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Prohormone supplement 3β-hydroxy-5α-androst-1-en-17-one enhances resistance training gains but impairs user health

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Granados J, Gillum TL, Christmas KM, Kuennen MR. Prohormone supplement 3β-hydroxy-5α-androst-1-en-17-one enhances resistance training gains but impairs user health. *J Appl Physiol* 116: 560–569, 2014. First published December 31, 2013; doi:10.1152/japplphysiol.00616.2013.—Prohormone supplements (PS) are recognized not to impart anabolic or ergogenic effects in men, but the research supporting these conclusions is dated. The Anabolic Steroid Control Act was amended in 2004 to classify androstenedione and 17 additional anabolic compounds as controlled substances. The viability of PS that entered the market after that time have not been evaluated. Seventeen resistance-trained men (23 ± 1 yr; 13.1 ± 1.5% body fat) were randomly assigned to receive either 330 mg/day of 3β-hydroxy-5α-androst-1-en-17-one (Prohormone; $n = 9$) or sugar (Placebo; $n = 8$) per os and complete a 4-wk (16 session) structured resistance-training program. Body composition, muscular strength, circulating lipids, and markers of liver and kidney dysfunction were assessed at study onset and termination. Prohormone increased lean body mass by 6.3 ± 1.2%, decreased fat body mass by 24.6 ± 7.1%, and increased their back squat one repetition maximum and competition total by 14.3 ± 1.5 and 12.8 ± 1.1%, respectively. These improvements exceeded ($P < 0.05$) Placebo, which increased lean body mass by 0.5 ± 0.8%, reduced fat body mass by 9.5 ± 3.6%, and increased back squat one repetition maximum and competition total by 5.7 ± 1.7 and 5.9 ± 1.7%, respectively. Prohormone also experienced multiple adverse effects. These included a 38.7 ± 4.0% reduction in HDL ($P < 0.01$), a 32.8 ± 15.05% elevation in LDL ($P < 0.01$), and elevations of 120.0 ± 22.6 and 77.4 ± 12.0% in LDL-to-HDL and cholesterol-to-HDL ratios, respectively (both $P < 0.01$). Prohormone also exhibited elevations in serum creatinine (19.6 ± 4.3%; $P < 0.01$) and aspartate transaminase (113.8 ± 61.1%; $P = 0.05$), as well as reductions in serum albumin (5.1 ± 1.9%; $P = 0.04$), alkaline phosphatase (16.4 ± 4.7%; $P = 0.04$), and glomerular filtration rate (18.0 ± 3.3%; $P = 0.04$). None of these values changed (all $P > 0.05$) in Placebo. The oral PS 3β-hydroxy-5α-androst-1-en-17-one improves body composition and muscular strength. However, these changes come at a significant cost. Cardiovascular health and liver function are particularly compromised. Given these findings, we feel the harm associated with this particular PS outweighs any potential benefit.

prohormone; 3β-hydroxy-5α-androst-1-en-17-one; resistance training

ANABOLIC STEROIDS (AS) INCREASE muscle mass and strength (6, 7, 43, 44, 49) but also cause marked cardiac (1, 2, 9, 13), hepatic (9, 14, 22), renal (29, 50), and psychological (16, 35, 36) dysfunction. The Anabolic Steroid Control Act of 1990, which regulated AS as a class of drugs under Schedule III of the Controlled Substances Act, was enacted for these reasons (21). An unintended consequence of this legislation was the emergence of prohormone supplements (PS) on the dietary supplement market. Recreational and competitive athletes were drawn to these supplements, which were marketed as legal alternatives to AS because they were not enzymatically activated to testosterone derivatives until after they had been ingested. Despite their widespread popularity, PS retained a remarkably low profile until the late 1990's, at which time controversy surrounding their unregulated use in major league baseball brought them substantial media attention.

That controversy effectively pulled PS out of the shadows. It also enticed sports scientists to conduct some of the first empirical research on their efficacy and side effects. Those research efforts provided conclusive evidence that the PS available at that time, namely dehydroepiandrosterone (DHEA), androstenedione, and androstenediol, did not impart anabolic or ergogenic effects in men (5, 10, 12, 28, 30, 37, 47–49). Those findings were summarized in a seminal review, which concluded that PS had no potential to confer resistance trainers with a competitive advantage (11). The sentiment expressed in that review article, which was published in August 2006, continues to be echoed today (14, 27). While true at that time, we feel that today this sentiment may be in error. That feeling is predicated on our knowledge of amendments that were made to the Anabolic Steroid Control Act in 2004, which reclassified androstenedione and 17 additional "anabolic" compounds as controlled substances (39). The language used in this 2004 amendment was explicit; it required PS distributors to either alter the formulation of their products or become subject to federal prosecution. Some PS manufacturers responded by hiring chemists to reverse engineer existing PS and AS compounds to make them compatible with federal law (4). Many of these efforts, which required the imposition of slight modifications to the structure of existing anabolic compounds, were directed toward developing precursors of 17β-hydroxy-5α-androst-1-en-3-one (33). More commonly known as 1-testosterone, this required the substitution of a 1,2-double bond for the 4,5-double bond that was normally found in the A ring of testosterone. Albeit minor, this conformational change allowed 1-testosterone to exert twice the anabolic potency of testosterone that was produced endogenously. Because 1-testosterone did not occur naturally in men and was more potent than endogenous testosterone, some argued it was more akin to a pro-steroid. Regardless, 1-testosterone was classified as a legal PS in the United States until 2005, at which time the enactment of amendments to the Anabolic Steroid Control Act reclassified it under Schedule III of the Controlled Substances Act (39). The viability of the 1-testosterone precursors that were developed after this time and used to circumvent the

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language expressed in this amendment to the Anabolic Steroid Control Act are unknown. Furthermore, to our knowledge no controlled experimental research has been conducted on any PS from 2006 to present day.

It was for these reasons that we undertook the present study, in which we assessed both the intended effects and the unintended consequences of ingesting the manufacturer recommended dose of a popular PS that is sold over the counter in our region. The active ingredient in this PS is 3β-hydroxy-5α-androstan-17-one, which the World Anti-Doping Association classifies as an "endogenous AS when administered exogenously." Upon ingestion, 3β-hydroxy-5α-androstan-17-one is sequentially converted by 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase enzymes to yield 17β-hydroxy-5α-androst-1-en-3-one (1-testosterone). Given that the anabolic potency of 1-testosterone was known, we hypothesized that ingesting this PS in combination with a 1-mo periodized resistance training program would contribute to superior improvements in the body composition and muscular strength of male resistance trainers. We further hypothesized that because this PS was administered per os (po), and thus subject to liver processing, men who received it would exhibit undesirable changes in their lipid profiles and their clinical blood chemistry markers of liver function. We also assessed participants for changes in psychological function because others have reported marked psychological dysfunction in male resistance trainers who use anabolic compounds (16, 35, 36).

MATERIALS AND METHODS

Participants

Eighteen young (18–35 yr of age), healthy [free from known cardiovascular, pulmonary, or metabolic disease; major signs or symptoms of these diseases; and ≤2 cardiovascular disease risk factors (34)], and resistance trained (≥1 yr of resistance training experience with a workout frequency of ≥4 sessions/wk) men participated in this study. All participants were known to be AS and PS free for a minimum of 6 mo prior to study onset, and written, informed consent was obtained from each volunteer. The study was approved by the ethics committee of West Texas A&M University (Canyon, TX) and complied with the principles expressed in the Declaration of Helsinki.

Experimental Protocol

Participants reported to our laboratory following an overnight fast. There they *1*) provided a venous blood sample; *2*) completed a series of psychological questionnaires; and *3*) had their body composition assessed. After completing these procedures, participants were released from our laboratory and instructed to consume a meal. Ninety minutes later they returned to our laboratory and completed one-repetition maximum (1-RM) strength testing on the back squat, bench press, and deadlift, in that order. These strength tests took ~90 min to complete. Participants were then provided a bottle containing 90 capsules of either the prohormone or the placebo supplement and explicit instructions on how and when the supplement should be ingested. Participants also received dietary advice and an individually-tailored workout plan at the conclusion of their baseline testing. Over the next month participants completed 16 bouts of resistance training exercise at a frequency of 4 sessions/wk. This was followed by a 2-day washout period, during which time participants continued with supplement ingestion but avoided structured exercise. Following an overnight fast, they returned to our laboratory and repeated all baseline testing procedures.

Supplementation

Participants were assigned to either the Prohormone or the Placebo group at random and supplement distribution was double blind. Each participant received 90 supplement capsules and their compliance with supplement ingestion was monitored weekly throughout the study. Each prohomone capsule contained 110 mg of 3β-hydroxy-5α-androst-1-en-17-one, the active compound, and 50 mg of 6,7,-dihydrobergamottin, a member of the furanocoumarin family that inhibits cytochrome P450 34A and was included to increase oral PS bioavailability. Each placebo capsule contained maltodextrin. The active compound (powder form) was assayed to be >99% pure by HPLC by an independent laboratory (San Rafael Chemical Services, Salt Lake City, UT). The combined PS (final product) was also sent to an independent and National Environmental Laboratory Accreditation Conference certified laboratory (ALS Global, Salt Lake City, UT); this laboratory used gas chromatography to confirm that the PS did not contain any off-label compounds. A third independent laboratory (Formulife, Dallas, TX) confirmed that the PS and placebo capsules were visually indistinguishable and did not differ in mass. PS and placebo capsules were provided to participants in identical containers and participants received identical instructions on supplement ingestion: one capsule was to be administered po 30 min before each of their three largest daily meals. This was done to slow PS absorption, minimizing first-pass metabolism and reducing the likelihood of anabolic-associated stomach pain. To ensure the study remained physiologically relevant, the daily dose (3 capsules provided 330 mg of 3β-hydroxy-5α-androst-1-en-17-one and 150 mg of 6,7-dihydroxybergamottin) was set in the middle of the range (2–4 capsules/day) suggested by the manufacturer.

Study Diet

Participants received explicit instructions on their diet. They were instructed to always eat until full to ensure a positive energy balance. They were also provided with a standard food/nutrient list to ensure the ratio of their macronutrient intake remained consistent throughout the study proper. Participants were required to monitor their dietary intake for 24 h before their baseline testing laboratory visit; they were instructed to replicate this diet for the 24 h preceding their final laboratory visit. On both dates, participants were instructed to arrive at the laboratory in a fasted but fully hydrated state and to avoid structured exercise, alcohol, and caffeine for 48, 24, and 12 h before testing, respectively. They were also told to consume identical meals before their baseline and posttest rounds of 1-RM strength testing. With these exceptions, participants were otherwise allowed to eat ad libitum for study duration.

Resistance Training Program

Participants received explicit instructions on how they should complete their resistance training, provided in the form of a periodized workout plan that they were to follow for study duration. This program was tailored to each individual; it specified the number of sets (4 sets), repetitions (6–10 repetitions/set), and the load (65–85% of individual 1 RM) participants were to use on each exercise completed. It also adhered to the guidelines established by the American College of Sports Medicine (34). Although loading was individualized to each participant based on their 1-RM levels, there was the possibility that this load could become insufficient due the skeletal muscle adaptations participants sustained over the 1-mo supplemented resistance training period. To control for this, participants were permitted to increase their loading if they felt it was needed and encouraged to strive to achieve momentary muscular fatigue on each lift they completed. With the exception of these things, the workout plan was identical for all participants, who logged the results of each of their workouts on the workout plan in real time. Workout plans

were collected weekly and analyzed to ensure the design and intent of this study remained intact.

Body Composition

Body composition was determined using the hydrodensitometry method. Underwater body mass measurements, taken on an autopsy scale (Chatillon C- 101076, AMETEK Measurement & Calibration Technologies Division, Largo, FL) accurate to 0.01 kg, were repeated until three consistent readings were obtained. Body volume was calculated as the difference between the body mass in water and the body mass in air, which was measured on a laboratory scale (Seca 869, Chino, CA), accurate to 0.2 kg. Body volume measurements were corrected for water density and residual lung volume, which was estimated using the Goldman-Becklake equation (17) that accounts for participant sex, age, and height. Height was measured with a stadiometer (Ross Laboratories, Accustat Ross Stadiometer, Bardonia, NY), accurate to 0.5 cm. Body density was calculated from the ratio of the body mass in air and the corrected body volume (24). Body density was converted to body fat percentage using the Siri equation (42). Body mass index, which was calculated as the ratio between participant body mass (kg) and height (m^2), was used to provide additional descriptive demographic data at baseline.

Maximal Strength Testing

Participants completed 1-RM strength testing on each of the back squat, bench press, and deadlift, in that order. On each strength test, participants performed 10 repetitions at 60%; 5 repetitions at 80%, and 2 repetitions at 90% of their estimated 1 RM. They next attempted their estimated 1 RM. If that lift was successful, they continued with additional 1-RM attempts until failure was achieved. Standard rest periods (3–5 min) were provided between successive sets. These procedures adhere to the guidelines established by the American College of Sports Medicine (34). In addition, the weight each participant lifted on their back squat, bench press, and deadlift 1 RMs were summed to calculate their competition total; this number is the standard by which performance is assessed in conventional powerlifting competitions.

Psychological Questionnaires

STAXI-2. The 44-item State-Trait Anger Expression Inventory-2 (STAXI-2) uses a four-point Likert scale ("not at all" to "almost always") and five subscales (state anger, trait anger, anger-in, anger-out, and anger control) to provide an index of the frequency at which anger is expressed (45). Validation studies report internal consistency (α) coefficients for the STAXI subscales ranging from 0.76 to 0.93 (45). The subscales are reasonably stable over time (8, 25).

POMS. The 30-item Profile of Mood States (POMS) uses a five-point Likert scale ("not at all" to "extremely") and seven subscales [anger, confusion-bewilderment, depression-dejection, fatigue, tension, vigor-activity, and total mood disturbance (which is calculated by summing scores on the tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment subscales and subtracting scores on the vigor-activity subscale)] to evaluate an individual's current level of distress (32). Validation studies report internal consistency (α) coefficients for the POMS subscales ranging from 0.76 to 0.95 (20). Test-retest reliability coefficients range from 0.65 to 0.74 (31).

Blood Sampling Procedure and Analysis

Blood samples, taken from an antecubital vein under nonstasis and posture controlled conditions, were collected into serum separator tubes (367988, BD Vacutainer, Franklin Lakes, NJ). Samples were allowed to clot at room temperature for 30 min and then centrifuged at 3,000 rpm for 10 min. The resulting serum was sent to a Clinical Laboratory Improvement Amendments certified (CLIA ID no. 4500883904) commercial laboratory (Physicians Preferred Laboratory, Amarillo, TX) for clinical blood chemistry analysis. There, a UniCel DxC 600 Synchron Access Clinical System and commercially available kits from Beckman Coulter (Brea, CA) were utilized to assay the serum samples for cholesterol (kit no. 467825), HDL (kit no. 650207), LDL (kit no. 969706), blood urea nitrogen (BUN) (kit no. 442750), creatinine (kit no. A40920), albumin (kit no. 442765), alkaline phosphatase (ALP) (kit no. 476821), aspartate transaminase (AST) (kit no. 476831), and alanine transaminase (ALT) (kit no. 476826), according to manufacturer's instructions. Glomerular filtration rate (GFR) and LDL-to-HDL (LDL/HDL), cholesterol-to-HDL (C/HDL), and BUN-to-creatinine ratios (BUN/creatinine) were calculated from these analytes.

Statistical Analyses

Descriptive statistics were used to describe the characteristics of subjects at baseline. Independent *t*-tests were used to verify that no differences existed between the Placebo and Prohormone groups. Study data were analyzed using a 2 × 2 (group: Placebo or Prohormone by time: *day 1* or *day 30*) ANOVA with repeated measures on the second factor. Main effects (time) were used to describe changes within each supplement group. Interaction effects (group × time) were used to determine whether the Placebo and Prohormone groups exhibited different responses to the 30-day resistance training program.

Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Nonnormally distributed variables were log transformed to approximate a normal distribution before applying a *t*-test or repeated-measures analysis. The repeated-factors assumption of sphericity was tested with Mauchly's sphericity test. When necessary, a Greenhouse-Geisser correction was applied to the *F*-ratio to correct for sphericity violations. Statistical significance was set at $P \leq 0.05$. All statistical analyses were performed with STATISTICA, version 7.1 (StatSoft, Tulsa, OK).

RESULTS

Participant Characteristics

Although 18 men enrolled in the study, one participant in the Placebo group discontinued the study before the final experimental session. His data were excluded from the analysis, leaving eight participants in the Placebo group and nine participants in the Prohormone group. Four of eight participants (50%) in the Placebo group and five of nine participants (56%) in the Prohormone group indicated they had utilized either AS or PS ≥ 6 mo before study onset. This did not amount to a significant difference between groups ($P = 0.517$). The descriptive data that are included in Table 1 provide further evidence that the Placebo and Prohormone groups were not different at baseline.

Body Composition

Participants in the Prohormone and Placebo groups did not differ on body mass ($P = 0.935$), lean mass ($P = 0.379$), or fat mass ($P = 0.263$) at study onset. Participants in the Prohormone group increased their body mass ($P = 0.008$) over the course of the study. More specifically, they increased their lean mass ($P \leq 0.001$) and decreased their fat mass ($P = 0.032$). Participants in the Placebo group did not increase their body mass ($P = 0.273$) or their lean mass ($P = 0.442$) over the course of the study. However, their fat mass was reduced ($P = 0.021$) as a result of the 1 mo resistance training regimen. These within-group differences were supported by significant

Table 1. *Baseline participant descriptive data*

	Age, yr	Height, cm	Mass, kg	BMI, kg/m^2	Body Fat, %	RT History, yr
Placebo	23.6 ± 1.5	178.8 ± 2.2	83.2 ± 3.5	26.0 ± 0.8	16.0 ± 2.0	4.5 ± 1.1
Prohormone	22.0 ± 1.5	175.8 ± 3.2	83.6 ± 3.8	27.1 ± 1.4	11.6 ± 2.2	6.3 ± 1.5
P value	0.451	0.479	0.935	0.485	0.162	0.343

Values are means ± SE. *P* value presents result of independent *t*-test, performed to verify between-group differences did not exist at baseline. BMI, body mass index; RT history, self-reported history of regular resistance training, in years.

interaction effects (supplement group × time) effects for each of body mass ($P = 0.014$), lean mass ($P = 0.004$), and fat mass ($P = 0.014$). These data indicate the improvements in body composition experienced by the Prohormone group exceeded those experienced by the Placebo group (Fig. 1).

Muscular Strength

Participants in the Prohormone and Placebo groups did not differ on their back squat ($P = 0.126$), bench press ($P = 0.078$), or deadlift 1 RMs ($P = 0.865$) at study onset. Their competition totals ($P = 0.191$) were also not different at baseline. The data participants provided on their individualized workout plans, which were collected weekly for study duration, indicated both groups adhered to the periodized resistance training program researchers had created and provided to them. The total amount of work performed over the course of the study was also not different between groups (Prohormone: 136,490 ± 8,198 kg, Placebo: 121,087 ± 9,297 kg; $P = 0.241$).

While the total amount of work these groups performed over the course of study was quite similar, the results the two groups experienced as a function of this resistance training regimen were remarkably different. Both the Prohormone and Placebo groups increased their back squat 1-RM ($P \leq 0.001$ and $P = 0.011$, respectively) and competition total ($P \leq 0.001$ and $P = 0.007$, respectively) over the course of the study. However, the interaction effects for both the back squat 1-RM and competition total were also significant ($P \leq 0.001$ and $P = 0.002$, respectively), indicating these gains were superior in the Prohormone group. The Prohormone group also improved their bench press ($P = 0.013$) and deadlift ($P \leq 0.001$) 1 RMs over the course of the study, while these values remained unchanged in the Placebo group ($P = 0.109$ and $P = 0.061$, respectively). While the interaction effects for the bench press ($P = 0.114$) and deadlift ($P = 0.086$) were not statistically significant, the clear directionality of all four measures of muscular strength indicates that participants in the Prohormone group exhibited superior gains (Fig. 2).

Lipid Profile

Participants in the Prohormone and Placebo groups did not exhibit any differences in their serum HDL ($P = 0.184$) and LDL ($P = 0.325$) concentrations at study onset. Their LDL/HDL ($P = 0.699$) and C/HDL ($P = 0.616$) were also not different at baseline. Major differences did become evident following the 1-mo supplemented resistance training period. Participants in the Prohormone group exhibited significant reductions in HDL ($P < 0.001$), significant elevations in LDL ($P = 0.001$), and significant elevations in both LDL/HDL ($P = 0.001$) and C/HDL ($P < 0.001$) over the course of the study. Participants in the Placebo group did not experience any of these changes ($P = 0.723$, $P = 0.895$, $P = 0.826$, and $P = 0.839$ for HDL, LDL, LDL/HDL, and C/HDL, respectively). The interaction effects for each of HDL ($P = 0.006$), LDL/HDL ($P = 0.003$), and C/HDL ($P = 0.001$) were also significant, while the interaction effect for LDL ($P = 0.110$) was not. These data provide clear and compelling evidence of detrimental changes in the lipid profile of the Prohormone group over the course of the 1-mo supplemented resistance training period (Table 2).

Kidney and Liver Function

Participants in the Prohormone and Placebo groups did not differ on their serum creatinine ($P = 0.916$), albumin ($P = 0.641$) ALP ($P = 0.503$), and AST ($P = 0.744$) concentrations at study onset. Their GFRs ($P = 0.961$) were also not different at baseline. Major differences did become evident following the 1-mo supplemented resistance training period. Participants in the Prohormone group exhibited significant changes in their serum creatinine ($P = 0.001$), albumin ($P = 0.025$), ALP ($P = 0.023$), and AST ($P = 0.053$) concentrations, as well as their GFRs ($P = 0.001$), over the course of the study. Not one of these variables changed in the Placebo group (creatinine: $P = 0.604$; GFR: $P = 0.580$; albumin: $P = 0.893$; ALP: $P = 0.407$; AST: $P = 0.577$). The interaction effects for serum creatinine ($P = 0.021$), albumin ($P = 0.044$), ASP ($P = 0.043$), and AST ($P = 0.016$) concentrations were also significant between groups, as was the interaction effect for the GFR ($P = 0.037$). While neither the Placebo ($P = 0.468$) nor the Prohormone ($P = 0.154$) groups exhibited significant increases in their serum ALT concentrations over the course of the study, large interindividual variability in the Prohormone group at posttest likely hindered our ability to detect a difference, if one existed. The interaction effect for ALT, which trended toward a worse outcome in the Prohormone group, but also did not achieve statistical significance ($P = 0.091$), provides further evidence in support of this statement. When combined, these changes in serum concentrations of creatinine, albumin, ALP, and AST, and the change in GFR provide conclusive evidence that detrimental changes in kidney and liver function occurred in participants who completed the 1-mo supplemented resistance training period in the Prohormone group (Table 3).

POMS

Participants in the Prohormone and Placebo groups did not differ on the anger-hostility ($P = 0.156$), confusion-bewilderment ($P = 0.982$), depression-dejection ($P = 0.805$), fatigue-inertia ($P = 0.237$), and tension-anxiety ($P = 0.827$) subscales of the POMS at study onset. As such, their levels of total mood disturbance ($P = 0.617$) were also not different at baseline. For the most part, participant scores on these subscales and the composite index did not change over the 1-mo supplemented

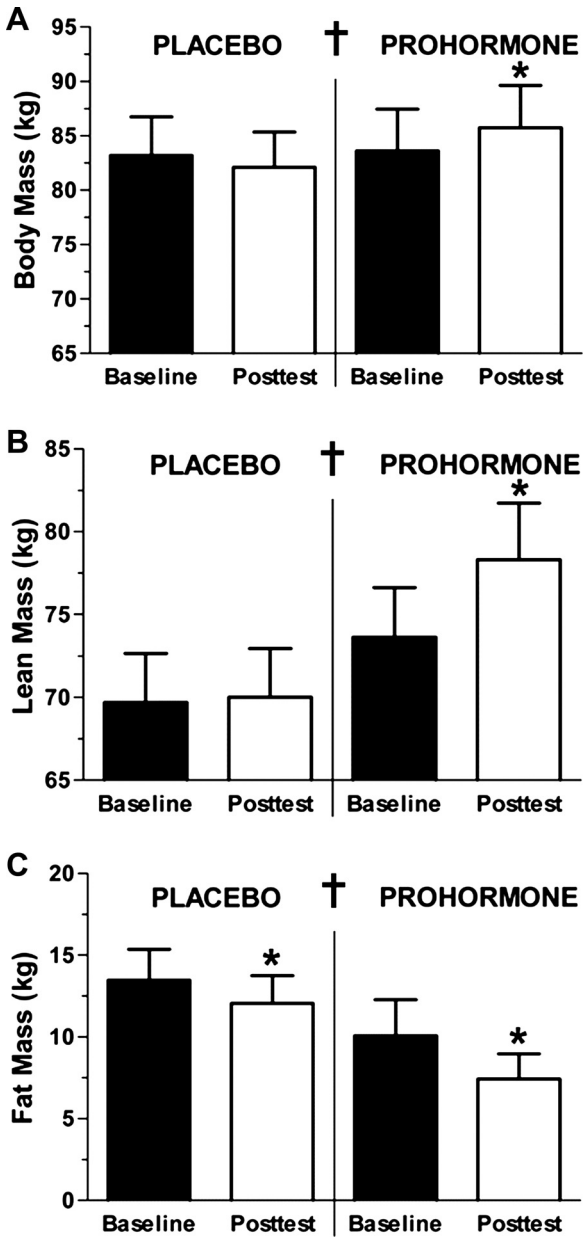

Fig. 1. Body composition. Participants body mass (*A*), lean mass (*B*), and fat mass (*C*) before (Baseline) and after (Posttest) they completed a 1-mo resistance training program during which they ingested either sugar pills (Placebo) or the prohormone supplement (Prohormone). Values are means ± SE; $n = 8$ (Placebo) and $n = 9$ (Prohormone). Significance was set at $P \leq 0.05$: *significant within-group difference; †significant between-group difference.

resistance training period in either the Prohormone or Placebo groups. More specifically, participants in the Prohormone and Placebo groups did not exhibit any changes in anger-hostility ($P = 0.782$ and $P = 0.384$), confusion-bewilderment ($P = 0.622$ and $P = 0.142$), depression-dejection ($P = 0.225$ and $P = 0.626$), fatigue-inertia ($P = 0.760$ and $P = 0.875$), and tension-anxiety ($P = 0.535$ and $P = 0.623$) subscales from pre- to posttest. They also did not exhibit any changes in total mood disturbance ($P = 0.168$ and $P = 0.954$) over the study period. These results were further confirmed by nonsignificant interaction effects for the anger-hostility ($P = 0.359$), confusion-bewilderment ($P = 0.316$), depression-dejection ($P = 0.390$), fatigue-inertia ($P = 0.883$), and tension-anxiety ($P = 0.933$) subscales, and for total mood disturbance ($P = 0.194$) over the study period.

The only evidence of a difference between the Prohormone and Placebo groups came on the vigor-activity subscale. While scores on this subscale did not differ between study groups at baseline ($P = 0.088$), they tended to increase ($P = 0.062$) in the Prohormone group, but did not change ($P = 0.995$) over the course of the study in Placebo. The interaction effect ($P = 0.084$) also supported this trend, but it is important to recognize that neither the within-groups analysis nor the interaction effect achieved statistical significance. For that reason, we conclude that scores on the POMS were largely unchanged in either group; there may be marginal evidence of a perceived increase in energy levels in the Prohormone group (Table 4).

STAI-2

Participants in the Prohormone and Placebo groups did not differ on the state-anger ($P = 0.420$), trait-anger ($P = 0.832$), anger expression-out ($P = 0.311$), anger expression-in ($P = 0.057$), and anger control-out ($P = 0.078$) subscales of the State Trait Anger Expression Inventory-2 (STAI-2) at study onset. Neither the Prohormone nor the Placebo groups exhibited significant changes in state-anger ($P = 0.588$ and $P = 0.590$), trait-anger ($P = 0.212$ and $P = 0.826$), anger expression-out ($P = 0.921$ and $P = 0.512$), anger expression-in ($P = 0.785$ and $P = 0.319$), or anger control-out ($P = 0.357$ and $P = 0.398$) from pre- to posttest. Nonsignificant interaction effects on each of state-anger ($P = 0.833$), trait-anger ($P = 0.394$), anger expression-out ($P = 0.612$), anger expression-in ($P = 0.458$), and anger control-out ($P = 0.995$) provided further confirmation that the angry feelings participants experienced and their ability to express this anger did not change in either group.

We did note one significant change on the STAI-2: scores on the Anger Control-In subscale, which did not differ between the Prohormone and Placebo groups at baseline ($P = 0.986$), improved in the Prohormone group ($P = 0.044$) and degraded in the Placebo group ($P = 0.023$) over the course of the 1-mo supplemented resistance training period. The interaction effect for the Anger Control-In subscale ($P = 0.006$) was also significant, providing further evidence that participants in the Prohormone group increased their ability to internalize anger from pre- to posttest, while this ability was reduced in Placebo (Table 5).

Self-Reported Supplement Effects

Desirable effects. Six of eight subjects (75%) in the Placebo group and all nine of the subjects (100%) in the Prohormone group reported desirable effects associated with the 1-mo supplemented resistance training protocol. These included perceived improvements in body size, muscle mass, and muscular strength, as well as fat loss. The frequency at which these effects occurred did not differ between groups ($P = 0.256$).

Adverse effects. Three of eight subjects (38%) in the Placebo group and six of nine subjects (67%) in the Prohormone group reported adverse responses to the study protocol. These included acne, headaches, muscle cramping, dehydration, and mood swings. The frequency at which these symptoms were reported did not differ between groups ($P = 0.125$).

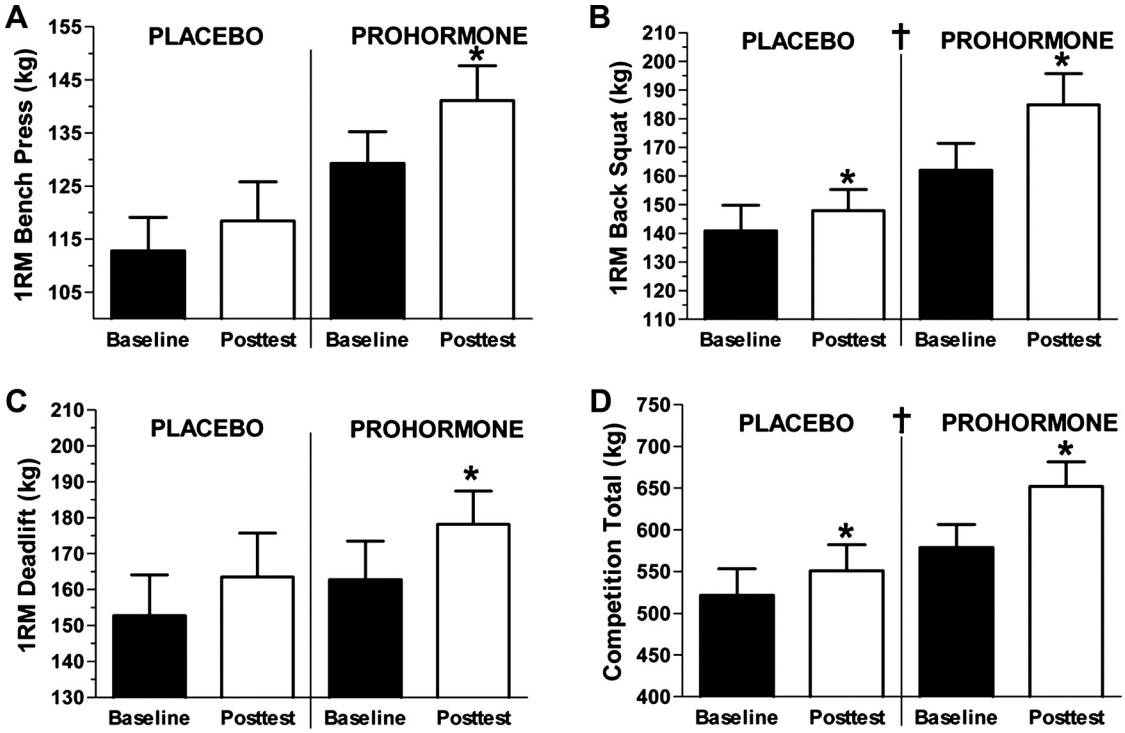

Fig. 2. Muscular strength. Participants performed 1-repetition maximum (1-RM) testing on the bench press (*A*), back squat (*B*), and deadlift (*C*) before (Baseline) and after (Posttest) they completed a 1-mo resistance training program during which they ingested either sugar pills (Placebo) or the prohormone supplement (Prohormone). *D*: the total weight each participant lifted on the bench press, back squat, and deadlift was summed to determine their competition total. Values are means ± SE; $n = 8$ (Placebo) and $n = 9$ (Prohormone). Significance was set at $P \leq 0.05$: *significant within-group difference; †significant between-group difference.

DISCUSSION

Men who ingested 330 mg of 3β-hydroxy-5α-androst-1-en-17-one and 150 mg of 6,7-dihydroxybergamottin/day and completed a 30-day periodized resistance training program exhibited greater improvements in body composition and muscular strength than their Placebo-supplemented counterparts. As such, this double-blind, placebo-controlled, intervention study is one of the first to attribute tangible benefits to a PS compound. To our knowledge, we are also the first to examine this particular PS in a controlled research setting. For that reason we feel it is important to note that participants who received the PS also exhibited a number of abnormalities in their cardiovascular, hepatic, and renal function. These complications, which were not present at baseline, but developed over the course of this 30-day study, should serve as a source of pause for anyone who is contemplating the use of this PS compound or any other.

Given that all prior research has reported PS to be ineffective in improving body composition, muscle mass, and muscular strength (5, 10–14, 27, 28, 30, 37, 47–49), we lack a reference value by which to compare the efficacy of the PS examined here. However, PS are intended to transform into testosterone derivatives in vivo. Noting the large body of research supporting improvements in body composition and muscular strength

Table 2. *Lipid profile*

Study Group	Baseline	Posttest	Change Score	Risk Factor Threshold
HDL cholesterol, mg/dl				
Prohormone	46.1 ± 3.5	27.3 ± 1.3*†	−18.7 ± 3.0	<40
Placebo	52.8 ± 3.2	51.9 ± 2.7	−0.9 ± 2.3	
LDL cholesterol, mg/dl				
Prohormone	99.7 ± 8.6	128.7 ± 13.7*†	29.0 ± 12.3	>130
Placebo	110.5 ± 5.7	109.7 ± 6.9	−0.9 ± 6.2	
LDL/HDL cholesterol				
Prohormone	2.2 ± 0.2	4.8 ± 0.6*†	2.6 ± 0.5	>3.6
Placebo	2.1 ± 0.2	2.2 ± 0.2	0.1 ± 0.2	
Total cholesterol/HDL				
Prohormone	3.6 ± 0.3	6.4 ± 0.6*†	2.8 ± 0.1	>5.2
Placebo	3.5 ± 0.2	3.5 ± 0.2	0.1 ± 0.2	

Values are means ± SE. LDL/HDL cholesterol, ratio of LDL to HDL cholesterol; total cholesterol/HDL, ratio of total cholesterol to HDL. Risk factor thresholds were set according to American College of Sports Medicine (ACSM) guidelines (34). Significance was set at $P < 0.05$: *significant within-group difference, †significant difference between groups.

Table 3. *Kidney and liver function*

Study Group	Baseline	Posttest	Change Score	Risk Factor Threshold
Creatinine, mg/dl				
Prohormone	1.1 ± 0.1	1.3 ± 0.1*†	0.2 ± 0.1	>1.4
Placebo	1.1 ± 0.1	1.0 ± 0.1	−0.1 ± 0.1	
Glomular filtration rate, ml·min^{-1}·1.72 m^{-2}				
Prohormone	88.3 ± 3.7	71.9 ± 2.9*†	−16.4 ± 3.4	<89.0
Placebo	88.6 ± 4.7	91.3 ± 5.8	2.6 ± 4.5	
Albumin, g/dl				
Prohormone	4.4 ± 0.1	4.2 ± 0.1*†	−0.2 ± 0.1	<3.50
Placebo	4.5 ± 0.1	4.4 ± 0.1	−0.1 ± 0.1	
Alkaline phosphatase, IU/l				
Prohormone	70.3 ± 5.8	58.6 ± 5.7*†	−11.8 ± 4.2	>126.0
Placebo	80.3 ± 13.9	82.8 ± 12.0	2.5 ± 2.8	
Aspartate transaminase, IU/l				
Prohormone	26.0 ± 1.5	41.4 ± 6.7*†	15.4 ± 6.6	>40.0
Placebo	27.0 ± 2.7	31.0 ± 8.6	4.0 ± 6.8	
Alanine transaminase, IU/l				
Prohormone	28.0 ± 3.2	49.4 ± 12.4	22.4 ± 14.0	>48.0
Placebo	28.6 ± 4.8	25.4 ± 3.7	−4.1 ± 5.4	

Values are means ± SE. Significance was set at $P < 0.05$: *significant within-group difference; †significant difference between groups. Risk factor thresholds were set according to ACSM guidelines (34).

with exogenous testosterone administration (6, 7, 40, 41, 46), we feel the reader would benefit from a comparison of the effects we reported with po PS administration to prior work that examined the same effects in participants who received intramuscular (im) testosterone enanthate administration. In one such study, subjects received a long-acting gonadotrophin-releasing hormone agonist to block endogenous testosterone administration and weekly im testosterone enanthate treatments over a 20-wk period (7). Testosterone enanthate at a dose of 300 mg/wk contributed to a doubling of subject's baseline circulating testosterone concentrations and increased their fat-free mass and leg press strength by 8.2 and 19.5%, respectively (7). These adaptations were noteworthy, as they came in the absence of resistance training (7). More recent work by Rogerson et al. (38) examined the effect of combining 3.5 mg/kg weekly doses of testosterone enanthate with a 6-wk resistance-training intervention. The body weight of subjects in that study averaged 79.2 kg, making the average testosterone enanthate dose used (~277 mg/wk) very similar to the 300-mg dose that we reported on in the prior reference. In the Rogerson et al. study, the combination of testosterone enanthate and resistance training contributed to a 6.4% increase in body mass and a 15% increase on both bench press and leg press exercise (38). We find it interesting that the improvements reported in both of these studies are remarkably similar to the improvements we report here, where 4 wk of daily po administration of 330 mg 3β-hydroxy-5α-androst-1-en-17-one and 150 mg of 6,7-dihydroxybergamottin contributed to a 6.4% increase in fat free mass and 9.2, 14.2, and 14.6% increases on the bench press, back squat, and deadlift, respectively. Collectively, these studies suggest that po administration of 330 mg 3β-hydroxy-5α-androst-1-en-17-one/day provides improvements in body composition and muscular strength that are similar to those

Table 4. *Profile of mood states*

Study Group	Baseline	Posttest	Change Score
Anger: hostility subscale			
Prohormone	0.7 ± 0.3	0.8 ± 0.5	0.1 ± 0.4
Placebo	1.8 ± 0.7	1.5 ± 0.9	−0.3 ± 1.0
Confusion: bewilderment subscale			
Prohormone	1.9 ± 0.4	2.1 ± 0.4	0.2 ± 0.4
Placebo	1.9 ± 0.4	2.6 ± 0.7	0.8 ± 0.5
Depression: dejection subscale			
Prohormone	0.8 ± 0.4	0.3 ± 0.2	−0.4 ± 0.3
Placebo	0.6 ± 0.5	0.9 ± 0.4	0.3 ± 0.5
Fatigue: inertia subscale			
Prohormone	2.6 ± 0.6	2.3 ± 0.7	−0.2 ± 0.7
Placebo	3.8 ± 0.7	3.5 ± 1.3	−0.3 ± 1.5
Tension: anxiety subscale			
Prohormone	2.7 ± 1.1	2.0 ± 7.8	−0.7 ± 1.0
Placebo	2.4 ± 0.6	2.0 ± 0.8	−0.4 ± 0.7
Vigor: activity subscale			
Prohormone	5.9 ± 1.3	7.8 ± 1.5*†	1.9 ± 0.9
Placebo	9.1 ± 1.2	9.1 ± 1.4	0.1 ± 1.1
Total mood disturbance			
Prohormone	2.7 ± 2.2	0.2 ± 1.2	−2.9 ± 1.9
Placebo	1.3 ± 1.6	1.4 ± 3.5	0.1 ± 2.1

Values are means ± SE. *Tendency ($P < 0.10$) toward a significant within-group difference. †Tendency ($P < 0.10$) toward a significant difference between groups.

Table 5. *STAI-2*

Study Group	Baseline	Posttest	Change Score
State anger subscale			
Prohormone	17.4 ± 1.4	16.6 ± 0.9	−0.9 ± 1.6
Placebo	16.1 ± 0.6	16.6 ± 0.9	0.5 ± 0.9
Trait anger subscale			
Prohormone	14.9 ± 1.1	14.0 ± 1.2	−0.9 ± 0.7
Placebo	15.3 ± 1.3	15.5 ± 2.0	0.3 ± 1.1
Anger expression: out subscale			
Prohormone	12.8 ± 0.8	12.7 ± 1.1	−0.1 ± 1.1
Placebo	14.3 ± 1.2	13.6 ± 1.6	−0.6 ± 0.9
Anger expression: in subscale			
Prohormone	14.2 ± 1.0	14.7 ± 1.3	0.4 ± 1.6
Placebo	17.9 ± 1.4	16.5 ± 2.0	−1.4 ± 1.3
Anger control: out subscale			
Prohormone	26.9 ± 0.9	27.7 ± 1.1	0.8 ± 0.8
Placebo	23.8 ± 1.4	24.6 ± 2.2	0.9 ± 1.0
Anger control: in subscale			
Prohormone	24.7 ± 1.6	26.6 ± 1.4*†	1.9 ± 0.8
Placebo	24.6 ± 1.8	21.3 ± 1.6*†	−3.4 ± 1.2

Values are means ± SE. Significance was set at $P < 0.05$. *Significant within-group difference. †Significant difference between groups.

shown when 300 mg/wk testosterone enanthate is administered im.

Anabolics that are administered po are known to exert more pronounced changes in HDL and LDL than those that are administered im (44). These effects are mediated via *1*) an inhibition of the synthesis of apolipoprotein A, the main apolipoprotein in HDL (23); *2*) stimulation of hepatic triglyceride lipase activity, which exerts a catabolic effect on HDL (3); and *3*) an increase in lipoprotein lipase activity (26). Hepatic triglyceride lipase and lipoprotein lipase both influence LDL production, helping to explain why changes in HDL and LDL often occur in concert. In the present study, participants who received 330 mg of 3β-hydroxy-5α-androst-1-en-17-one and 150 mg of 6,7-dihydroxybergamottin/day po exhibited a 40% reduction in HDL and a 30% elevation in LDL, while total cholesterol and plasma triglycerides were essentially unchanged. These changes are quite different than what has previously been reported following po PS administration. In one such study, subjects received 150 mg DHEA and 300 mg androstenedione po each day and completed an 8-wk resistance training program (12). In that study, HDL levels fell by 12%, while LDL, very low-density lipoprotein, triglyceride, and total cholesterol levels were not changed (12). The same authors reported essentially the same findings in a prior study that utilized a similar study design but had subjects ingest 300 mg/day of androstenedione alone (28). From these studies, we conclude that the lipid profile changes attributable to this PS are much worse than those that were attributed to the first generation of PS. A recent review of the AS literature reported average declines in HDL from 30 to 50% with virtually no change in LDL (43). Based on this review, the effects attributable to this PS appear to be as bad as, if not worse than, those that are attributed to AS. This is a concern because reductions in HDL and elevations in LDL are highly predictive of future atherosclerotic cardiovascular disease (34). However, we must also acknowledge that lipid profile changes induced by short-term anabolic usage are known to self-resolve when anabolic usage is discontinued (23). For that reason, at the present time, we can only state that short term po PS administration causes severe alterations in both HDL and LDL, the long-term consequences of which remain to be delineated.

Anabolics that are administered po are metabolized in the liver; for that reason they tend to be more hepatotoxic than those that are administered im (23). The PS examined in the present study, which was administered po, contributed to a myriad of undesirable changes in markers of liver function. Albumin, which is made by the liver and is the main protein in human plasma, was reduced. Low albumin levels are associated with liver dysfunction. ALP, an enzyme found in the cells that line the biliary ducts of the liver, was reduced. Low ALP levels are an indicator of hepatocellular disease or dysfunction. AST, a liver enzyme that catalyzes the transfer of an amino group from aspartic acid to α-ketoglutaric acid, was elevated. Elevated AST levels are an indication of acute liver damage. ALT, a liver enzyme that catalyzes two reactions of the alanine cycle, also tended to be elevated. Elevated ALT levels are an indication of hepatocellular injury.

We did our best to compare our present findings to prior work that examined PS and AS, but were limited by the fact that very little research has been published in this area. In one study, where subjects ingested a combination PS containing 150 mg of DHEA and 300 mg of androstenedione each day, in concert with an 8-wk resistance training program, no changes were noted in either AST or ALT (12). The same authors have reported that liver transaminases are similarly unaffected by 8 wk of po administration of 150 mg/day DHEA alone (13). In contrast, im testosterone enanthate administration at dosages ranging from 150 to 600 mg/wk has been shown to increase AST from 23 to 29 U/l (26%) over a 6-wk period (39). While significant, that increase in AST is only one-half the magnitude of what we reported in the present study, where AST increased from 26 U/l at baseline to 41 U/l at *week 4* (58%). While this prior examination of changes in liver markers in response to im testosterone ethanthate did not report values for either ALP or ALT, it did report changes in HDL, the C/HDL, and plasma albumin levels. We found it interesting that each of those changes, which included a decrease in HDL from 47.95 mg/dl at baseline to 37.12 mg/dl at *week 6* (23% decline), an increase in the C/HDL from 3.9 at baseline to 4.7 at *week 6* (21% increase), and a decline in plasma albumin from 47 g/l at baseline to 46 g/l at *week 6* (2% decrease) was also of approximately one-half the magnitude of what we report here, where HDL declined by 41%, the C/HDL increased by 78%, and plasma albumin levels decreased by 5%. We would like to direct the reader's attention to the fact that this same anabolic (testosterone enanthate), at approximately this same dosage (~300 mg/wk), was to what we made our previous comparisons of changes in body composition and muscular strength. Our improvements in body composition and muscular strength with PS were equitable to those reported in subjects who received im testosterone enanthate injections. While these desired effects may have been similar between po PS and im testosterone enanthate, the fact that changes in markers of liver function were approximately twofold greater in PS suggest that it should be avoided if one is concerned with one's liver health.

Creatinine is a breakdown product of the phosphocreatine energy system that is eliminated from the body via the kidneys. Elevated creatinine levels are an indicator of kidney dysfunction and are used to calculate the GFR. In the present study, participants who received po PS administration exhibited elevated levels of serum creatinine and reductions in GFR. This suggests that their kidney function may have been altered. However, it is important to note that elevated serum creatinine levels alone are a relatively insensitive index of kidney function. To create a more sensitive index of kidney damage, these values should be combined with BUN to calculate the BUN/creatinine (50). Elevated BUN/creatinine levels are known to be a strong indicator of kidney dysfunction. In the present study, participants who ingested the PS did not exhibit an elevated BUN level. Their BUN/creatinine were also not increased. In fact, both BUN and the BUN/creatinine decreased in subjects who received the prohormone compound ($P = 0.034$ and $P = 0.002$, respectively). Thus the likelihood that PS subjects experienced kidney damage is minimal. When combined with the reductions in both BUN and the BUN/creatinine, we interpret the increased creatinine levels exhibited by PS subjects as further evidence of acute liver damage.

AS are also known to induce psychotic symptoms like mania, aggression, and anger (among others) in a dose-dependent fashion (16, 35). While psychological dysfunction associated with prolonged or protracted AS use tends to be generally well accepted, more recent evidence suggests that the

results of these studies may be overly influenced by a few participants and, therefore, not uniform across all users (36). Given these issues, we felt it was important to determine whether the PS we examined would lend to similar findings. Interestingly, we did not see any evidence of psychological dysfunction in subjects who received PS. In fact, we saw just the opposite. Subjects who received the PS tended to report greater improvements on the vigor-activity subscale of the POMS, suggesting that hypomania, which can present as an increased sense of well-being and productivity, may have occurred in concert with PS ingestion. Alone, this finding is underwhelming. However, we feel that it becomes more interesting when one considers that participants who received PS also reported improved scores on the anger control-in subscale of the STAI-2. Given that this subscale measures how often a person attempts to relax, calm down, and reduce angry feelings before they are allowed to get out of control, we take the combination of these findings to suggest that participants who received the PS in combination with the 1-mo resistance training intervention may actually have felt better over the course of the study. This sense of well-being may have manifested as an increased ability to keep their emotions under control. These observations leave us tempted to conclude that this PS may actually contribute to positive changes in psychological function, which would certainly be a novel finding. However, because we recognize the potential danger associated with making such a bombastic statement, in particular when this statement aligns in direct opposition to the preponderance of prior work that has been performed in this area, we instead suggest that further study needs to be conducted in this area before any firm conclusions can be made.

Perspectives and Significance

A large body of literature published between 1990 and 2006 caused many to conclude that PS did not impart anabolic or ergogenic effects in men (5, 10, 12, 13, 28, 30, 37, 47–49). While that adage was true at the time, the present study calls into question whether it remains true today. Contrary to those prior reports, we found overwhelming evidence of anabolic properties associated with a publicly available PS compound. Recent ex vivo research has shown the active ingredient in this PS (3β-hydroxy-5α-androstan-17-one) to be one of the main transformation products of the AS testosterone (17). However, before one rushes to purchase this PS, it is important to note that the World Anti-Doping Association identifies 3β-hydroxy-5α-androstan-17-one as an endogenous anabolic-androgenic steroid when administered exogenously. As such, this PS is prohibited from athletic use. Prior research has shown that a single 115-mg dose of this PS (subjects ingested 330 mg/day in the present study) remains detectable in the urine for a full 7 days following supplementation (33). Therefore, athletes are strongly cautioned against using this or any other PS. Given that, in addition to being banned, this PS also contributed to marked dysfunction in nearly all of the cardiovascular and hepatic markers we examined, we conclude that the harm associated with this particular PS outweighs any potential benefit.

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No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.G. and M.R.K. conception and design of research; J.G. and M.R.K. performed experiments; J.G., T.L.G., K.M.C., and M.R.K. analyzed data; J.G. and M.R.K. prepared figures; J.G. and M.R.K. drafted manuscript; T.L.G., K.M.C., and M.R.K. edited and revised manuscript; M.R.K. interpreted results of experiments; M.R.K. approved final version of manuscript.

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