8 ± 36.9	78.0 ± 80.9	91.6 ± 101.1	102.5 ± 124.9	75.3 ± 73.9
Estriol (pg/mL)	0.06 ± 0.03	0.10 ± 0.05	0.12 ± 0.04	0.13 ± 0.05	0.07 ± 0.04	0.07 ± 0.05	0.10 ± 0.02	0.11 ± 0.04
FEI	4.1 ± 4.6	4.1 ± 5.3	4.5 ± 5.3	4.1 ± 4.5	4.3 ± 4.3	5.7 ± 5.3	6.4 ± 6.7	4.29 ± 2.9
SHBG (pg/mL)	18.3 ± 5.4	17.3 ± 5.17	17.1 ± 5.2	17.5 ± 5.7	19.2 ± 7.9	16.5 ± 7.3	16.2 ± 8.2	18.1 ± 8.3
LH (pg/dL)	3.5 ± 1.5	4.7 ± 2.1	4.4 ± 1.9	3.4 ± 1.6	3.9 ± 2.2	4.6 ± 2.3	4.1 ± 2.8	3.3 ± 2.1
FSH (pg/mL)	19.3 ± 29.0	20.2 ± 29.9	18.26 ± 26.9	18.1 ± 27.1	19.0 ± 24.8	20.3 ± 27.1	19.8 ± 26.7	17.9 ± 23.2
Cortisol (pg/mL)	32.8 ± 5.7	31.9 ± 9.1	29.8 ± 6.1	31.1 ± 6.6	30.9 ± 5.1	29.3 ± 68	33.2 ± 6.4	31.7 ± 5.0
GH (pg/mL)	111.9 ± 141.8	63.4 ± 120.9	83.1 ± 114.6	101.5 ± 144.5	81.6 ± 118.5	30.9 ± 18.7	59.5 ± 75.1	58.4 ± 120.5

PSA indicates prostate-specific antigen; FEI, free-estrogen index; SHBG, sex-hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; and GH, growth hormone. No significant differences were observed between groups throughout the 11-wk study for the hormone variables included above ($P > 0.05$).

Table 3 Body-Composition Values for Total Body Mass, Total Body Water, Fat-Free Mass, and Percentage Body Fat for the Placebo and Novedex Groups at Weeks 0, 4, 8, and 11, Mean ± SD

	Placebo				Novedex			
	Week 0	Week 4	Week 8	Week 11	Week 0	Week 4	Week 8	Week 11
Total body mass (kg)	87.6 ± 10.4	87.8 ± 10.2	87.6 ± 10.1	88.2 ± 11.27	95.8 ± 17.6	96.7 ± 16.9	95.6 ± 16.8	95.9 ± 17.2
Total body water (kg)	48.9 ± 4.7	49.4 ± 3.8	49.3 ± 3.9	50.8 ± 5.3	54.1 ± 9.5	56.1 ± 8.9	56.6 ± 7.9	55.7 ± 7.8
Fat-free mass (kg)	71.1 ± 5.8	70.6 ± 5.8	70.8 ± 5.7	70.8 ± 6.4	80.1 ± 13.2	81.1 ± 13.1	81.5 ± 12.9	80.6 ± 13.2
Body fat (%)	18.4 ± 6.3	19.4 ± 6.3	18.7 ± 6.5	19.1 ± 6.9	16.1 ± 5.6	15.8 ± 5.7	15.3 ± 5.3	15.6 ± 5.6

No significant differences were observed between groups throughout the 11-wk study for total body mass, total body water, or fat-free mass ($P > 0.05$).

Table 4 Whole-Blood Clinical-Chemistry Markers for the Placebo and Novedex Groups During Weeks 0, 4, 8, and 11, Mean ± SD

	Placebo				Novedex			
	Week 0	Week 4	Week 8	Week 11	Week 0	Week 4	Week 8	Week 11
WBCC (K/μL)	5.8 ± 1.5	5.9 ± 1.1	5.5 ± 0.7	5.4 ± 1.2	4.7 ± 1	4.9 ± 1.4	5.4 ± 2.4	5.4 ± 1.9
RBCC (M/μL)	5.1 ± 0.39	5.1 ± 0.42	5.2 ± 0.29	5.2 ± 0.35	5.5 ± 0.8	5.1 ± 0.31	5.3 ± 0.29	5.0 ± 0.39
Hemoglobin (g/dL)	15 ± 0.08	15 ± 1.3	15 ± 0.5	15 ± 1.1	17 ± 1.6	16 ± 0.83	16 ± 0.85	15 ± 0.1
Hematocrit (%)	44 ± 2.6	44 ± 3.4	44 ± 1.4	45 ± 3.3	47 ± 2.8	45 ± 2.2	47 ± 2.0	44 ± 2.8
MCV (fL)	87 ± 3	86 ± 3	86 ± 3	87 ± 3	87 ± 1.5	88 ± 2.2	89 ± 2.0	88 ± 1.7
MCH (pg)	30 ± 1.2	30 ± 1.5	30 ± 1.0	30 ± 1.0	31 ± 0.6	30 ± 0.6	30 ± 0.5	30 ± 0.4
MCHC (g/dL)	34 ± 0.63	35 ± 1.2	34 ± 0.82	33 ± 1.8	35 ± 0.76	34 ± 0.75	33 ± 0.65	34 ± 0.58
Neutrophils	2.8 ± 0.9	3.0 ± 0.44	3.0 ± 1.1	2.7 ± 0.55	2.4 ± 0.6	2.6 ± 0.8	3 ± 1.6	2.9 ± 1.3
Lymphocytes	1.9 ± 0.57	1.9 ± 0.53	2.2 ± 0.56	1.9 ± 0.70	1.7 ± 0.36	1.6 ± 0.4	1.7 ± 0.66	1.7 ± 0.58
Monocytes	.49 ± 0.23	.55 ± 0.19	.63 ± 0.47	.43 ± 0.18	.36 ± 0.09	.40 ± 0.14	.44 ± 0.22	.47 ± 0.21
Eosinophils	.25 ± 0.19	.18 ± 0.12	.17 ± 0.11	.19 ± 0.10	.14 ± 0.09	.14 ± 0.09	.13 ± 0.08	.16 ± 0.12
Basophils	.06 ± 0.02	.06 ± 0.02	.06 ± 0.02	.06 ± 0.01	0.05 ± 0.02	.06 ± 0.04	.07 ± 0.04	.05 ± 0.03

WBCC indicates white-blood-cell count; RBCC, red-blood-cell count; MCH, ■; and MCHC, . No significant differences were observed between groups throughout the 11-wk study for whole-blood clinical-chemistry variables ($P > 0.05$).

Table 5 Serum Clinical-Chemistry Markers for the Placebo and Novedex Groups During Weeks 0, 4, 8, and 11, Mean ± SD

	Placebo				Novedex			
	Week 0	Week 4	Week 8	Week 11	Week 0	Week 4	Week 8	Week 11
Triglyceride (mg/dl)	96 ± 57	80 ± 34	91 ± 40	105.3 ± 54	92 ± 35	96 ± 57	86 ± 39	72 ± 12
Cholesterol (mg/dl)	189 ± 24	178 ± 14	185 ± 12	179 ± 16	187 ± 29	187 ± 31	183 ± 36	175 ± 43
HDL (mg/dL)	66 ± 19	61 ± 13	57 ± 18	59 ± 12	50 ± 11	53 ± 15	48 ± 15	51 ± 19
LDL (mg/dL)	100 ± 17	94 ± 16	102 ± 12	95 ± 12	108 ± 18	109 ± 12	111 ± 24	99 ± 20
GGT (U/L)	44 ± 17	43 ± 21	35 ± 14	39 ± 17	40 ± 16	34 ± 12	38 ± 18	30 ± 18
LDH (U/L)	139 ± 28	156 ± 37	144 ± 27	143 ± 14	170 ± 44	155 ± 32	154 ± 16	171 ± 58
Uric Acid (g/dl)	6 ± 1.1	6 ± 1.3	5.5 ± 1.1	6.3 ± 1.2	7 ± .8	6.5 ± 1.5	6.5 ± 1.3	6 ± 1.2
Glucose mg/dl	92 ± 20	90 ± 7	92 ± 19	85 ± 18	93 ± 7.5	96 ± 7.7	84 ± 4	85 ± 8
BUN (mg/dL)	24 ± 6	20 ± 5	18 ± 5	18 ± 3	20 ± 4	26 ± 2	20 ± 5	15 ± 3
Creatinine (mg/dl)	1.2 ± .4	1.2 ± 0.2	1.2 ± 0.2	.94 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	1.4 ± 0.15	3.2 ± 4.9
Ca (mg/dl)	10 ± 1.3	9.7 ± 3.6	9.5 ± .29	9.6 ± .67	9.7 ± .0.33	9.9 ± .26	9.7 ± .42	9.4 ± .43
Total protein g/dL	7.9 ± 1.1	7.7 ± 0.5	7.9 ± 0.8	7.8 ± 0.6	7.6 ± 0.4	7.8 ± 0.4	7.88 ± 0.4	7.3 ± 0.6
Albumin g/dL	5.1 ± 0.58	4.9 ± 0.3	5.5 ± 1.1	5.5 ± 0.3	4.9 ± 0.2	5 ± 0.25	5 ± 0.27	4.8 ± 0.36
Total bilirubin (mg/dl)	0.8 ± 0.2	0.7 ± 0.0	1.4 ± 1.7	0.7 ± 0.4	0.7 ± 0.25	0.6 ± 0.4	0.9 ± 0.3	0.6 ± 0.3
ALP (U/L)	81 ± 22	77 ± 15	70 ± 13	74 ± 17	71 ± 16	67 ± 15	72 ± 18	69 ± 15
AST (U/L)	22 ± 5	27 ± 9	24 ± 6	24 ± 6	44 ± 22	35 ± 19	27 ± 7	27 ± 8
ALT (U/L)	38 ± 9	44 ± 13	31 ± 10	26 ± 9	41 ± 8	35 ± 12	28 ± 7	30 ± 6
CK (U/L)	183 ± 71	475 ± 630	214 ± 143	264 ± 266	179 ± 186	560 ± 541	180 ± 92	304 ± 251

HDL indicates high-density lipids; LDL, low-density lipids; GGT, ; LDH, ; BUN, ; Ca, ; ALP, ; AST, ; ALT, ; and CK, ■. No significant differences were observed between groups throughout the 11-wk study for serum clinical-chemistry variables ($P > 0.05$).

Table 6 Urine Clinical Safety Markers for the Placebo and Novedex Groups During Weeks 0, 4, 8, and 11, Mean ± SD

Week	Placebo				Novedex			
	Week 0	Week 4	Week 8	Week 11	Week 0	Week 4	Week 8	Week 11
Glucose	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Ketones	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Blood	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Protein	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Nitrite	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Bilirubin	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Leukocytes	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Specific gravity	1.02 ± 0.01	1.02 ± 0.01	1.01 ± 0.01	1.02 ± 0.01	1.02 ± 0.01	1.02 ± 0.01	1.02 ± 0.01	1.02 ± 0.01
pH	5.5 ± 0.76	5.6 ± 0.58	5.9 ± 0.90	5.4 ± 0.68	5.8 ± 1.13	5.8 ± 1.13	5.8 ± 1.13	5.8 ± 1.13
Urobilinogen (E.U./dL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Glucose	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

Zeroes indicate the lack of detectable variable in the urine. No significant differences were observed between groups throughout the 11-wk study for urinary clinical-chemistry variables ($P > 0.05$).

Novedex XT supplementation to be an effective means of increasing endogenous testosterone production in healthy, young eugonadal men. Specifically, our results demonstrated that the Novedex group underwent significant decreases in fat mass and increases in total and free testosterone and DHT, with no changes in PSA levels and only modest corresponding nonsignificant increases in the 3 estrogen hormones over the course of the supplementation period. Our hypothesis was supported, however, on the premise that Novedex XT supplementation was well tolerated by all participants because they reported no side effects, and similar to previous studies using the AI anastrozole (16, 18), there were no significant changes observed in any of the clinical safety markers, indicating 8 wk of Novedex XT at 72 mg/d to be safe within the confines of the study's design (see Tables 2–4).

Testosterone and E2 do not completely circulate freely in the blood once produced, and both are almost 100% bound in blood to proteins, with 40% bound to albumin, 40% bound to SHBG, and 17% bound to other proteins (7). The small fraction of both hormones not bound is considered the free and bioactive component of the hormone, and the ratio between SHBG and total testosterone and E2 can be used to estimate the amount of unbound, bioactive hormone. Our results in the placebo group highlight this relationship; although we observed no changes in androgen or estrogen level we did observe free testosterone and the FEI to be significantly correlated at weeks 0 ($r = 0.904$, $P = 0.004$), 4 ($r = 0.954$, $P = 0.002$), 8 ($r = 0.986$, $P = 0.001$), and 11 ($r = 0.988$, $P = 0.001$). We also observed no changes in SHBG in the placebo group over the course of the 8-wk supplementation period; however, although not statistically significant ($P > 0.05$), there was an average 15% decrease in SHBG in the Novedex group. Because we observed significant increases in serum androgen levels for the Novedex group, our results are consistent with previous data demonstrating that an elevation in serum androgens decreases SHBG concentration (22).

The results of this study demonstrate that over the course of the 8-wk supplementation period no changes in serum androgens or estrogens were noted in the placebo group ($P > 0.05$). The Novedex group, however, had average increases of 283%, 625%, and 566% for total testosterone, free testosterone, and DHT ($P < 0.05$), respectively, and all 3 androgens returned to baseline levels after the 3-wk washout period. Furthermore, in the Novedex group we did not observe decreases in estrogen levels during the supplementation period but, rather, overall average nonsignificant ($P > 0.05$) increases of 27%, 24%, and 7%, respectively, for E1, E2, and E3. Novedex XT is marketed as a 4-hydroxyandrostenedione (4-OHA) steroidal AI structurally related to the natural substrate androsteneione■ that is metabolized to an intermediate and then irreversibly binds to the active site of the aromatase enzyme, thereby rendering it inactive. Although our data suggest Novedex XT to be effective in increasing endogenous testosterone levels, it does not appear to completely inhibit aromatase activity. In the presence of an AI, however, the levels of free testosterone and E2 are inversely typically proportionate to one another (17); therefore, our observed effectiveness of Novedex XT can be further supported by the overall average increase in the T:E of 438% we observed in the Novedex group that was significantly correlated with the levels of free testosterone at weeks 4 ($r = 0.806$, $P = 0.016$) and 8 ($r = 0.870$, $P = 0.013$).

Because E2 is a crucial mediator of hormonal feedback at the pituitary and hypothalamus in men, aromatase inhibition would be expected to promote pitu-

itary stimulation of testicular testosterone production (13). Novedex's effect on androgen production is likely directly mediated by the lack of significant increases in estrogen production. By Novedex XT partially blunting aromatase activity and E2's apparent negative feedback on the pituitary and hypothalamus, although not significant, the 9% increase in pituitary LH secretion might have been sufficient to trigger increases in endogenous testosterone production. Although it is apparent that Novedex XT effectively limited aromatase activity to cause significant increases in T:E, our data suggest an incomplete effect on lowering E2 levels. For example, at week 4 the Novedex group exhibited increases of 711% for free testosterone and 17% for E2, whereas free testosterone and E2 were increased 563% and 30%, respectively, at week 8 and were significantly correlated with one another (r = 0.854, P = 0.007).

There is an association between serum testosterone and DHT (12), and although androgen levels did not increase in the placebo group, we did observe total testosterone and DHT to be significantly correlated at weeks 0 (r = 0.848, P = 0.004), 4 (r = 0.954, P = 0.001), 8 (r = 0.986, P = 0.001), and 11 (r = 0.988, P = 0.001). Despite the large increase in DHT in the Novedex group over the course of the supplementation period, the levels of PSA did not change and remained within normal limits (Table 3), suggesting that the increases in DHT levels induced by Novedex XT were not associated with any concomitant increases in PSA. Moreover, the levels of DHT and total testosterone at weeks 4 (r = 0.776, P = 0.024) and 8 (r = 0.812, P = 0.021) were shown to be significantly correlated to one another, thereby suggesting a role of Novedex in up-regulating the 5α-reductase enzyme concomitant with the significant increase in total testosterone. Because DHT is a nonaromatizable androgen (16), however, and considering the supraphysiological levels of testosterone present at the 4- and 8-wk time points, it is conceivable that the apparent testosterone aromatization occurring was in part responsible for the observed elevations in E2.

It should be noted, however, that over the 8-wk supplementation period, the Novedex group underwent an overall nonsignificant increase of 42% in the FEI (P > 0.05), although the FEI was significantly correlated to E2 at weeks 0 (r = 0.964, P = 0.001), 4 (r = 0.965, P = 0.001), 8 (r = 0.907, P = 0.002), and 11 (r = 0.910, P = 0.002), thereby indicating that aromatase activity was not completely inhibited throughout the 8-wk period. The increase in the FEI was apparently overshadowed, however, by the robust significant increase in the T:E, which suggests that our observed changes in the T:E and FEI are likely a result of central feedback from the pituitary and hypothalamus, which we demonstrated to produce respective increases of 10% and 9% in FSH and LH, respectively. Although the increases in FSH and LH were modest and nonsignificant (P > 0.05), they could have been enough to cause the observed elevations in testosterone, thereby providing more substrate and blunting the effectiveness of Novedex XT. This assumption can be partially explained on the premise that E2 and FSH were significantly correlated at weeks 0 (r = 0.937, P = 0.001), 4 (r = 0.926, P = 0.001), 8 (r = 0.964, P = 0.001), and 11 (r = 0.976, P = 0.001). Therefore, our results might solidify this issue of pituitary and hypothalamic feedback relative to E2 and FSH, because we also demonstrated that the FEI and FSH were significantly correlated at weeks 0 (r = 0.912, P = 0.002), 4 (r = 0.917, P = 0.001), 8 (r = 0.933, P = 0.001), and 11 (r = 0.907, P = 0.002).

In men undergoing increases in endogenous testosterone concentrations, the serum testosterone level is a reasonable surrogate measure for potential muscle growth and increased strength (1) and can be a reasonable predictor of significant ergogenic effects. Because the Novedex group was shown to undergo marked increases in serum total- and free-testosterone levels in young, eugonadal men over the course of the 8-wk supplementation period, our data suggest that this type of AI nutritional supplement might effectively increase muscle mass. The fact that we failed to detect significant increases in fat-free mass could possibly be attributed to the relatively short duration of the supplementation period. Testosterone in supraphysiological blood concentrations increases muscle mass and strength in healthy, eugonadal men (1). It has previously been shown (16), however, that specific blockade of the aromatase enzyme with anastrozole for 10 wk did not have catabolic effects on protein metabolism, and it did not affect body composition or muscle strength; these data suggest that in light of the 50% suppression in E2, the reciprocal 58% elevation in circulating testosterone was not enough to mediate changes in protein kinetics, body composition, and muscle strength. Conversely, in young men 10 wk of severe hypogonadism induced by the GnRH analog lupron was associated with decreased rates of whole-body protein turnover and synthesis, decreased fat-free mass and fat oxidation, and increased adiposity, thereby supporting the role of androgens in maintaining normal body composition in men (14).

Unfortunately, in the present study we did not determine muscle strength or mass; however, we did assess body composition and found that Novedex XT had no effect on fat-free mass (an indirect indicator of muscle mass) but was effective at producing a modest but significant 3.5% decrease in fat mass when compared with placebo. This decrease in fat mass was further verified by an effect size of 0.60. Increased androgens associated with hypergonadism have been shown to stimulate lipolysis because of increases in the activity of hormone-sensitive lipase (10) and to also increase heat production in brown adipose tissue because of the increased expression of uncoupling protein-3 (5). On the other hand, hypogonadism is known to be associated with less-efficient fat oxidation and a concomitant decrease in the resting energy expenditure, which is the likely reason that this condition is associated with increases in adiposity and decreases in fat-free mass. Our results, however, suggest the contrary; in the placebo group we observed significant correlations at week 11 between E2 and percentage fat ($r = 0.858$, $P = 0.003$) and fat mass ($r = .770$, $P = 0.015$), whereas at week 11 in the Novedex group we observed a significant correlation between percentage fat and LSH ($P = 0.726$, $P = 0.041$) and fat mass and LSH at weeks 4 ($r = 0.839$, $P = 0.009$) and 11 ($r = 0.737$, $P = 0.037$).

E2 inhibits IGF-1 and might attenuate the circulating IGF-1 responses to GH (9), primarily based on the premise that estrogen might down-regulate hepatic GH receptors, alter the hypathopituitary–adrenal axis (HPTA), and impede tissue responsiveness to GH (16). In light of this, we were interested in determining the effects of Novedex XT supplementation on serum GH and cortisol. For the placebo and Novedex groups, we observed no changes in serum cortisol; although not significant, over the course of the supplementation period there was an average 45% decrease in serum GH in the Novedex group. Although we did not measure serum IGF-1, in the context of incomplete inhibition of aromatase activity with Novedex XT, it is plausible that the suppression in the HPTA and potential

GH-receptor down-regulation might have affected the hepatic release of IGF-1, thereby possibly negating any observable increases in fat-free mass. This assumption can be partly supported by previous data showing that complete E2 suppression with anastrozole had no effect on serum GH but decreased IGF-1 (16) and that a 38% suppression of E2 with exemestane had no effect on IGF-1 (15).

Although AI drugs such as anastrozole and exemestane are not new, AI nutritional supplements are relatively new to the fitness community. AI drugs have been used for years as a method of preventing and treating various types of cancer such as breast cancer. Although there are data available on AI-inhibiting drugs used in human clinical trials, currently there appear to be no published data on the effects of nutritional supplements that are alleged to function as aromatase inhibitors. The results of this study indicate that 8 wk of Novedex XT supplementation had no effect on PSA and other clinical safety markers but incompletely inhibited aromatase activity and significantly increased endogenous androgen levels that were attenuated after a 3-wk washout period. Our results also indicate that Novedex XT decreases fat mass; however, this effect does not appear to be correlated with the observed increase in endogenous androgen levels.

Acknowledgments

This study was funded by Gaspari Nutrition, Neptune, NJ.

References

1. Bhasin, S., T. Storer, N. Berman, N. Callegari, B. Clevenger, J. Phillips, T. Bunnell, R. Tricker, A. Shirazi, and R. Casaburi. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* 335(1):1-7, 1996.
2. Bhasin, S., T. Storer, N. Berman, K. Yarasheski, B. Clevenger, J. Phillips, W. Lee, T. Bunnell, and R. Casaburi. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J. Clin. Endocrinol. Metab.* 82(2):407-413, 1997.
3. Bross, R., R. Casuburi, T. Storer, and S. Bhasin. Androgen effects on body composition and muscle function: implications for the use of androgens as anabolic agents in sarcopenic states. *Baillieres Clin. Endocrinol. Metab.* 12(3):365-378, 1998.
4. Ferrando, A., K. Tipton, D. Doyle, S. Phillips, J. Cortiella, and R. Wolfe. Testosterone injection stimulates net protein synthesis but not tissue amino acid transport. *Am. J. Physiol.* 275(5 Pt 1):E864-E871, 1998.
5. Hampl, R., L. Starka, and L. Jansky. Steroids and thermogenesis. *Physiol. Res.* 55(2):123-131, 2006.
6. Hayes, F. Testosterone: fountain of youth or drug of abuse? *J. Clin. Endocrinol. Metab.* 85(9):3020-3023, 2000.■
7. Hayes, F., S. Seminara, S. Decruz, P. Boepple, W. Crowley. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. *J. Clin. Endocrinol. Metab.* 85(9):3027-3035, 2000.
8. Herbst, K., and S. Bhasin. Testosterone action on skeletal muscle. *Curr. Opin. Clin. Nutr. Metab. Care.* 7(3):271-277, 2004.
9. Holloway, L., G. Butterfield, R. Hintz, N. Gesundheit, and R. Marcus. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. *J. Clin. Endocrinol. Metab.* 79(2):470-479, 1994.
10. Hossian, A., and C. Hornick. Androgenic modulation of lipid metabolism at subcellular sites in cholestatic rats. *Horm. Metab. Res.* 26(1):19-25, 1994.

11. Ismail, A., and J. Barth. Endocrinology of gynecomastia. *Ann. Clin. Biochem.* 38(6):597-607, 2001.
12. Jockenhovel, F., C. Bullmann, M. Schubert, E. Vogel, W. Reinhardt, D. Muller-Wieland, and W. Krone. Influence of various modes of androgen substitution on serum lipids and lipoproteins in hypogonadal men. *Metabolism.* 48(5):590-596, 1999.
13. Leder, B., J. Rohrer, S. Rubin, J. Gallo, and C. Longcope. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. *J. Clin. Endocrinol. Metab.* 89(3):1174-1180, 2004.
14. Mauras, N., V. Hayes, S. Welch, A. Rini, K. Helgeson, M. Dokler, J. Veldhuis, and R. Urban. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J. Clin. Endocrinol. Metab.* 83(6):1886-1892, 1998.
15. Mauras, N., J. Lima, D. Patel, A. Rini, E. diSalle, A. Kwok, and B. Lippe. Pharmacokinetics and dose finding of a potent aromatase inhibitor, aromasin (exemestane), in young males. *J. Clin. Endocrinol. Metab.* 88(12):5951-5956, 2003.
16. Mauras, N., K. O'Brien, K. Klein, and V. Hayes. Estrogen suppression in males: metabolic effects. *J. Clin. Endocrinol. Metab.* 85(7):2370-2377, 2000.
17. Orwoll, E., L. Lambert, L. Marshall, K. Phipps, J. Blank, E. Barrett-Connor, J. Cauley, K. Ensrud, and S. Cummings. Testosterone and estradiol among older men. *J. Clin. Endocrinol. Metab.* 91(4):1336-1344, 2006.
18. Plourde, P., E. Reiter, J. Hann-Chang, P. Descochers, S. Rubin, B. Bercu, F. Diamond, and B. Backeljauw. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* 89(9):4428-4433, 2004.
19. Simpson, E. Genetic mutations resulting in estrogen insufficiency in the male. *Mol. Cell. Endocrinol.* 145(1-2):55-59, 1998.
20. Snyder, P., H. Peachey, P. Hannoush, J. Berlin, L. Loh, D. Lenrow, J. Holmes, A. Dlewati, J. Santanna, C. Rosen, and B. Strom. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J. Clin. Endocrinol. Metab.* 84(8):2647-2653, 1999.
21. Taxel, P., D. Kennedy, P. Fall, A. Willard, J. Clive, and L. Raisz. The effect of aromatase inhibition on sex steroids, gonadotropins, and markers of bone turnover in older men. *J. Clin. Endocrinol. Metab.* 86(6):2869-2874, 2001.
22. Zumoff, B., G. Strain, L. Miller, W. Rosner, R. Senie, D. Seres, and R. Rosenfeld. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. *J. Clin. Endocrinol. Metab.* 71(4):929-931, 1990.