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Review

Nonpharmacological Interventions for the Management of Testosterone and Sperm Parameters: A Scoping Review

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ABSTRACT

Purpose: Testosterone replacement and associated pharmacologic agents are effective strategies to treat male hypogonadism; however, nutraceutical agents and lifestyle modification approaches have gained medical interest. The purpose of this scoping review is to highlight the evidence (or lack thereof) of nutraceuticals and lifestyle modification approaches in the management of testosterone levels and sperm parameters.

Methods: A scoping review of nonpharmacologic interventions (supplements, herbal medicines, diets, sleep, and exercise) with the potential to improve male health was undertaken to elucidate changes in testosterone levels and sperm parameters in men with hypogonadism or infertility compared with healthy patients.

Findings: A multitude of nutraceuticals and functional nutrients are purported to stimulate testosterone production; however, only a select few have had promising results, such as zinc, vitamin D (in case of hypovitaminosis D), L-arginine, mucuna, and ashwagandha, based on well-controlled randomized clinical trials of men with low testosterone levels and related problems. Except for L-arginine, these natural agents, as well as tribulus and ω3 fatty acids, can improve some degree of sperm parameters in infertile men. Before implementing these nutraceutical agents, adequate sleep, exercise, and weight loss in patients with obesity are imperative. The effects of nonpharmacologic interventions on testosterone levels are modest and hence do not directly translate into clinical benefits. Correspondingly, androgen receptor content, but not endogenous androgens, has been regarded as the principal factor in muscle hypertrophy.

Implications: A limited number of supplements and herbal medicines can be considered as adjunctive approaches in the management of testosterone levels and sperm parameters, primarily in men with low testosterone levels and infertility, whereas most nonpharmacologic supplements appear to lack evidence. Although proper physical exercise, sleep, and diet are indisputable approaches because of the general benefits to health, the use of nutraceuticals, if considered, must be personalized by physicians and/or registered dietitians. (*Clin Ther.* 2022;000:1–21.) © 2022 Elsevier Inc.

Key words: Bodybuilding, Herbal medicines, Male hypogonadism, Steroids, Testosterone.

INTRODUCTION

Male hypogonadism is an increasingly common condition that affects progressively younger males.[1] The diagnosis of hypogonadism requires the combination of clinical manifestations unexplained by other diagnoses and biochemical characterization of reduced serum testosterone.[2,3] Symptoms may include sexual-related dysfunctions, such as impaired libido, erectile dysfunction, decreased ejaculation volume, and

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infertility, as well as systemic and unspecific symptoms, such as impaired cognitive function, attention-deficit/hyperactivity disorder–like symptoms, depression, fatigue, weakness, normocytic normochromic anemia, obesity, and decreased bone density and muscle mass.[4] Although sexual symptoms may seem more specific, those related to erectile function and libido are more commonly related to nonhormonal causes.[5,6] Conversely, in the absence of other diseases, a decrease in overall quality of life encompassing decreased energy levels and cognitive function may be more specific to hypogonadism than sexual symptoms.[7,8] As such, weaker correlations between sexual manifestations and hypogonadism have been identified than those related to general health.[9]

The prevalence of male hypogonadism ranges from 2% to 13% in middle-aged to older Europeans and Americans, with an estimated 12 new cases per 1000 person-years,[10] and appears to be increasing across all ages.[11–13] Although the major concern of hypogonadism is among middle-aged and older men (≥45 years of age),[4] younger males may also present with hypogonadism, particularly in those with metabolic and inflammatory dysfunctions, such as obesity, diabetes, abuse of anabolic steroids for aesthetic purposes, and prolonged exposure to endocrine disruptors.[14–17] The first-line therapy for male hypogonadism is testosterone replacement; however, testosterone replacement may lead to a decrease in fertility and further inhibition of the gonadotropic axis.[18] When fertility is desired and inhibition of endogenous testosterone production is unwanted, other therapy modalities may be considered, including drug enhancers of the endogenous production of testosterone that may act on different levels of the gonadotropic axis, including clomiphene (the most used drug for this purpose), human chorionic gonadotropin, tamoxifen, and anastrozole.[19,20]

Alternatives strategies, including nutraceuticals alone or in combination with allopathic pharmacotherapy, have been hypothesized as adjunct strategies to treat male hypogonadism by improving testosterone levels and sperm parameters.[21–23] Despite the widespread use of nutraceuticals in this regard, to date, no guidelines from various endocrine societies have included them as a treatment modality for male hypogonadism.[13,24,25] In this scoping review, we address the effects of nutraceutical agents (herbal medicines and supplements) that have become popular as testosterone boosters and provide further underpinnings of potential dosages that could be proposed as adjunct strategies to improve both testosterone levels and sperm parameters. In addition, we highlight the importance of lifestyle modification, dietary strategies, sleep quality, physical exercise, and body composition on testosterone production.

METHODS

A scoping review of nonpharmacologic interventions (supplements, herbal medicines, diets, sleep, and physical exercise) with the potential to manage male hypogonadism in healthy patients was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). The PRISMA-ScR checklist is given in Supplemental Table I.

The PubMed, Web of Science, Scopus, and Cochrane databases were searched using the following key words: *amino acids* OR *arginine* OR *creatine* OR d-*aspartic acid* OR *herbal medicines* OR *ashwagandha* OR Mucuna pruriens OR Tribulus terrestris OR *lipids* OR *cholesterol* OR *dehydroepiandrosterone* OR *ω3* OR *magnesium* OR *vitamin D* OR *zinc* OR *nuts* OR *calorie restriction* OR *physical exercise* OR *sleep* AND *infertility* OR *hypogonadism* OR *total testosterone* OR *free testosterone* OR *oligozoospermia* OR *sperm* OR *semen*. Although there is a plethora of herbal medicines and nutrients, we focused on those with the greatest clinical potential, as selected by the above-mentioned key words. Randomized clinical trials (RCTs) were selected to draw clinical causal conclusions, whereas other types of studies were allowed only to expand the rationale for mechanisms of action. Only articles written in the English language were included, and the literature search covered studies published until 2022. In addition to men with hypogonadism or infertility, studies with healthy men were also included because of the scientific interest in nonpharmacologic interventions in the management of testosterone in middle-aged and elderly men, as well as in those who exercise.

MALE HYPOGONADISM

Primary and Secondary Hypogonadism

The origin of hypogonadism is multifactorial, typically related to metabolic or inflammatory dysfunctions, senescence, or genetic, anatomical, or organic causes, as well as by abnormalities in the testicles (primary, peripheral, or hypogonadotropic hypogonadism)

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or in the hypothalamic-pituitary axis (secondary, central, or hypergonadotropic hypogonadism).[2,26] Its can be present before puberty, when the development of secondary sexual characteristics does not occur, during or after adolescence, as well as in adulthood.[27]

Primary hypogonadism can be differentiated from secondary hypogonadism by the gonadotropic hormones, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).[28] Because the site of abnormality of primary hypogonadism is the testicles, increased LH and FSH are usually detected, accompanied by increased levels of sex hormone–binding globulin (SHBG) because SHBG is produced in the liver in response to LH and FSH.[29,30] Conversely, secondary hypogonadism is caused by abnormalities in the pituitary or hypothalamus or by factors that stimulate or inhibit gonadotropin-releasing hormone in the hypothalamus, and LH and FSH levels are usually in the low or abnormally normal range (within the reference range).[31,32] Both LH and FSH are considered to be abnormally normal because under low testosterone levels LH and FSH levels are expected to be high to stimulate testosterone production, as per normal homeostasis of the gonadotropic axis.[33,34] Once a dysregulation of these hormones is detected, semen analysis can also be performed for an initial laboratory screening for infertile men because endogenous testosterone is required for maturation and production of sperm cells.[35–37] The testosterone range is discussed below.

Clinical Measurement of Serum Testosterone

Low testosterone levels accompanied by related clinical symptoms constitute hypogonadism.[38] However, the reference range for testosterone is still debated, particularly in the lower limit. In general, studies with a large number of males indicate that normal total testosterone (TT) levels ranged from 220 to 260 ng/dL to 900 to 915 ng/dL, with mean levels of 500 ng/dL, whereas males with obesity presented with slightly lower testosterone levels.[39] No differences in terms of risk or benefits are usually found when males in the lowest quartile are compared with males in the highest quartile.[39] Hence, except for select cases, it is not reasonable to try to reach the upper limits of testosterone levels. Of importance, testosterone secretion follows a circadian cycle, with higher levels during sleep[40] and peaks between 5 AM and 10 AM,[41] when blood collection for determining serum testosterone is preferred.[41–43] The testosterone peak in the early morning may partially justify the occurrence of the awakening erection,[44] which is used to evaluate clinical signs of testosterone.

NUTRIENTS AND NUTRACEUTICAL STRATEGIES

Vitamins and Minerals

Vitamins and minerals are essential elements for humans.[45,46] Screening of their status by serum levels and amount ingested may be useful in the management of male hypogonadism, in particular those that have roles in testosterone production and in antioxidant status of testes, including zinc, magnesium, and vitamin D. Their physiologic roles are described below.

Zinc

Better than many herbal medicines and nutraceuticals, zinc supplementation, if adequately prescribed, can be an adjunct therapy to several comorbidities.[47,48] Several meta-analyses support the benefits of zinc supplementation in clinical settings,[49–52] and there are several interventions and epidemiologic studies that support zinc.[53,54]

Supplementing with ZMA, a formulation of zinc, magnesium, and vitamin B6, is propagated unsubstantially by the supplement manufacturing industry as a testosterone booster and even a muscle-building promoter. In addition, care should be taken with funded studies because there is a link between ZMA-producing companies and original research.[55] Despite the ZMA controversy, zinc administration cannot be generalized as ineffective at increasing testosterone because the amount of elemental zinc in ZMA is less than the zinc dosage proposed to increase testosterone concentrations and improve semen analysis.[21]

Taken together, a practical suggestion of zinc dosage for the treatment of male hypogonadism is approximately 220 mg of zinc sulfate (equivalent to 50 mg of elemental zinc) once or twice a day for 1 to 4 months because this dosing regimen is capable of ameliorating both TT levels (expected increase of approximately 50-400 ng/dL) and sperm parameters.[21] An increasing body of evidence considers this daily dosage to be effective and tolerable.[21,49,50,56] Specifically, Prasad et al[57] examined semen quality after 30-mg elemental zinc gluconate anion supplementation in marginally zinc-deficient elderly men (approximately 65 years of age, n = 9) for 6 months and found

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a mean (SD) increment in serum TT of 251 (182) ng/dL to 461 (127) ng/dL ($P = 0.02$). In another study on seminal fluid, 220-mg zinc sulfate supplementation 3 times daily for 4 to 8 weeks increased the mean (SD) serum TT levels of infertile men (n = 10) from 493 (50) ng/dL to 852 (222) ng/dL.[58] Despite the small sample size of pioneering studies,[57,58] in a more recent study with a greater sample size (n = 100) of male patients with end-stage renal disease undergoing hemodialysis, 250 mg/d of zinc sulfate for 6 weeks almost doubled testosterone levels.[59] Thus, increased serum testosterone concentrations and improvement in sperm parameters can be expected with this zinc supplementation for patients with male hypogonadism. However, whether the increase in testosterone levels with zinc supplementation can increase muscle mass is unknown. The amount of daily elemental zinc prescribed is critical rather than the dosage of its different salts because underuse of zinc as a supplement may be ineffective.

Special attention to zinc status should be given to athletes because this population may be more susceptible to zinc deficiency, particularly in those athletes in endurance sports.[60] A meta-analysis of cross-sectional studies found that athletes have lower serum zinc concentrations when compared with the untrained control population, although they ingested a greater amount of dietary zinc;[60] in terms of values, the mean reduction in serum zinc was 0.93 μmol/L. Given that the laboratory reference for serum zinc is approximately 10 to 18 μmol/L,[61,62] this reduction is not surprising. Regarding the higher consumption of zinc, the athletes ingested approximately 2.5 mg/d more than the control subjects,[60] which is equivalent to a common piece of meat or a few tablespoons of oats or oilseeds.[63]

Magnesium

Mechanistically, magnesium can increase testosterone production by decreasing systemic inflammation and increasing sperm motility via adenosine triphosphate (ATP) production.[64] Indeed, cellular energy production processes are composed of many magnesium-dependent enzyme reactions, such that mitochondria are the main organelles of intracellular magnesium storage, whereas dysregulation of mitochondrial magnesium homeostasis can negatively alter mitochondrial ATP generation and impact morphology.[65] Because sperm are dependent on the metabolism of mitochondria, mitochondrial magnesium is important for sperm motility, mainly because of the production of ATP.[66]

In a cohort of older men, magnesium levels were strongly associated with TT concentrations.[67] In another study, magnesium levels were lower in males with increased leukocyte counts in the seminal fluid than in those with normal leukocyte counts.[68] However, supplementing with 10 mg/kg daily of magnesium sulfate had no clinical relevance for increasing baseline TT levels in sedentary eugonadal men and in taekwondo athletes when viewed in general, although resulting in a mean (SD) free testosterone increase from 17.78 (4.45) ng/dL to 22.20 (4.15) ng/dL ($P < 0.05$), collected at rest, for the athletes.[69] In addition, in an RCT of men with idiopathic infertility, treatment with magnesium at a dose of 3000 mg/d for 3 months did not lead to a significant improvement in sperm variables compared with controls.[70] Of interest, despite the high dose of magnesium, circulating magnesium levels did not increase.[70]

Hypothetically, a favorable time to administer magnesium supplements is before bed because of its central depressant effect.[71] However, excess magnesium can be unhealthy because of the risk of morning diarrhea,[72] and, above all, there is a lack of evidence on its effects as a testosterone booster.

Vitamin D

Biochemically, vitamin D participates in testosterone synthesis by upregulating the expression of genes related to this hormone as well as preserving testicular cells because of its effects in suppressing inflammatory factors,[73,74] although it is vital for sperm cells by increasing their motility, calcium handling, capacitation, acrosin reaction, and lipid metabolism.[75] Clinically, nonetheless, there is insufficient evidence to consider vitamin D administration as an effective testosterone booster as viewed as a whole[23]; however, a couple of RCTs found a mild to modest increase in TT and improvement in sperm parameters for patients with hypovitaminosis D.[76,77]

There is a positive association between serum 25-hydroxy vitamin D (25[OH]D) levels with TT and free testosterone, as confirmed in a study of 1362 men.[78] Pilz et al[76] provided 3332 IU of vitamin D for 1 year (n = 31) or placebo (n = 23) for middle-aged men. Compared with baseline values, in the vitamin D group, a significant increase was found in TT levels from 309 to 387 ng/dL and in free testosterone levels from 6 to

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8 ng/dL, whereas the placebo group did not increase these parameters.[76] Regarding the serum variation of 25(OH)D in the group that supplemented vitamin D, the level went from 13.02 ng/mL (insufficiency value) to 34.61 ng/mL (sufficiency value).[76]

Both increased TT and decreased estradiol were found in middle-aged men after treatment for 25(OH)D deficiency (<30 ng/mL).[77] A total of 102 patients received an oral solution of 600,000 IU of ergocalciferol (vitamin D_2). The frequency of dose administration was indicated according to the response of serum 25(OH)D. The treatment started with 600,000 IU per month, and as soon as the patient reached 30 ng/mL of serum 25(OH)D levels, 600,000 IU per 2 months was administered; the entire protocol lasted for a 1-year follow-up period. Because the serum target for 25(OH)D was 30 to 80 ng/mL, those patients who exceeded 80 ng/dL had a reduced frequency of administration, using 600,000 IU per 3 months to avoid toxic effects. The TT level increased from 359 ng/dL to 469 ng/dL after 3 months, remaining at approximately 460 ng/dL in the consecutive months, whereas the LH did not change at any time, remaining at approximately 3.60 IU/L. Concerning the estradiol levels, approximately 24 pg/mL at the baseline decreased to approximately 20 pg/mL after 3 months and to approximately 19 pg/mL at the 9th and 12th months, representing only a small biological reduction.[77] There was an improvement in erectile function,[77] but there was no placebo group, which is a considerable bias because libido is affected by psychological factors.[79]

Vitamin D administration did not increase testosterone in healthy men through a study of 50 middle-aged men who were randomized to receive 20,000 IU per week of vitamin D_3, whereas 50 received placebo for 12 weeks.[80] In the group that supplemented vitamin D, the mean serum 25(OH)D values of 52 nmol/L increased to 82 nmol/L. Despite the increase in serum 25(OH)D levels, neither TT nor free testosterone changed, and body composition based on fat and lean body mass also did not change. A strength of this study was the randomized, placebo-controlled design, with a primary purpose to examine testosterone status, as opposed to several cross-sectional and other observational studies.

In a recent RCT of infertile men with asthenozoospermia and 25(OH)D deficiency (n = 86), 4000 IU/d of vitamin D_3 for 3 months did not increase circulating TT, but there was an improvement in sperm parameters—seminal volume did not increase, but there was an increase in total and progressive sperm motility (from 34% to 39% and from 19% to 24%, respectively) after supplementation.[81] Circulating 25(OH)D was corrected after supplementation (from approximately 18 ng/mL to approximately 32 ng/mL) so that TT was maintained because the mean was within the reference range (approximately 400 ng/dL). To our knowledge, no RCTs investigating the effects of administration of vitamin D on testosterone levels in men with hypogonadism have yet been performed; hence, a future study is warranted.

LIPIDS AND RELATED COMPOUNDS

ω3 Polyunsaturated Fatty Acids

Limited evidence exists regarding the effects of ω3 polyunsaturated fatty acid (n-3 PUFA) supplementation on testosterone levels, but there is scientific progress in several parameters. Correspondingly, a meta-analysis found that n-3 PUFA supplementation increased sperm motility and semen docosahexaenoic acid (DHA) concentration in infertile patients.[82] On the other hand, there was no increase in the number of sperm or in the concentration of DHA when compared with control groups. Only 3 studies were included, with 147 patients in the supplementation group and 143 in the control group. The dosage varied between 400 and 800 mg/d of DHA for 12 weeks, 1120 mg of eicosapentaenoic acid plus 720 mg of DHA for 32 weeks, and 930 mg of DHA for 12 weeks. In our view, at best, it would be worth considering n-3 PUFA supplementation as a mere adjunct strategy in the condition of male infertility or during postcycle therapy (ie, postuse of anabolic-androgenic steroids)[83] because many people do not ingest an adequate amount.[84]

Cholesterol

Low-fat diets are associated with low testosterone levels, as recently observed by a meta-analysis of RCTs,[85] thereby shedding light on the importance of fat intake on testosterone status. Dietary cholesterol accompanying animal fat could be important because cholesterol is a substrate for the formation of testosterone.[86] We are aware of a proposal for cholesterol intake and increased testosterone in sports, with a focus on resistance-training individuals. Thus, it is also speculated that increased cholesterol consumption

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would be interesting for hypogonadism induced by the use of anabolic steroids in postcycle therapy.[87]

The ketogenic diet is the dietary model with the highest cholesterol intake, which is a substrate for the formation of testosterone.[88] In general, 500 to 1000 mg/d of cholesterol are typical on the ketogenic diet, which may reflect an increase in TT of approximately 100 ng/dL in trained men.[88,89] However, it is disproportionate to affirm that a ketogenic diet increases testosterone levels to the extent of providing supraphysiologic conditions, and the ketogenic diet is not the primary treatment for male hypogonadism.

In a recent RCT with 30 resistance-trained young men, daily intake of 3 whole eggs (672 mg of cholesterol) for 12 weeks increased posttraining serum TT levels by approximately 240 ng/dL versus approximately 70 ng/dL (time × group <0.001) for isonitrogenous quantity consisting of 6 egg whites (0 mg of cholesterol) daily.[90] Whole egg consumption was considered more favorable for improving muscular strength, but there were no group differences in muscle mass.[90] Both interventions cited[89,90] were performed on young eugonadal men; therefore, more research is needed on the relationship between cholesterol consumption and testosterone concentrations, especially in patients with hypogonadism.[90]

DHEA

Because of the physiologic decrease in DHEA production between 20 and 30 years of age, DHEA supplementation has increased in the antiaging and overall health fields.[91–93] DHEA has also gained popularity among resistance-training practitioners, and sponsored athletes claim benefits of using DHEA on body composition and well-being. In contrast, the effect of DHEA supplementation on testosterone production seems to be more promising for women as a means of stimulating testosterone synthesis through the adrenal cortex.[94,95] Because of the testes, men have testosterone production >10 times greater than women, so that testosterone screening is not indicated for monitoring women's health.[96,97]

Therefore, DHEA supplementation can be sex dependent, whereas it may increase testosterone and estrogen concentrations. In support, a well-designed, 1-year interventional study of 50 mg/d of DHEA supplementation found increased serum concentrations of estrogens (estrone and estradiol) in older women and men, whereas there was an increase in TT concentrations for women only.[98] In addition, bone mineral density was examined, which was mediated by estrogens but not by testosterone.[98] Such a finding is in line with the literature base, which reports some support for DHEA administration, especially in older women and in those with adrenal insufficiency,[94,95] whereas there is no concrete evidence supporting DHEA supplementation for men with hypogonadism.

AMINO ACIDS AND DERIVATE COMPOUNDS

l-Arginine

In a recent meta-analysis, L-arginine supplementation, from 1500 to 5000 mg/d, improved parameters of erectile dysfunction compared with placebo.[99] Patients had mild to moderate erectile dysfunction. The authors emphasize the effectiveness of L-arginine in combination with other agents. Taking into account the combination therapy of L-arginine and yohimbine, L-arginine acts as an important substrate for the production of nitric oxide, whereas yohimbine blocks presynaptic α_2-adrenergic receptors, hence releasing more nitric oxide and increasing blood flow in the penile artery by nonadrenergic and noncholinergic mediation.[100,101] Seemingly, supplementation with L-citrulline can physiologically provide the same effect as L-arginine because it may increase plasma concentrations of L-arginine more efficiently than arginine supplementation.[102]

A recent study found that the oral use of L-arginine in conjunction with tadalafil improved libido and testosterone concentrations more than the isolated treatment of both substances.[103] This study was a double-blind RCT of 108 patients with diabetes and erectile dysfunction who were placed in 4 groups of 8-week treatments: 5 g of L-arginine, 10 mg of tadalafil, 5 g of L-arginine plus 10 mg of tadalafil, and placebo. Thus, daily use of L-arginine with tadalafil increased erectile function and testosterone concentrations by 144%. Testosterone concentrations were 275 ng/dL at the beginning and increased to 647 ng/dL at the end of the intervention. Isolated interventions with L-arginine and tadalafil were also effective in improving erectile function and increasing testosterone levels, but the combination was superior. In addition, when compared with placebo, the other groups were superior. Given that the patients had diabetes, a population whose circulatory system is impaired, there is reasonable

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biological plausibility for the role of the investigated compounds in improving erectile dysfunction.[104]

Ultimately, for dietitians, the isolated use of L-arginine can be legal and effective as a testosterone booster and an adjunct to erectile function in those who have low testosterone levels and erectile dysfunction. For physicians, a combined protocol of L-arginine plus tadalafil can further enhance the patient's treatment in these circumstances.

d-Aspartic Acid

In a rat model, D-aspartic acid (D-Asp) administration increases the release and synthesis of LH through the involvement of cyclic guanosine monophosphate as a second messenger in the pituitary, with an ensuing increase in the synthesis and release of testicular testosterone on cyclic adenosine monophosphate activity as a second messenger.[105] In a systematic review published in 2017, D-Asp supplementation enhanced testosterone levels in male animal studies, but the results were inconsistent with human studies.[106] Of importance, only 4 human research studies were included of which 3 studies[107–109] were performed on resistance-trained or physically active men and 1 study on male volunteers at *in vitro* fertilization.[105] Regarding the latter, the patients were healthy young adults (n = 23; 27 to 37 year of age) and thus had normal testosterone levels. Regardless of this clinical condition, 3.12 g/d of sodium D-Asp supplemented for 12 days led to an increase in mean (SD) serum TT levels from 450 (60) ng/mL to 640 (80) ng/mL ($P < 0.0082$) and from 4.2 (0.5) mIU/mL to 5.6 (0.9) mIU/mL ($P < 0.0001$) in LH levels; however, the supplement contained vitamin B_6, folic acid, and vitamin B_{12}, which are elements with proposed effects on reproduction.[110]

After this systematic review, RCTs were published that found the ineffectiveness of supplementing D-Asp for athletic individuals.[111,112] One study randomized 16 climbers to 3 g/d of D-Asp or placebo for 2 weeks;[111] the other randomized healthy resistance-trained men to 6 g/d of D-Asp or placebo for 12 weeks in conjunction with a resistance training program.[112]

Creatine

Creatine is an endogenous compound derived from 3 nonessential amino acids: L-methionine, L-arginine, and L-glycine.[113] Although creatine is stored primarily in muscle cells and used for energy production to support muscular contractions, its effects on sperm cells are promising because these cells are dependent on mitochondrial metabolism, whereby adenosine triphosphate drives intracellular energetic reactions.[114]

Lower creatine concentrations in semen are associated with reduced sperm motility, as found in a recent study.[115] To reach this result, the researchers compared 35 men with reduced sperm motility with 53 men without this ailment. In addition, increased creatine kinase activity was associated with poor sperm quality.[115] On the other hand, there is a paucity of evidence and biological rationale to supplement creatine as a testosterone booster. For instance, short-term creatine treatment (20 g/d for 5 days) did not increase the testosterone levels after resistance training sessions in healthy young male volunteers.[116] Likewise, 3 weeks of creatine supplementation (25 g/d for 7 days followed by 5 g/d for 14 days) did not increase testosterone levels of rugby players.[117]

HERBAL MEDICINES

Mucuna (*Mucuna pruriens* L DC., Fabaceae) and ashwagandha (*Withania somnifera* L Dunal, Solanaceae) are herbal medicines that produce interesting results in increasing serum testosterone concentrations and improving sperm parameters when clinically compared with other herbal medicines, for example, maca (*Lepidium meyenii* Walp, Brassicaceae), long Jack (*Eurycoma longifolia* Jack, Simaroubaceae), fenugreek (*Trigonella foenum-graceum* L, Fabaceae), and black seeds (*Nigella sativa* L, Ranunculaceae).[22] In patients with oligozoospermia (n = 75), 5000 mg/d of mucuna seed powder for 12 weeks significantly increased TT levels by 151 ng/dL (from 389 to 540 ng/dL).[118] In a similar fashion, 5000 mg/d of ashwagandha root powder for 12 weeks significantly increased TT levels by 143 ng/dL (from 351 to 494 ng/dL) in patients with oligozoospermia (n = 75).[119]

To date, although there is a lack of evidence for tribulus (*Tribulus terrestris* L) as a testosterone booster,[22] a systematic review corroborates the improvement in sperm parameters in men with idiopathic infertility receiving tribulus treatment,[120] with the daily dose of tribulus ranging from 250 to 500 mg/d in 6 studies and 1 study using 12 g/d (6 g twice daily). It is therefore important to further research tribulus in men with hypogonadism. Despite the inconclusive evidence on the use of tribulus to increase testosterone concentrations, the administration of this herbal medicine can help improve sperm parameters in men with idiopathic infertility.[120]

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NUTS

Nuts are emerging as a food matrix to aid male fertility thanks to α-linolenic acid (ALA), zinc, magnesium, selenium, folate, vitamin E, and antioxidants, which collectively are proposed to protect sperm from oxidative damage while improving sperm morphology.[121] Particular attention has been paid to walnuts because they are the main source of ALA (ie, the plant source of n-3 PUFAs among other nuts).[84] In 2 RCTs, Robbins et al[123] found that 42 g/d[122] or 75 g/d[123] of walnuts for 3 months improved sperm parameters in men seeking clinical care for male factor infertility and healthy young men, respectively. In addition to improving sperm vitality, motility, and morphology, they observed increased seminal content of n-3 and n-6 PUFAs, as well as ALA, for the walnut (75 g/d) group compared with the control group.[123]

In the FERTINUTS study, apparently the RCT with the largest sample size in the field of nuts and male fertility (119 healthy men), a Western-style diet enriched with 60 g/d of a nut mixture (30 g of walnuts, 15 g of almonds, and 15 g of hazelnuts) for 14 weeks improved sperm parameters (total sperm count, vitality, total motility, progressive motility, and morphology of sperm) compared with the control group (Western-style diet without nuts).[121] That said, adding nuts (primarily walnuts) to the diet may be a viable strategy to achieve some improvement in sperm parameters, but little is known about the effects in men with male hypogonadism or a severe degree of infertility; therefore, the clinical magnitude is questionable. At best, nuts are healthy foodstuffs that are highly indicated as part of dietary plans.[124–126]

RELATIONSHIP BETWEEN SLEEP AND TESTOSTERONE

Adequate sleep is critical for health, mainly because of extensive metabolic regulation, including testosterone status.[127] In an American cohort study of 1312 elderly men, those with lower TT levels (<250 ng/dL) had lower sleep efficiency, with increased nocturnal awakenings and less time in slow-wave sleep as well as a higher apnea-hypopnea index and more sleep time with oxygen saturation levels <90%.[128] Among 2295 American men 16 to 80 years of age from the National Health and Nutrition Examination Survey (NHANES) dataset, with a mean serum TT level of 377 ng/dL and 7 hours of sleep, the serum TT level decreased by 5.85 ng/dL per hour of sleep loss ($P < 0.01$).[129] In addition, a 1-week intervention of sleep restriction is capable of reducing serum TT concentrations by 10% to 15% in the morning, as found in a study in which 10 healthy men were included—they slept approximately 8 to 9 h/d and underwent approximately 5 h/d of sleep in the week of restriction.[40] As discussed in the aforementioned sections, many nutraceutical agents proposed to increase testosterone do not cause a 10% to 15% change in TT levels.[21,106] Therefore, adjusting sleep may be more important before considering the use of nutraceutical and even pharmacologic agents.

WEIGHT LOSS AND CALORIC DEFICIT ON TESTOSTERONE LEVELS: PROS AND CONS

Not only is adequate sleep important, but it is also important to consider body composition before considering the use of any nutraceutical or even drug treatment to increase testosterone concentrations, particularly in obesity-associated hypotestosteronemia, which is a nonpermanent state that may be reversible by adopting a weight loss plan.[14] Cohort studies confirm an association between low testosterone levels and excess body fat.[128,129] In the NHANES dataset, serum TT levels decreased by 6.18 ng/dL per unit of body mass index increase ($P < 0.01$).[129]

A recent meta-analysis of RCTs found that calorie restriction in patients with overweight or obesity leads to increased serum TT levels.[130] Accordingly, in the case of obesity, the "simple" process of losing weight can be sufficient to improve plasma testosterone concentrations, apart from the countless benefits.[131] Remarkably, weight loss achieved by adhering to physical exercise and diet plans, as well as bariatric surgery, are also associated with increased levels of TT.[132]

Young healthy adults with normal levels of testosterone may present with a reduction in testosterone levels with the abusive practice of physical exercise and under high caloric deficit, reaching hormone insufficiency. For instance, in the study by Longland et al,[133] which was composed of young men undergoing a low-calorie diet (−40% of daily caloric requirement) plus combined training (resistance training and high-intensity interval training) for 4 weeks, the TT levels of the groups were approximately 500 to 600 ng/dL at baseline and reached approximately 100 ng/dL after the intervention.[133] In addition, individuals increased lean body mass while losing body fat regardless of the decrease in serum testosterone concentrations, but

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the researchers found the greater benefits in body composition under a high-protein diet (2.4 g/kg of protein daily) compared with lower protein intake (1.2 g/kg of protein dialy).[133] Nonetheless, given that <300 ng/dL is a sign of impaired testosterone production,[134] these data may be important clinically, especially if maintained for several months. Moreover, such a protocol is not viable in the long term, and most people are unable to follow it.[135] Thus, normalization of serum testosterone concentrations can be expected naturally after an escalated increase in caloric intake and a reduction in training volume.

PHYSICAL EXERCISE AND TESTOSTERONE: THE YIN AND YANG

Research in the early 2000s speculated about the importance of training-induced short-term increases in testosterone secretion as a means of stimulating gains in muscle mass and enhancing strength.[136] A few years later, however, a cohort had no significant correlations between the exercise-induced elevations in free testosterone levels and gains in lean body mass as well as leg press strength.[137]

There is a negative association between serum testosterone and cortisol in the recovery from physical exercise, whose event is manifested particularly on abundant physical stress.[138] At the molecular level, androgen and glucocorticoid receptors form heterodimers and have mutually inhibitory effects on each other's hormone-dependent transcription activity, hence leading to decreased testosterone levels when hypercortisolism is present.[139]

Men performing excessive physical exercise may have lower serum testosterone levels compared with those who do not exercise. For example, in men (mean [SD] age, 36.3 [9.2] years) who ran a mean of of 81 km/wk, approximately265 ng/dL of TT was detected, whereas in men who did not exercise the level was approximately 467 ng/dL.[140] Of interest, there was no change in serum cortisol concentrations between the groups. Therefore, excessive physical exercise may be associated with lower levels of serum testosterone regardless of the increase in serum cortisol.

Despite the massive prevalence of administration of testosterone and its derivatives in bodybuilding,[141] natural bodybuilding is an attractive way to discuss the physiologic testosterone levels under the best aesthetic performance. In a prospective case study[142] of a high-level, amateur natural bodybuilder, baseline TT levels of approximately 543 ng/dL decreased significantly to approximately 197 ng/dL immediately before the competition but returned to normal levels afterward (TT levels of approximately 595 and 702 ng/dL on the 30th and 60th days after the competition, respectively). Baseline SHBG levels (the higher the SHBG level, the lower the testosterone bioavailability because it is a protein that binds to testosterone) significantly increased from approximately 43.1 nmol/L to approximately 56.3 nmol/L immediately before the competition but, like the testosterone status, levels returned to normal afterward. Throughout the preparation period, the bodybuilder used a high-volume, high-frequency, full-body training program alongside a low-calorie, high-protein diet, altering his weight of 99.5 kg and his 8% to 9% body fat to approximately 89 kg and approximately 5% on the day of the competition day, respectively.

ANDROGEN RECEPTOR: THE CORNERSTONE

Prostate, adrenal gland, epididymis, and skeletal muscle are some examples of androgen target tissues in which the androgen receptor (AR) is largely expressed as modulating many intracellular processes.[143,144] The actions of testosterone and dihydrotestosterone (DHT) are orchestrated via the AR, with the interplay between AR and androgens being responsible for maintaining libido, spermatogenesis, erythropoiesis, bone mineral density, muscle mass, and strength.[143] Importantly, DHT is more biologically active than testosterone, binding to AR with a 2-fold higher affinity and a 5-fold decreased dissociation rate compared with testosterone.[144]

Instead of circulating hormones, AR has been regarded to be the key potential therapeutic target for the treatment of clinical conditions, such as cancer.[145] Because of its crucial role in altering cellular function, AR has been proposed as a determinant in hypertrophy as well.[142] A decisive study found that, despite circulating and even intramuscular testosterone and DHT concentrations, intramuscular AR content was the determinant for a greater hypertrophic response of the human skeletal muscle after a resistance-training intervention in previously trained men.[142] This finding helps to support clinical situations in which a better aesthetic and physical response are noted in individuals with lower hormone levels than those with higher levels.

Furthermore, short-term AR signaling response to mechanical loading on skeletal muscle seems to be

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mediated by the equated volume and intensity of resistance training irrespective of the intramuscular testosterone and DHT content.[146] More recently, Cardaci et al[146] observed significantly greater increases in sarcoplasmic β-catenin content—an activator of AR—by approximately 94% and AR-DNA binding activity by approximately 74% but without elevations in serum or muscle androgen concentrations or AR protein content for high-load resistance exercise when compared with low load.

DECISION-MAKING PRACTICE AND PERSONALIZED STRATEGIES

Before any adjunct agent or functional nutrient is sought to boost testosterone levels, it is pivotal to manage lifestyle factors, such as avoiding sleep deprivation, a balanced routine of physical exercise, and reducing weight mainly in patients with obesity. In addition to obesity-associated hypotestosteronemia, other obesity-related diseases, such as diabetes and hypertension, should also be considered; therefore, controlling blood pressure and blood glucose is of paramount importance in this context. For instance, approximately one-third of men with type 2 diabetes mellitus have low testosterone levels, which may be generated by vascular complications of diabetes in itself as well as by increased status of low-grade inflammation resulting from visceral adiposity.[147, 148]

Moreover, although smoking is intriguingly associated with higher serum testosterone levels,[149,150] this is also strongly associated with erectile dysfunction,[151] a common problem among patients seeking medical care to increase testosterone levels. Thus, quitting

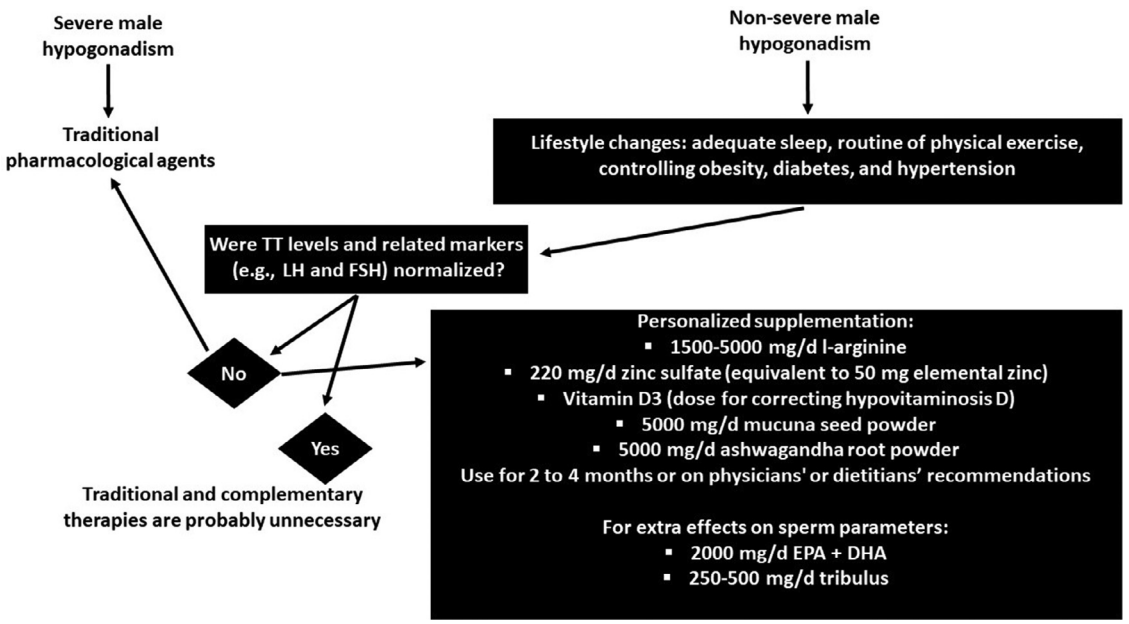

Figure 1. Proposed nonpharmacologic based interventions in the management of testosterone levels (male hypogonadism). Improvements in lifestyle, such as avoiding sleep deprivation, a proper routine of physical exercise, decrease in weight mainly in patients with obesity, and controlling obesity-related diseases, such as diabetes and hypertension, are more important than cogitating the use of supplements and herbal medicines for raising testosterone levels in the case of nonsevere male hypogonadism. Afterward, if the total testosterone (TT) levels and related markers (eg, luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are not normalized, zinc, vitamin D (in case of hypovitaminosis D), l-arginine, mucuna, and ashwagandha could be designed in personalized dosages alone or in combined treatment to increase TT levels. Except for l-arginine, these natural agents, as well as tribulus and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can improve some degree of sperm parameters. Personalized dosing regimens should be made by physicians and/or registered dietitians.

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Table I. Mechanisms and clinical dosing regimens regarding the effects of nutraceutical agents on testosterone levels and sperm parameters.

Nutraceutical agent	Summary of mechanisms based on animal and human research	Evidence and suggestions for humans
Amino Acids		
Arginine	An essential substrate for the production of nitric oxide, helping the testosterone production via improved testicular blood flow.[103,157] Upregulation of LH secretion, enhancing the antioxidant system and increasing the expression of testosterone synthesis-related genes (steroidogenic acute regulatory protein, steroidogenic factor 1, 17β-hydroxysteroid dehydrogenase 3, and 17α-hydroxylase/17,20-lyase) in rat testes.[158,159]	Supplementation at 1500 to 5000 mg/d improves erectile dysfunction in patients with mild to moderate erectile dysfunction.[99] For testosterone increase, 5000 mg/d alone increased TT by 156 ng/dL and combined with 10 mg/d tadalafil by 372 ng/dL for patients with diabetes and erectile dysfunction on 8-week treatment.[103]
Creatine	Substrate for sperm cell by assisting the motility via ATP production.[115]	Although lower creatine concentrations in semen are associated with reduced sperm motility,[115] its supplementation has failed to increase testosterone levels in physically active individuals.[116,117]
D-aspartic acid	Increases the release and synthesis of LH through cGMP actions as a second messenger in the pituitary, increasing synthesis and release of testicular testosterone on cAMP activity.[105]	In healthy patients and young adults (27–37 y), 3.12 g/d of sodium d-aspartate supplemented for 12 days increased serum TT levels by 190 ng/mL (from a mean [SD] of 450 [60] ng/mL to 640 [80] ng/mL, $P < 0.0082$) and luteinizing hormone levels from 4.2 (0.5) mIU/mL to 5.6 (0.9) mIU/mL ($P < 0.0001$). The product also consisted of vitamin B_6, folic acid, and vitamin B_{12}. Despite the presence of a supplement brand, the authors declare that they have no competing interests.[105]
Herbal Medicines		
Ashwagandha	Stress-relieving effects via the hypothalamic-pituitary-adrenal axis may afford higher testosterone levels because of the harmful effects of high cortisol status on DHEA and testosterone synthesis.[160,161] Plays antioxidant actions on testes as well.[22]	5000 mg/d of ashwagandha root powder for 12 weeks significantly increased TT levels by 143 ng/dL (from 351 to 494 ng/dL) and improved sperm parameters in patients with oligozoospermia.[119]
Mucuna	As a source of l-DOPA, attenuates in part the antagonist action of prolactin on testosterone by increasing l-DOPA and dopamine levels.[162] l-DOPA also directly increases testosterone levels via stimulation on GnRH and LH.[118] Mucuna's antioxidant action on testes could favorable the testosterone synthesis.[22,163]	5000 mg/d of mucuna seed powder for 12 weeks significantly increased TT levels by 151 ng/dL (from 389 to 540 ng/dL) and improved sperm parameters in patients with oligozoospermia.[118]

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Table I. (*continued*)

Nutraceutical agent	Summary of mechanisms based on animal and human research	Evidence and suggestions for humans
Tribulus	Indirect stimulation of LH and testosterone production from Leydig cells mediated by enhanced antioxidant capacity accompanied with decreased tissue peroxidation on testes.[164,165]	To date, there is no evidence of tribulus as a testosterone booster,[22] but a systematic review corroborates the improvement in sperm parameters in men with idiopathic infertility on tribulus treatment,[120] where tribulus daily dose ranged from 250 to 500 mg/d in 6 studies and 12 g/d (6 g twice daily) was used in 1 study.
Lipids and Related Compounds		
Cholesterol	Matrix of all androgens.[166]	Ketogenic diet (500–1000 mg of cholesterol per day) may increase the TT by approximately 100 ng/dL in resistance-trained men.[88,89] Three whole eggs (672 mg of cholesterol) for 12 weeks increased the post–resistance training serum testosterone levels by approximately 240 ng/dL.[90]
DHEA	Prohormone produced by the adrenal cortex that intermediate the conversion of cholesterol precursors into estrogens or testosterone.[167]	Evidence supports an increase in TT concentrations for women only but increases serum concentrations of estrogens (estrone and estradiol) in both older women and men.[98]
n-3 PUFAs	Substrate for sperm cell whereby their storage to the membrane could mitigate inflammatory pathways.[168]	Meta-analysis found that n-3 PUFA supplementation increased sperm motility and semen DHA concentration in infertile patients.[82] In 3 studies, the dosage varied from 400 to 800 mg/d of DHA for 12 weeks, 1120 mg of EPA plus 720 mg of DHA for 32 weeks, and 930 mg of DHA for 12 weeks. No human trial was conducted for testosterone levels, only for sperm parameters.
Vitamins and Minerals		
Magnesium	It could increase testosterone by decreasing systemic inflammation and sperm motility by energy production.[64]	High doses of magnesium do not increase the TT in sedentary eugonadal men and in taekwondo athletes[69] and do not improve sperm variables in males with idiopathic infertility.[70]

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Table I. (*continued*)

Nutraceutical agent	Summary of mechanisms based on animal and human research	Evidence and suggestions for humans
Vitamin D	1,25(OH)2D3 stimulates the testosterone production on Leydig cell via nuclear heterodimers (nuclear receptor retinoid X receptor plus other nuclear receptors), leading to increased mitochondrial actions of the P450scc in the conversion of cholesterol into pregnenolone and thus increasing testosterone levels in the endoplasmic reticulum.[23] It is vital for sperm cells by increasing their motility, calcium handling, capacitation, acrosin reaction, and lipid metabolism.[75]	Increases are questionable regardless of daily or mothy protocols. For instance, 3332 IU of vitamin D for 1 year increased TT levels from 309 ng/dL to only 387 ng/dL in middle-aged men,[78] whereas 600,000 IU of ergocalciferol per month (or per 2 months) during a 1-year intervention increased TT from 359 to 469 ng/dL after 3 months of treatment and remained in the consecutive months.[77] 4000 IU/d of vitamin D_3 for 3 months increased total and progressive sperm motility in infertile men with asthenozoospermia.[81]
Zinc	Triggers miscellaneous antioxidant and steroidogenic enzymatic actions on testes thanks to the cellular processes mediated by the variety of zinc transporters (eg, zinc-regulated transporter 1 and 2).[21,169]	220 mg of zinc sulfate (equivalent to 50 mg of elemental zinc) once or twice a day for 1 to 4 months are feasible dosages as an adjuvant to the treatment of male hypogonadism by increasing TT (approximately 50–400 ng/dL) and improving sperm parameters.[21]

ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DHA = docosahexaenoic acid; DHEA = dehydroepiandrosterone; EPA = eicosapentaenoic acid; LH = luteinizing hormone; n-3 PUFAs = ω3 polyunsaturated fatty acids; RCTs = randomized clinical trials; TT, total testosterone.

smoking is a point that ought to be included in lifestyle changes as well. Equally important, ethanol directly inhibits testicular testosterone synthesis,[152,153] affecting semen quality as well.[154] Higher doses of ethanol can partially suppress testosterone production, as found in pioneering studies of ethanol-induced intoxication performed by Välimäki et al.[155,156]

The summary of mechanisms and studied dosage from RCTs regarding the efficacy (or the lack thereof) of the nutraceutical agents discussed in this review are given in Table I. Furthermore, those agents with a potential level of evidence can be seen in Table II.

Zinc, vitamin D (in case of hypovitaminosis D), L-arginine, mucuna, and ashwagandha could be designed in personalized dosages alone or in combined treatment to increase TT levels into a physiologic range when embarking on a decision-making strategy in which pharmacologic drugs are not urgent. Except for L-arginine, these natural agents, as well as tribulus and n-3 PUFAs, can improve sperm parameters to some degree in infertile men. Viewed collectively, a proposed nutraceutical approach to the management of testosterone levels and sperm parameters can be seen in the Figure 1.

It may be reasonable to prioritize zinc and vitamin D primarily over circulating deficiency of both because they are essential nutrients. Likewise, EPA and DHA are essential nutrients for which their supplementation must be prioritized mainly when their dietary intake is low; however, orders for circulating status are not common in clinical practice. Supplementing L-arginine should be considered regardless of dietary intake.

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Table II. Nutraceutical agents that can be classified as level 1 evidence for increasing total testosterone or sperm parameters.*

Nutraceutical agent	Efficacy
Arginine	↑TT in patients with erectile dysfunction[103]
Ashwagandha	↑ TT and ↑sperm parameters in patients with oligozoospermia[119]
Mucuna	↑TT and ↑sperm parameters in patients with oligozoospermia[118]
Tribulus	↑Sperm parameters in infertile men[120]
n-3 PUFAs	↑Sperm parameters in infertile patients[82]
Vitamin D	↑TT in middle-aged men with 25(OH)D deficiency[77] and ↑sperm parameters in infertile men with 25(OH)D deficiency[81]
Zinc	↑TT and ↑sperm parameters in men with low TT levels and infertility[59,170]

25(OH)D = 25-hydroxy vitamin D; n-3 PUFAs = ω3 polyunsaturated fatty acids; RCT = randomized clinical trial; TT = total testosterone.

*Increases (↑) in TT and sperm parameters did not exceed supraphysiologic ranges in any study. This table summarizes the nutraceutical agents that can be considered as level 1 evidence for increasing TT changes or sperm parameters. Several nutraceutical agents listed in Table I are not included here because of a lack of evidence. Level 1 evidence was considered as the presence of large RCTs (preferably with a total samples size >100), with proper randomization, and/or systematic review of RCTs, as endorsed by tools used for clinical practice guidelines.[171] Such a level of evidence cannot be compared to traditional pharmacological agents, given that the clinical magnitude is different. It is imperative to consider Table I and the Figure 1 to obtain the details on dosing regimens and mechanisms of action, as well as to be aware of limitations.

Because herbal medicines are nonessential products, they ought to be considered after controlling for the mentioned essential nutrients.

Particular food items, such as whole eggs and nuts, are not included in the Figure 1 because the evidence remains more limited than the nutraceuticals discussed; they should only be considered as part of the dietary plan if the individual likes the taste and, preferably, through calculations made by a nutritionist. We did not discuss the effects of B vitamins, particularly folate, because there is great heterogeneity among RCTs and the effects are often in combination therapies.[172]

Indeed, proposed nonpharmacologic-based interventions are geared toward nonsevere male hypogonadism (ie, a condition for which pharmacologic therapy is not urgently needed and thus alternative strategies can be tested first without the risk of serious consequences caused by treatment delay). Erectile dysfunction, low libido, low seminal volume, and infertility are some untoward effects of nonsevere male hypogonadism (although this is part of severe hypogonadism as well), whereas severe hypogonadism can be related to conditions that represent high-risk of mortality, such as muscle-wasting disorders (cachexia and sarcopenia)[173] and loss of bone mass (osteoporosis),[174] in which the effects of pharmacologic agents cannot be postponed.

CONCLUSIONS

Several nutraceutical agents and functional nutrients have putative actions in increasing testosterone levels, but only a few have potential based on the available evidence. Although most clinical research using eugonadal and healthy individuals has found null effects, in in individuals with low testosterone levels and related problems, well-controlled RCTs corroborate a potential to increase testosterone levels mainly from zinc, vitamin D (in case of hypovitaminosis D), L-arginine, mucuna, and ashwagandha (at proper dosages). Except for L-arginine, these natural agents, as well as tribulus and n-PUFAs, can improve sperm parameters to some degree in infertile men. Personalized dosing regimens must be made by physicians and/or registered dietitians based on the best existing evidence and patient conditions.

Taking into account that testosterone is often associated with body composition and health, before considering supplementing with these potential testos-

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terone boosters, it is imperative to verify whether the patient is of normal weight and achieves adequate sleep and physical exercise because these lifestyle factors have a much more robust and effective response than any nutraceutical. Furthermore, a modest increase in circulating testosterone levels does not necessarily translate into clinical benefits. Therefore, the total AR content, but not endogenous androgens such as testosterone, has been considered the leading factor of hypertrophy.

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DECLARATION OF INTEREST

S.C. Forbes served as a scientific advisor for a company that sells creatine products. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIALS

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