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Testosterone Boosters: How Real Are Their Effects?

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Abstract

In the past decade, there has been an increased interest in alternative treatments to testosterone (T) and androgen derivatives. This has led to the development of supplements known as "testosterone boosters" (*T-boosters*) or "testosterone enhancers." The internet is the main source for the purchase of these products with sales reaching millions of dollars. The search for *T-boosters* is focused on improvement in sexual performance, muscular strength, and increased muscle mass using agents considered "natural," which are thereby presumed to lack serious adverse effects. Some of these supplements have been used since antiquity. Commercially sold T-boosters nearly always comprise multiple supplements, and none of these combinations have undergone rigorous evaluations, as would be required for regulatory approval for pharmaceutical products. This makes it challenging to evaluate marketing claims. However, a limited scientific literature does exist for the primary individual agents in most T-boosters. The most commonly used agents are *Tribulus terrestris*, fenugreek, zinc, maca, and ashwaganda ("Indian ginseng"). Those studies form the basis of this review. Although some studies have offered suggestive results indicating possible increases in serum T, the data are inconsistent, and studies differ widely in methods, including supplement dosage. In addition, serious adverse events have been reported. Currently, the existing literature fails to support the use of these products.

Keywords: testosterone; testosterone boosters; androgens; supplements; sexual drive; muscle gain

Introduction

Testosterone (T) therapy is an efficacious and safe treatment in cases of male T deficiency, and interest on the research into its approach in different fields has been recently increasing. The American Association of Clinical Endocrinologists (AACE), the American Urological Association (AUA), and the European Association of Urology recommend the use of T in patients with clear signs and symptoms of hypogonadism.[1–3] T therapy has been shown to have well-documented beneficial effects on erectile function, bone marrow, muscle mass, strength, and fatty tissue, as well as on metabolism control.[4–6]

The past decade has seen an increase in the search for alternative treatments that may provide similar benefits as androgens on muscle mass, strength, and

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fatty tissue without the side effects most feared by athletes and bodybuilders, such as testicular atrophy and infertility that has led to a surge in use of various agents that increase T, approved by the Food and Drug Administration (FDA), with narrow indications.[7–9] Physicians should be aware of the information regarding efficacy and toxicity for those substances commonly used by their patients. These products may interfere with the hypothalamic–pituitary–testicular axis affecting hormonal balance, fertility, and sexual performance.[10]

Although there are a number of alternative medical therapies to T therapy, including human chorionic gonadotropic, aromatase inhibitors, and selective estrogen receptor modulators,[10] there is considerable public interest for nonprescription, "natural" treatments, often called "testosterone boosters," or "testosterone enhancers." These agents are often marketed as improving sex drive and sexual performance, strength, and muscle mass. They are also claimed to be "safe" because they have the "advantage" of being composed of natural ingredients.[11–16] Since there is no scientific literature that reviews the effects of T-boosters, which are usually composed of multiple agents, we here review the available data for the individual supplement components that are frequently found in T-boosters.

Testosterone boosters

The term "*testosterone booster*" (T-boosters) will be used throughout this review to refer to any food supplement based on plants or nutrients marketed as food supplements advertised for allegedly increasing serum levels of total T or free T, enhancing the effects of T, or improving symptoms usually associated with hypogonadism. It should be noted that said supplements are not regulated by the FDA as medications and are marketed as food supplements.[9,11]

There is considerable variability in the amount of information provided for individual products regarding package contents. On average, *T-boosters* include a combination of 8 different ingredients, although there are options containing >50 ingredients. Among these we find mostly plant and herbal extracts, vitamins, minerals and some other micronutrients.[11,17]

The internet has become the main site for the purchase of the mentioned products, more so than physical stores, mainly because its sale is not commonly available in physical pharmacies or drug stores and since the sale of these supplements in different web sites warrants high levels of exposure and accessibility.[11] In 2013, T supplements achieved sales representing >2.1 billion USD[18] and global sales of dietary supplements reached tens of billions of dollars annually. The cost of T-boosters generally ranges from $16 to $400 dollars for a 30-day supply.[10,19]

History of T-boosters

Many of the components in *T-boosters* have a history of empirical use dating thousands of years. Aphrodisiac and rejuvenating properties have been reported in traditional Indian ayurvedic and Unani medicine.

At present, with the emergence of fitness and weight control as important and popular health goals, the pursuit of these food supplements is based on naturally increasing the production of endogenous T. However, there is no evidence supporting their use.[9] The use of T supplementation tripled between 2001 and 2011, thus representing an exponential growth in the pursuit of new therapeutic options in the pharmaceutical industry.

The escalating costs of pharmaceutical T products, as well as the limited coverage of these therapies by medical insurance companies, have restricted their use, despite growing awareness of the benefits of T therapy, and clinical guidelines that provide clear indications for their use.[11] This has led to a search for more affordable alternatives to relieve the symptoms of T deficiency, as well as to enhance the physical performance of athletes, and obtain the anabolic effect sought by bodybuilders.

Thus, the prevalence of use of T supplements is higher among this population.[19] T-boosters are well known among regular and new as a natural product that naturally improves T levels while ensuring lower cost and comparable efficacy such as T, and also sales slogans reinforce this nonscientific data.

There are few available studies on the effects of some of the most common ingredients in *T-boosters*. Most of them have methodological deficiencies that prevent them from being considered as objective information sources, and others tend to favor or highlight certain effects provided by their consumption.

Our findings upon performing a search about the effects of the most common ingredients in *T-boosters* on the serum levels of T and free T were as follows.[11]

Materials and Methods

A structural search in Pubmed was performed using the keywords "testosterone booster," "testosterone AND booster," "testosterone supplements," and

"testosterone AND replacement AND alternative." No randomized controlled trials, double-blind controlled trials, or clinical trials performed in humans or animals reviewing the effect of any T-booster could be found. However, there are meta-analysis and reviews of the effects of some of the most common ingredients that are components of this kind of supplements.

Subsequently, on the basis of the information obtained from some reviews,[9,10,20] the authors searched for studies providing information on each of the main ingredients found in *T-booster* supplements using the following keywords for this search: "testosterone AND *Tribulus*," "testosterone AND *Tribulus terrestris*," "testosterone AND *Zigophillacae*," "testosterone AND fenugreek," "testosterone AND *Trigonella*," "testosterone AND *Trigonella foenum*," "testosterone AND zinc," "testosterone AND *ashwagandha*," "testosterone AND *withania somnífera*," "testosterone AND *maca*," "testosterone AND *Lepidium meyenni*," and "testosterone AND melatonin."

We focused on recent studies published since 2014.

Results

Tribulus terrestris

Among the most frequently used ingredients in T-boosters are derivatives of *T. terrestris* (*Zygophillacae*). It is found in ~50% of the most common supplements sold in the United States[10,13,21] *T. terrestris* is a plant found in the Mediterranean and in tropical areas, with active metabolites (furostan saponin and protodioscin) that presumably increase T levels.

We were unable to identify any studies investigating the effects or mechanisms of action of this supplement. Results of published studies are generally unfavorable. One study found evidence of a significant rise in serum T levels in humans after a daily dose of 750 mg of *Tribulus* extract for 3 months. However, this analysis was only performed on the baseline and final T levels in each participant, without any comparison between groups.

In contrast, at least two literature reviews, three randomized controlled trials (RCTs), and one double-blind RCT failed to demonstrate any significant differences in T levels, nor improvement in sports performance, muscle mass, or sexual performance.[10,13,17,21] A systematic review showed an improvement in sperm count, sperm morphology, and motility after supplementation of 250–500 mg per day of *T. terrestris* extract in men with idiopathic subfertility.

The available data fail to indicate a reliable beneficial effect with *T. terrestris* in healthy or infertile men. This may be due to the inconsistencies in study methodologies, including different dosages. Moreover, contrasting results may have occurred due to the lack of comparison between the placebo and Tribulus-supplemented group, as well as the variability in the inclusion and exclusion criteria.[22]

Adverse effects have been reported to include hepatotoxicity, gastric mucosa alterations, hyperbilirubinemia that progressed into renal failure, and severe neurological disorders after consumption of high doses of these formulations.[13,17,21,23] The formulations containing this plant also include β-carboline-type alkaloids, which may cause weakness and loss of voluntary limb control.

Fenugreek

The extract called fenugreek comes from *Trigonella foenum-graecum* plant. It has been marketed for more than a decade as a food supplement that augments T levels. Available studies have important methodological deficiencies and report inconsistent results. The androgenic effect of the plant is attributed to the glycosylated saponins, which allegedly exhibit an inhibitory effect on 5-α-reductase, although we are unable to identify any studies to support this claim.[24] Specific claims noted in multiple publications are that fenugreek seed is capable of increasing free T and bioavailable T levels without increasing total T levels, and reduces dihydrotestosterone levels.[17,23–26]

An 8-week double-blind placebo-controlled randomized controlled trial (RCT) included 88 participants: 44 participants were supplemented with a patented extract of *T. foenum-graecum* and *Lespedeza cuneata* and 44 participants were supplemented with placebo. This study found an increase of both free and total T when compared with baseline.[23] The supplement received by the participants was a combination of *L. cuneata* extract, so the effect cannot be directly attributed to fenugreek. Significant changes in T levels were only observed in 34% of the participants in the group receiving the supplement. However, these changes were significant only when compared with baseline levels, and not when compared with the placebo group.[23]

In total, 30 participants per group in another randomized double-blind study were treated twice daily with either 300 mg of a glycosylated extract of fenugreek seeds or placebo for 8 weeks while doing

resistance training. The results showed a gain in strength when comparing repetitions with failure and one repetition maximum versus baseline, as well as a significant body fat loss in the group with fenugreek supplementation.

However, the differences were significant when comparing with baseline and there were no statistically significant differences in any parameter when comparing between groups.[24] A significant reduction in leukocyte count was observed without reaching leukopenia, as well as a moderate nonsignificant increase in alkaline phosphatase in the group receiving fenugreek compared with the control group.[23]

Zinc

A relationship between deficiency in zinc (Z) and hypogonadism was first described in 1960, a condition that was reverted after the supplementation with this microelement, and even marginal Z deficiencies caused a significant reduction in T levels.[10] In contrast, there have been no reports of an increase in T in humans with Z supplementation.[20,27] The FDA recommends a daily intake of 11 mg of Z, and *T-boosters* contain on average 272% of this element.[9] According to existing data, slightly high Z intake can interfere with copper and iron metabolism, and a higher intake of Z can cause anemia, neutropenia, and altered immune functions.[9] To date, there is no clear evidence that Z supplementation in healthy individuals causes an increase in serum T.[28]

Ashwagandha

Ashwagandha, also known as "Indian ginseng," is obtained from the *Withania somnífera* plant, and is a main ingredient or component of this group of food supplements. Among the active metabolites found in the *ashwagandha* root, we find ergostane steroids, alkaloids, sitoindosides, and saponins.[13,21,29,30] There are four double-blind RCTs in which the powder or extract from this plant's root was administered versus placebo, two in men with no known conditions and two in men with either infertility or overweight and fatigue. In three of these, a significant increase of serum T levels was observed compared with the placebo group.[17] Nonetheless, the supplement that was administered in all four studies comes from two different exclusive patented formulations that are not commonly available.

In a systematic review that included available studies performed in men with infertility or subfertility, results showed a statistically significant increase of an average of 100 ng/dL of serum total T, an improvement of semen parameters such as semen volume, sperm motility, sperm count, and an increase in the percentage of sperm normal forms. This analysis also reviewed one double-blind RCT that reported an increase in luteinizing hormone serum levels as well as follicle-stimulating hormone, prolactin and T, after supplementation with this root extract for 90 days.[29]

Although these results seem promising, only one was a double-blind RCT and the other studies were observational. They were performed in men with sperm alterations or known infertility. Furthermore, the statistically significant increase in serum levels was observed in comparison with baseline, however, there are no differences when comparing between groups.[13,21,29,30]

In another double-blind RCT, 50 subjects received either 300 mg of a high concentration ashwagandha root extract or 300 mg of starch-based placebo twice a day for 8 weeks, together with resistance training. A significant difference in gained muscle mass, strength, serum T levels, and a loss of body fat was observed when comparing the placebo group versus the group supplemented with ashwagandha extract. Despite the promising results of the evaluated studies, it should be noted that they all have limitations, including the sample size, the time the subjects were followed, and the limited profile of the subjects.[30]

Studies should be performed including a larger sample, men with pre-existing conditions, and men with hypogonadal symptoms and infertility. A follow-up of the tolerability profile was performed by means of a symptom questionnaire and for a maximum period of 12 weeks. No blood tests for liver enzymes or renal function was obtained, so safety has not been established.

Maca

Maca (*Lepidium meyenii*) is a Peruvian plant traditionally used to treat erectile dysfunction and to improve physical activity in general. It is the most common component in marketed food supplements. Although its mechanism of action is unknown, it is postulated that its effects come from alkamides called "macamides," which might also aid in improving sperm count and motility.[13,21] Other studies have revealed the possibility of increasing serum T levels in rats by stimulating the steroidogenic ability of Leydig cells, together with the fact that another study found that it protected testes from the toxic effect of cyclophosphamide.[10,20]

Studies in animals and humans are limited, and they also lack objective information that could be pertinent to the clinical setting. To date, existing studies have not found any increase in total T after the supplementation with maca powder at different doses.[17]

The safety profile of maca has been barely explored, however, one trial showed evidence of an increase in aspartate aminotransferase (AST) and diastolic pressure after supplementation with maca. As with the trend observed with the previously mentioned elements, despite the fact that there are on average 28 published studies on this plant, none provides any clear or conclusive evidence favoring its use.[11,13] Reviews of maca fail to recommend it since the effective dose and the toxic dose are not standardized, and especially because of the absence of a safety profile in the short, medium, and long term.

Melatonin

Melatonin is a hormone found in different species and is widely used as a sleep aid. There is evidence that it increases T levels in several animal species and attenuates the decrease in T resulting from agents with known testicular toxicity.[31,32] In clinical trials in humans, there has been evidence of an increase in T levels after supplementation with this hormone. The research on its effects and mechanisms has been limited due to the lack of adequate animal models. However, an article was recently published that found that melatonin has a protective effect on Leydig cells by suppressing the mitochondrial signaling of *Bax/Bcl-2* apoptosis, in addition to increasing T production and enhancing sperm quality in mammals.[32]

Another study found an antioxidant, anti-inflammatory effect on diabetic rat testes, in addition to a stimulating effect on the expression of the membrane T receptor.[33,34] Another recent study showed the protective effect of melatonin against the testicular toxicity induced by etoposide, cisplatin, and bleomycin regimen by attenuating nitro-oxidative stress, apoptosis, and inflammation in rats.[31] Although preliminary animal studies are promising, there are no available studies in which supplementation with melatonin has shown an increase in serum T levels in humans.

Discussion

T-boosters are widely marketed as nonprescription products to improve a variety of male concerns, such as libido, sexual function, energy, and muscle mass and strength. The explicit or implied mechanism of action of these products is to increase T, and the marketing hook is that these products are touted as being "natural." Yet there is limited information available to determine whether any of these claims are accurate. Whereas bodybuilders, athletes, and men with hypogonadal symptoms have historically been the most vulnerable population to consume these supplements, the general public's interest in health, fitness, and well-being has broadened the target population for T-boosters.[19]

In this article, we review the available information for several of the main components found in currently available *T-boosters*. This information should benefit clinicians in their decision making when patients seek counseling regarding the possible use of these supplements. In Table 1, we provide a summary for each of these agents. Although the evidence on the use of several of the herbal extracts is conflicting, and is important to emphasize that even though the FDA oversees the safety of over-the-counter supplements, its studies and data requirements are not as rigorous as for pharmaceutical agents. Not surprisingly, the quality of the studies has also been less rigorous.

Hence, the formulation of these supplements may differ between studies, concentrations of the components cannot be considered reliable or accurate. Many T-boosters fail to provide the exact amount of each ingredient contained either per dose or tablet. As previously described, *T-boosters* have an average of eight ingredients, and there are some with >20 in their formulations. Data for any of these combination products are lacking, and for this reason we focused our review on studies of the underlying components.

Not only does the use of multiple agents confound the interpretation of beneficial results, if present, but it also raises the risk of adverse events, including anaphylaxis, liver damage, and renal or neurological damage. There is evidence of the untoward effects on health from some of the components, however, no restrictions have been issued by regulatory authorities. There are no studies evaluating the safety or efficacy profile of those formulations including these elements together, but only some studies superficially evaluating the biosafety profile of some of the components individually and for periods of no more than 12 weeks.

This supports the fact that, although they are with the assumption that by being "natural" they lack side effects, in truth, their long-term safety is unknown. Also, according to their advertisings, there are no contraindications for discontinuing their intake after a certain period.

Table 1. Effects, Mechanisms, and Quality of the Information Available of the T-Boosters' Ingredients in Serum Testosterone and Hypogonadism Symptoms

T-booster ingredient	Postulated mechanism	Human or animal trials	Type of available studies	Effect after supplementation	Reported adverse effects
Tribulus terrestris	Increase in T levels attributed to furostan saponin and protodioscin	Human and animal trials available	Randomized controlled trials and double-blind randomized controlled trials	• No difference in T levels • No difference in sports performance • No difference in muscle mass • No difference in sexual performance.	Hepatotoxicity, gastric mucosa alterations, hyperbilirubinemia, renal failure, weakness, loss of voluntary limb control, and neurological alterations.
Fenugreek (*Trigonella foenum-graecum*)	1. Inhibitory effect on 5-α-reductase attributed to glycosylated saponins 2. Increase in free T and bioavailable T levels without increasing total T levels	Human and animal trials available	Double-blind randomized controlled trials	• Increase in serum T levels** • Increase in sport performance** • Increased fat loss** **Only when compared with baseline data and not when compared with placebo	Reduction in leukocyte counts and elevation in alkaline phosphatase
Zinc	Association of zinc deficiency with hypogonadism	Human and animal trials available	Randomized controlled trials	• Improvement in sperm parameters** • No increase in serum T *Only in subfertile men	Interference in copper and iron metabolism, anemia, neutropenia, and altered immune function
Ashwagandha (*Withania somnifera*)	Presence of ergostane steroids, alkaloids, sitoindosides and saponins	Human trials available	Double-blind randomized controlled trials and observational studies.	• Improvement in semen parameters* • Increase in serum T, FSH, and LH levels*,** *Only in subfertile men **Only when compared with baseline and not with placebo	No biochemical alterations profile available, tolerability profile obtained only by symptom questionnaire.
Maca (*Lepídium meyenií*)	1. Improvement in sperm count and motility attributed to alkamides called "macamides" 2. Increase in serum T due to the stimulation of steroidogenic ability of Leydig cells	Animal and human trials available	Randomized controlled trials and double-blind randomized controlled trials	• No improvement in serum T	Elevation of AST and diastolic pressure although the safety profile is poorly studied
Melatonin	1. Suppresses Leydig cell apoptosis by suppressing Bax/BCL2 mitochondrial signaling 2. Stimulates the expression of the membrane T receptor 3. Antioxidant and anti-inflammatory effect on the testis	Only animal studies available	Observational and experimental studies	• Increases in serum T† • Decreases in testicular toxicity due to different etiologies† • Enhances sperm quality† †Only studied in animal models	No adverse effects reported

AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

It should be noted that the formulation of those few extracts evaluated in double-blind studies is not that usually found in the family of *T-boosters*, therefore, any observed beneficial results may not be applicable to commercially available T-boosters that contain those agents. At present, there is inadequate evidence to support the use of *T-boosters* to increase total, free, or bioavailable T, for treatment of symptoms of T deficiency, male infertility, or to increase strength and muscle mass or enhance training endurance.

Although isolated studies may show favorable results in one or more of these areas, the quality and reliability of those that do are questionable. In addition, some of these studies have reported that their ingredients are not harmless, and although no alerts have been issued regarding any product in particular,

there is a report of a case of acute hepatotoxicity due to *T-booster* intake.[35]

Nevertheless, one cannot be certain regarding the quality and efficacy of such products for several reasons, among others the lack of inadequate storage conditions and their origin in unreliable sources. It is also important to point out that the supplements and extract used in the studies evaluated are highly purified and/or concentrated forms, which is not the presentation we found in *T-booster* supplements; hence, we cannot extrapolate these trial results to everyday practice.

Counseling should be offered to patients about the insubstantial data available of the effects of *T-boosters* on T levels, improvement in sexual performance, and hypogonadism symptoms. The studies available cannot provide either consistent or reliable information about raising T levels, mostly because the supplementation protocols and sampling timelines were uneven, leading to an unfeasibility to make accurate comparisons.[11]

Throughout the years, some consumers of *T-boosters* have complained of renal and liver anomalies that might be related to the use of T-boosters. There have been cases of inadequate administration of such products, since it is possible that athletes do not fully follow the instructions in the package, which may cause many side effects.

As reported by Reyes-Vallejo,[8] the use of anabolic steroids and the lack of regulation have become a health problem among athletes and bodybuilders. The deficient knowledge regarding the management of anabolic steroids among the medical community limits the access to information by the vulnerable population, so they resort to the empirical practice of nonmedical personnel, which increases the risk of complications from the use and abuse of these substances.

To date, there appears to be no studies or clinical trials with any T-booster currently available on the market. Nor are there any head-to-head clinical trials comparing T therapy and T-boosters or individual supplements. Therefore, the true effects of T-boosters are unknown. Although it remains possible that these agents may have some degree of efficacy, and that this may be demonstrated in the future with adequate studies, at this time it is impossible to recommend any of them.

Conclusion

The current scientific literature fails to provide adequate data to support the use of T-boosters or their underlying components. Use of these products should be discouraged, at least until there is solid evidence demonstrating benefits and safety. Health care professionals should ask about supplement use when patients come seeking medical advice.

The consequences of these products on public health and the economy are unknown. This issue demands the immediate attention and further study from health authorities and practitioners worldwide.

Authors' Contributions

A.A.A.-M. contributed to methodology, investigation, writing—original draft, and visualization. A.M. was involved in writing—review and editing. L.A.R.-V. was in charge of conceptualization, writing—review and editing, project administration, and correspondence.

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Abbreviations Used

FDA = Food and Drug Administration
FSH = follicle-stimulating hormone
LH = luteinizing hormone
RCT = randomized controlled trial
T = testosterone
T-boosters = "testosterone boosters"