

Protein supplements for physical enhancement and male reproductive health: Are there potential reasons for concern in an uncontrolled, unregulated, and widespread abuse scenario?



A dietary supplement is a generic expression used to describe any orally ingested substance that contains elements able to complete or provide an arguably nutritional upgrade to a regular normal diet. Commercialized frequently as pills, liquids, gels, powders, shakes, or bars, the enormous myriad of available options can be derived from plants, vitamins, amino acids, proteins, minerals, carbohydrates, and so on. Protein supplements (PSs) are by type divided in casein, whey protein, egg protein, and soy protein, among others. The distribution channel helps the widespread and uncontrolled use because these products are sold online and in gyms, supermarkets, hypermarkets, chemist stores, nutritional stores, health food markets, local stores, and drugstores—everywhere. However, the paradox is that its numerous self-reported beneficial arguments lack serious scientific evidence for the common individual. The multitude of self-alleged positive effects of these fast-acting products, such as rapid muscle, skin, and hair repair, energy boost, weight loss, lowered cholesterol, strengthened immunity, prevention of cardiovascular disease, and improvement of sexual performance, are driving their increasing use also as snack-based meal replacements, making them attractive options in the post-modern era (1).

Of note, these products were originally engineered and developed to help elite athletes cope with extended training sessions, including high-performance competitive bodybuilding. One primary technical use is for military personnel during active duty with unique occupational demands or the specific warfighter with protein intake restrictions during deployment cycles; these are extreme conditions in harsh environments.

The obsession for results beyond what is humanly reasonable in a short period brings the willingness of adding “enhancement” products originated from a variety of sources. Surveys report an overall steroid contamination rate of 15%–25%, directly associated with hypogonadotropic hypogonadism in men and related to decreased semen quality and male infertility (2).

Therefore, regulatory agencies worldwide could demand greater product traceability and authenticity, because each country has different scenarios, cultural characteristics, food sources, and nutritional habits. Unfortunately, some compound pharmacies play a key-role in this uncontrolled environment, providing countless “on-demand” formulations, supported and fueled by attractive names like “nutrition genomics” specialists, “dietitian and metabolic” experts, and a growing “anti-aging” community whose advocated knowledge is based strictly on basic principles of biochemistry,

bypassing biological assays and clinical trials. Knowing that the majority of protein-based supplements consumers are males in the reproductive age group, the next question is what about semen quality?

To answer that question is not a simple task. Commencing with a trusted research “environment” for this particular issue, this translated as a country with high educational level, reliable data recovery and analysis, and capable of following the health status of the population throughout most of one’s lifetime. In addition, it is necessary to be able to verify for confounding factors from early childhood and infancy and account for potential lifestyle and habit-related factors with a culturally homogeneous population. Denmark fills these prerequisites. In fact, the article by Tottenborg et al. (3) used data obtained from patients whose mothers were enrolled in a program that connects birth data with their pregnancies. The questionnaire included the use of common energy supplements limited to “creatine” or “protein supplement” (PS) or a combination of both in the form of powder or bars. The study also checked for covariates such as exercise, acetyl-salicylic acid (ASA) use, tobacco smoking, e-cigarette, vaping, alcohol intake, marijuana, ecstasy, and cocaine use. The majority (57%) of the current and former users reported use of PS only, whereas 26% used a combination of protein and creatine. Here is a crucial point. The fact that they used pure PSs with or without creatine only, is a key element for the understanding of PSs effects on the male reproductive system, as these are the major components of a large amount of supplements in the market. In this study, semen concentration and total sperm count were not statistically higher in the PS group as compared with the nonusers, which is in contrast with one previous pilot study that observed more than twice the median sperm concentration and total sperm count after cessation of PSs use in 20 subfertile men, also in Denmark (4). Of note is that the infertile men enrolled in this preliminary study were all bodybuilders, whereas in the present study from Tottenborg et al. (3) the 770 men were more representative of the entire population. The second difference may be related to the type of PS used and the likelihood of pro-androgenic contaminants present in the PSs used by bodybuilders in contrast with the regular soy or whey protein supplements purchased by average people with different desires and goals toward health. In fact, the majority of PSs available in fitness centers, gyms, and online shops contain not exclusively pro-androgenic and androgenic anabolic steroids contaminants, either declared or hidden on the label. Using liquid chromatography coupled with Orbitrap high-resolution mass spectrometry, a reliable technique to identify adulteration of PSs with prohibited substances not declared on the labels, a meticulous analysis was able to identify 105 substances in different commercial brands of whey protein, in products originated from different countries. The extensive list of adulterated substances include, but are not limited to: ASA, pro-androgenics, xenoestrogens, estrogens, selective androgen-receptor modulators, nonsteroidal antiestrogens, anti-hypertensives, beta blockers, diuretics, vasodilators, statins, adrenaline derivatives, tocolytic drugs used to stop premature labor, selective beta-2-adrenergic stimulants, beta-2-receptor agonists,

bronchodilators and anti-asthma medications, coughing inhibitors, a wide array of amphetamines, painkillers, stimulants, appetite inhibitors, and even cocaine (5). The abundance of adulterants in not just a few formulations makes one believe that it might be a purposeful act, not a simple contamination. Therefore, it could, if proved, be ruled as a criminal activity and be subject to criminal charges and codes of ethics. However, in some parts of the world, some regional or state laws protect a certain percentage of the formulations from disclosure on the labels due to alleged patent and commercial protection rights, leaving room for inclusion of many substances without warning. Many of these substances target and act by binding to and blocking/inhibiting intracellular androgen receptors in target tissues, including testes, prostate, skin, and hair follicles. In particular, antitumor activity found in toluidine derivatives with nonsteroidal antiandrogens is structurally related to drugs designed to treat advanced prostate cancer, whereby forming inactive complexes, which cannot translocate into the cell nucleus, consequently inhibiting androgen-dependent DNA and protein synthesis, resulting in the arresting of cellular growth and transient tumor regression. The technicality is that these patients do not have any tumors to inhibit and this intracellular metabolic mess is likely to cause other metabolic dysregulations, not limited to electrolyte misbalances and heart, liver, pancreatic, thyroid, kidney, and bone dysfunctions, in addition to hormonal-axis negative feedback and other hypothalamic dysfunctions.

One important point of discussion is that there are no compatible regulations between countries, which makes the comparisons almost impossible. The well-conducted study by Tottenborg et al. (3) dissected here, gives the positive insight that, in a very specific scenario of regular, healthy men, not in the elite athlete group or competitive bodybuilding, when consuming specific and noncontaminated nor adulterated PS, the impact on semen quality is not significant. That is helpful information and will be useful to counsel our patients in the daily office routine.

Traditionally, the diagnosis of male infertility has depended on a descriptive evaluation of the human ejaculate, with emphasis on the concentration, motility, and morphology of the spermatozoa. The downside of this oversimplification is that male fertility is erroneously defined and classified in terms of a threshold concentration of motile, morphologically normal spermatozoa that must be exceeded if a given patient is to be classified as fertile. This simplistic view often leads to excessive use and abuse of assisted reproductive technologies and lack of proper andrological evaluation that definitely provides better cost-effective, reversible, or correctable approaches to the male component (2). As clinical experience has revealed, it is not so much the absolute number of spermatozoa that predicts fertility, but rather their

functional competence. Therefore, a variety of biochemical markers have been developed in the last two decades and are constantly under improvement by andrologists providing information on such factors as the efficiency of spermiogenesis, the presence of oxidative stress, and the generation of reactive oxygen species (ROS) (2).

Excessive protein intake may indeed generate not only ROS and a cascade of lipid peroxidation leading to sperm DNA fragmentation, but also reactive nitrogen species that can be as dangerous to sperm cell membranes as ROS or worse. Therefore, to accurately determine the safety of PSs beyond the elegant article by Tottenborg et al. would be to measure oxidative stress byproducts in PSs that have no adulterations and optimal quality, such as seems to be the case from Denmark. Unfortunately, the conclusions drawn by this study cannot be automatically interpreted as a worldwide green light toward unrestricted safety of PSs, male reproductive health, and semen abnormalities. The yellow light should indicate a warning that future guidelines are needed on how regulatory counsels and food and drug administration agencies should undergo meticulous one-by-one investigation before products can be freely offered to customers.

Jorge Hallak, M.D., Ph.D.^{a,b,c,d}

^a Androscience, Science and Innovation Center in Andrology and High-Complex Clinical and Research Andrology Laboratory; ^b Division of Urology, ^c Men's Health Study Group, Institute for Advanced Studies, and ^d Reproductive Toxicology Unit, Department of Pathology, University of São Paulo, São Paulo, Brazil

<https://doi.org/10.1016/j.fertnstert.2020.05.019>

You can discuss this article with its authors and other readers at

<https://www.fertsterdialog.com/users/16110-fertility-and-sterility/posts/30524>

REFERENCES

1. Morrison LJ, Gizis F, Shorter B. Prevalent use of dietary supplements among people who exercise at a commercial gym. *Int J Sport Nutr Exerc Metab* 2004;14:481-92.
2. Hallak J. A call for more responsible use of Assisted Reproductive Technologies (ARTs) in male infertility: the hidden consequences of abuse, lack of andrological investigation and inaction. *Transl Androl Urol* 2017;6:997-1004.
3. Tottenborg SS, Glazer CH, Haervig KK, et al. Semen quality among young health men taking protein supplements. *Fertil Steril* 2020;114:89-96.
4. Ketheeswaran S, Haahr T, Povlsen B, Laursen R, Alsbjerg B, Elbaek H, et al. Protein supplementation intake for bodybuilding and resistance training may impact sperm quality of subfertile men undergoing fertility treatment: a pilot study. *Asian J Androl* 2019;21:208-11.
5. Roiffé RR, Sardela VF, Lima ALS, Oliveira DS, Aquino Neto FR, Lima KSC, et al. Determination of adulterants in whey protein food supplements by liquid chromatography coupled to Orbitrap high resolution mass spectrometry. *Braz J Food Technol* 2019;22:e2018206.