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"Andro" or "No go": Evaluating the Risks of Androstenedione in Boosting Athletic Performance

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## Introduction

The steroid hormone androstenedione's reputation was launched from relative obscurity to the topic of daily conversations in the summer of 1998, when a journalist noticed a bottle of the performance-enhancing drug in major league slugger Mark McGwire's locker. Until then, androstenedione was only known among bodybuilders. But when McGwire admitted that he was taking the anabolic steroid and subsequently went on to shatter the single season home run record, athletes-and the general public-ran to their local nutrition stores to take home some of their own "andro."

Androstenedione, a precursor to testosterone, is normally produced in both male and female adrenal glands and gonads (1). It is synthesized from dehydroepiandrosterone and subsequently converted to testosterone by 17-b-hydroxysteroid dehydrogenase, an enzyme located in most tissues (2). Testosterone is believed to increase skeletal muscle growth, along with other anabolic changes. Years ago, researchers discovered that a similar form of androstenedione is produced in plants. This plant compound has been purified and marketed as a safe and natural alternative to conventional anabolic steroids, which directly increase blood testosterone concentrations via injection.

Conventional anabolic steroids have been shown to produce dangerous side effects in both men and women. For men, the performance-boosting drugs can cause gynecomastia, premature balding, decreased high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), thrombolytic disorders, liver tumors, testicular atrophy, and decreased sperm count. Women taking anabolic steroids may suffer from clitoral hypertrophy, decreased breast tissue, deepened voice, hirsutism, kidney and liver dysfunction, and menstrual irregularities (3). Increased testosterone levels enhance the rate of estradiol synthesis from testosterone via aromatization (1). Thus, the reported side effects are a result of increased estradiol concentrations as well as high testosterone levels.

Yet, not much is known about androstenedione supplementation and its effects on the body's hormone chemistry. And no wonder: prior to McGwire's androstenedione revelation, the only study that had investigated the effect of oral androstenedione administration on blood testosterone levels was in 1962. In that study, two women were given a single dose of 100mg of androstenedione. The researchers observed a 4- and 7-fold increase in testosterone levels, respectively, in the subjects (1).

Following the summer of 1998, a number of studies have attempted to analyze the consequences of androstenedione supplementation on testosterone concentration and skeletal muscle anabolism. The evidence has not been consistent, and further studies are needed to confirm the findings. But, perhaps more important, early results suggest that androstenedione may be just as harmful as conventional anabolic steroids.

### Initial Study Raises Doubts

In 1999, King et al (1) conducted an experiment to determine if short- and long-term androstenedione administration in men increases testosterone concentrations in blood serum. In addition, they measured skeletal muscle fiber size and strength to evaluate androstenedione's anabolic effects. The experiment was supported by the Iowa State University Human Subjects Committee, and funded by Experimental and Applied Sciences, Inc., a manufacturer of oral androstenedione.

In the long-term arm of the study, twenty healthy males aged 19-29 were asked to undergo 8 weeks of whole-body resistance training. During weeks 1, 2, 4, 5, 7, and 8, the subjects were randomly administered either androstenedione at 100 mg/day 3 times daily or a placebo medication. Throughout the training period, muscle strength, body composition, blood chemistry, and muscle histochemistry were assessed. In the short-term arm of the study, 10 men were randomly assigned to take a single 100-mg dose of androstenedione or placebo. Blood samples were obtained before and every 30 minutes after ingestion for 6 hours (1).

The results of the study were puzzling. The drug's purported role as a testosterone precursor was well-established. However, serum free and total testosterone levels were not altered by short- or long-term androstenedione supplementation. The short-term experiment showed that serum androstenedione peaked 90 to 270 minutes after ingestion; androstenedione levels remained above baseline until 270 to 360 minutes after administration. But the single dose did not change serum concentrations of testosterone (1).

The long-term experiment confirmed this finding. In the androstenedione group, the drug's serum concentration was 100 percent above baseline after 2 and 5 weeks of training; its levels remained elevated after 8 weeks. However, serum testosterone levels did not change between the two groups either before or during treatment. In addition, the authors reported no differences between the two groups in strength, muscle histochemistry, or body composition. Muscle strength and lean-body mass increased similarly in both groups, while fat mass decreased in parallel. The absence of strength and size gains in androstenedione subjects is consistent with the fact that testosterone levels remained constant between experimental and control groups; elevated testosterone is needed to increase muscle growth (1).

### Critiques and a Flurry of Studies

While King et al's experiment was fundamentally sound, some researchers cautioned the public from accepting the study as the definitive word on androstenedione. They argued that, as the first real study on the steroid hormone, there are going to be some problems and limitations. For instance, the subjects had never performed any resistance training in their lives. Thus, they may have exhibited relatively large strength gains from the novel training alone. This large increase in muscle strength may have masked any possible gains from androstenedione (4).

Sparked by these critiques and the increasing popularity of androstenedione, various groups have tried to disprove King et al's conclusion. These studies, for the most part, have been unsuccessful. Ballantyne and colleagues (5) administered 200 mg/day of oral androstenedione to 10 males over 2 days and compared their testosterone concentrations to baseline levels. They observed that the supplement did not increase testosterone levels, and, thus, is unlikely to provide male athletes with any anabolic benefit (5).

Rasmussen et al (6) directly measured skeletal muscle anabolism by measuring muscle protein kinetics using a complex three-compartment model. 100 mg/day of androstenedione was given to 6 healthy males over a 5-day period. Once again, after drug ingestion, plasma testosterone did not differ from basal levels. Compared to the placebo group, moreover, androstenedione did not affect muscle protein synthesis and breakdown, or phenylalanine net balance. Their conclusion: oral androstenedione has no anabolic effect on muscle protein metabolism (6).

### A Victory for "Andro"

Though the above studies strongly suggested that androstenedione does not increase testosterone concentrations nor increase muscle growth, there was still an argument for the contrary. Namely, the doses used in the experiments, though above some manufacturer-recommended doses, is low compared with the 500- to 1200-mg doses promoted in advertisements for other androstenedione products (4).

Interestingly, around the same time as Ballantyne's and Rasmussen's studies, Earnest and colleagues (7) demonstrated that oral androstenedione is capable of producing *in vivo* increases in testosterone levels. As in the Ballantyne study, the male subjects were administered 200 mg/day of the steroid. But the consequences of the two studies were opposite (7).

In February 2000, Leder et al (2) provided the first substantial evidence that androstenedione-induced serum testosterone increases are dosage-dependent. The randomized controlled trial involved 42 men aged 20-40 years with no prior history of steroid use. The subjects received a placebo or 100 mg or 300 mg of androstenedione daily for 7 days. The mean change in serum testosterone was negative 2 percent for the placebo group, negative 4 percent for the 100-mg group, and positive 34 percent for the 300-mg group (2).

The researchers concluded that the 300-mg daily dose of androstenedione increases serum testosterone concentrations in some healthy men. This dosage is probably in close accordance with the actual consumption by athletes who seek performance enhancements. By the same reasoning, if individuals ingest much higher and frequent dosages of the supplement—which is very likely in competitive sports—they may experience sustained and even larger increases in testosterone levels, and thus, skeletal muscle anabolism.

### Risks of Supplementation

The Leder study gives renewed credence to the long-held belief that androstenedione increases serum testosterone levels and athletic performance. It is reasonable to claim, consequently, that the popularity of this "natural" anabolic steroid will soar even higher than before. However, secondary evidence attained from the experimental subjects' hormonal profiles shows that the increasing popularity may be extremely alarming from a public health perspective.

In addition to serving as a precursor to testosterone—which, in high concentrations, is aromatized to estradiol—androstenedione may be converted into estrogens directly. In all the published studies to date measuring estrogen concentrations, serum estradiol levels increased significantly in the androstenedione group (1,2,5,6). For example, in the Leder experiment, the mean change in serum estradiol concentrations was 4 percent for the placebo group, 42 percent for the 100-mg group, and 128 percent for the 300-mg group (2). These results suggest that androstenedione is normally aromatized at a high rate. This could explain the unchanged testosterone levels when the supplement is given at relatively low doses; in order to increase testosterone synthesis, enough androstenedione must be administered to overcome aromatization.

Increased estradiol levels may predispose the individual to adverse consequences, almost all of which are possible side effects of conventional anabolic steroids. Elevated estradiol has been linked with gynecomastia in men, cardiovascular disease, breast cancer in women, and pancreatic cancer in men (1).

The elevated serum androstenedione itself may also predispose the drug-taker to major health risks. For example, in the King study, the authors reported a 12 percent reduction in serum high-density lipoprotein cholesterol (HDL-C) in the androstenedione group, yet another known side effect of conventional steroids (1). Though the mean HDL-C didn't drop to 35 mg/dl, the level considered to be a risk factor for cardiovascular disease, the decrease is still clinically relevant (1). In addition, increased blood androstenedione levels may be associated with prostate cancer and pancreatic cancer in men (1). Finally, when enough androstenedione is given to produce an increase in serum testosterone concentrations, the subject is at risk for all the possible side effects of conventional anabolic steroids.

### Conclusion

Approximately 4.9% of male and 2.4% of female adolescents in the U.S. have used illegal androgenic/anabolic steroids (2). Since androstenedione is classified as a dietary supplement and not a controlled substance, it is readily available without a prescription. Coupled with its rising popularity and use by sports role models, the number of people regularly ingesting androstenedione is probably much greater. This is despite well-respected studies establishing a potential link between androstenedione and cardiovascular disease, breast cancer, pancreatic cancer, and other major health concerns.

These health risks should be used to not only increase public awareness of androstenedione's dangerous effects, but also to stimulate further investigation of the drug's long-term health implications. This is of special concern to competitive athletes, who may take very high doses of androstenedione, thinking, "if 1 pill works, 10 will do wonders."

"Natural" does not always mean safe. So, whether or not androstenedione actually enhances athletic performance, one fact is clear: it is an anabolic steroid and possesses the same risks as the illegal testosterone injections.

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