A Randomized, Double-blind, Clinical Trial To investigate the Impact of a Testosterone-booster Supplement in Increasing Sexual function and Libido.

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ABSTRACT

Male sexual hormones – also known as androgens – are the key for development of male sexual characteristics during puberty and optimum functioning of sexual function. Testosterone is the principle androgen. Although produced by the Leydig cells of the testes, the secretion of testosterone is under control of the Hypothalamo-pituitary-gonadal (HPG) axis.

Male hypogonadism increases with age. Middle-aged and older men reflect the majority of those suffering from androgenic hypogonadism.

Restoring normal circulating levels of testosterone forms the basis of therapeutic treatment in secondary male hypogonadism. There is ample evidence to suggest that restoring testosterone levels to pre-hypogonadal state, can help relieve symptoms and improves libido, sexual desire and vigor.

Notwithstanding the ambiguous evidence of risks associated with hormone replacement therapy, it does help the improvement of male hypogonadism. However, since most physicians are skeptical to administer testosterone therapy to hypogonadal men due to potential negative side-effects; availability of natural herbal secretagogues to help elevate testosterone levels, is an exciting therapeutic advancement.

In this study, we investigate the claim of one such herbal supplement -- AlphaViril™, to help treat male hypogonadism. We conducted a randomized, double-blind, clinical trial to prove or refute the claim.

120 participants of the study were randomly divided into 2 groups of 60 men and assigned to the test and control groups.

The test group were supplemented with AlphaViril™ as recommended by the manufacturers – 4 capsules an hour before sexual activity or exercise sessions. On 'non-performing' days, participants were asked to take 2 capsules twice daily with a glass of water. The dosage scheduling was similar for the control group. However, instead of AlphaViril™, they were supplemented with a placebo pill.

The findings of our study revealed that AlphaViril™ caused a significant increase in plasma testosterone and free testosterone levels and help relieve symptoms associated with male hypogonadism.

BACKGROUND

As sated already, male sexual hormones – also known as androgens – are the key for development of male sexual characteristics during puberty and optimum functioning of sexual function.

Testosterone is the principle androgen. Although produced by the Leydig cells of the testes, the secretion of testosterone is under control of the Hypothalamo-pituitary-gonadal (HPG) axis. In response to stimulus from the testes, the hypothalamus secretes gonadotropin-releasing hormone (GnRH). GnRH stimulates the anterior pituitary to secrete follicle-stimulating hormones (FSH) and luteinizing hormones (LH). Whereas FSH acts on the Sertoli cells to stimulate the production of sperms, LH causes the production and release of testosterone from the Leydig cells (Bagatell & Bremner, 1996; Costanzo, 2006).

The HPG axis is under a 'negative-feedback control', in response to high circulating levels of T, the Sertoli cells secrete glycoprotein hormone inhibin (GHI). Testosterone and GHI in turn inhibit the secretion of LH and FSH respectively (Costanzo, 2006).

Daily secretion of T is about 7mg per day (Seidman, 2007). In older men, this rate of secretion tends to reduce (Hijazi & Cunningham, 2005) causing male hypogonadism.

Incidence Of Male Hypogonadism

Male hypogonadism increases with age. Middle-aged and older men reflect the majority of those suffering from androgenic hypogonadism. According to an estimate, by 2025, there will be 60 million (17.9% of the population) individuals aged 65 or more. No doubt then that the prevalence of male hypogonadism will also increase concurrently (US Census Bureau, 2012).

The HIM study – Hypogonadism in Males study – estimated that almost half of American men over 45 years of age have hypogonadism (Mulligan, Frick, Zuraw, Stemhagen, & McWhirter, 2006). Sadly though, only a miniscule percentage of these were treated (Gooren, Behre, Saad, Frank, & Schwerdt, 2007; Seftel, 2006).

Normal Testosterone Levels In Blood

Of the total testosterone secreted into blood, 98-99% is bound to plasma proteins, either albumin (40-50%) or globulin (50-60%) – sex hormone binding globulin (SHBG).

Only 1-2% of testosterone in blood is present in the free form (Dandona & Rosenberg, 2010).

It should be of interest to know that free T and that bound to albumen is available for physiological action (Zitzman, 2006) whilst T bound to SHBG is too tightly linked to be of any use.

Pathophysiology of Hypogonadism

Low circulating serum levels of testosterone (T) are held responsible for hypogonadism. Deficiency of T is also being increasingly associated with obesity, diabetes mellitus – type 2, cardiovascular diseases and metabolic syndrome (Dandona & Rosenberg, 2010).

The Endocrine Society defines male hypogonadism as such – '*a syndrome resulting from failure or testes to produce normal physiological levels of testosterone and hence the normal number of spermatozoa caused by disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis*' (Bhasin et al., 2013).

Other endocrinal bodies have also defined male hypogonadism in their own way (Petak, Nankin, Spark, Swerdloff, & Rodriguez-Rigau, 2002; Wang et al., 2008; Morales, Schulman,

Tostain, & Wu, 2006). However, that low levels of T (either due to testicular-hypothalamic causes or others like trauma) causes hypogonadism is agreed upon by all.

Symptamatology of male hypogonadism includes decreased libido and erectile dysfunction, decreased lean muscle mass, increased fatness, loss of bone minerals (and increased risk of osteoporosis). Additionally, low testosterone levels cause loss of vigor, easy fatigability and depression. Diagnosis of hypogonadism is a combination of low serum levels of testosterone and presence of symptoms of hypogonadism (as stated above).

Types of Male Hypogonadism

Classically, male hypogonadism is classified as primary and secondary.

Primary hypogonadism, also referred to as *hypergonadotrophic hypogonadism*, is due to organic defect in the testes. The cause of this defect can be – physical trauma, infection, alcohol abuse, radiation therapy, cancer chemotherapy (Petak et al., 2002; Seftel, 2006).

Genetic defects affecting normal development of testes are also classified as primary hypogonadism – for instance Klinefelter syndrome (Dandona & Rosenberg, 2010).

Secondary hypogonadism, on the other hand, is characterized by a defect in the central mechanism responsible for regulating testosterone secretion – the hypothalamus or the anterior pituitary (Dandona & Rosenberg, 2010). Low levels of FSH and LH secreted by the pituitary lead to insufficient stimulus of the testes; testosterone levels and spermatogenesis are therefore hampered. Secondary hypogonadism is also known as hypogonadotrophic hypogonadism; this is treated with hormone replacement therapy.

Therapeutic Treatment Of Hypogonadism

Testosterone replacement therapy forms the basis of treating hypogonadotrophic hypogonadism.

Restoring normal circulating levels of testosterone forms the basis of therapeutic treatment in secondary male hypogonadism. There is evidence to suggest that restoring T level to pre-hypogonadal state relieves symptoms and improves libido, sex life, muscle strength, lean body mass and reduces chances of bone rarefaction (Fraietta, Zylberstejn, & Esteves, 2013).

Additionally, fertility is also restored using testosterone replacement therapy. Since high intra-testicular testosterone levels are needed for spermatogenesis to progress in a normal way (Zitzmann & Nieschlag, 2000), male hypogonadism is characterized with oligospermia and deranged fertility. Testosterone replacement therapy induced restoration of plasma and intra-testicular testosterone levels, thus, results in restoration of fertility (Zitzmann & Nieschlag, 2000; Fraietta et al., 2013).

It must be noted here that since primary hypogonadism is due to primary testicular failure, it wouldn't respond to testosterone medication (Darby & Anawalt, 2005; Zitzmann & Nieschlag, 2000; Fraietta et al., 2013).

STUDY DESIGN

We decided to conduct a randomized, double-blind, clinical trial to investigate the claims of a proprietary herbal preparation (Aphaviril^{TM}) in treating male hypogonadism in middle-aged men.

PARTICIPANTS

We advertised the conduction of our study in the local media and newspaper. To the 178 middle aged men (>40 years of age) who responded to the above, we posted self-addressed envelopes of questionnaires confirming their signs and symptoms.

Of these, 150 were invited for further screening.

Inclusion Criteria For Selecting Participants

According to the Endocrine Society, a human male is considered hypogonadal only in the presence of both low plasma levels of testosterone and signs & symptoms suggestive of low testosterone.

Clinics were conducted for detailed history taking and enquiring for signs and symptoms related to testosterone deficiency.

Plasma testosterone tests were conducted on those with a 'positive history' suggestive of testosterone deficiency – in keeping with the recommendation of the AACE – we considered men with testosterone levels lower than 200ng/dl to be hypogonadal (Petak et al., 2002). 18 men with levels higher than 300ng/dl and 12 men with absence of symptoms/signs were excluded from participation in the study.

Eventually, a total of 120 hypogonadal men were shortlisted – in keeping with the guidelines of the Endocrine Society (as stated earlier), all of these 120 men had low testosterone levels and exhibited signs and symptoms of low testosterone in their blood.

METHODOLOGY

120 participants of the study were randomly divided into 2 groups of 60 men and assigned to the test and control groups.

The test group were supplemented with AlphaViril™ as recommended by the manufacturers – 4 capsules an hour before sexual activity or exercise sessions. On 'non-performing' days, participants were asked to take 2 capsules, twice daily with a glass of water. The dosage scheduling was similar for the control group. However, instead of AlphaViril™, they were supplemented with a placebo pill.

Additionally, all the participants in the study were given regular counseling sessions for improving their sexual performance. They were also directed to follow an exercise program and a healthy lifestyle.

The duration of the study was 12 weeks.

Given the sensitive nature of the condition, strict confidentiality was promised and maintained throughout the process of selecting the candidates for the study, conducting the study and whilst reporting of findings.

RESULTS

As stated earlier, before commencing the study, all 120 participants were screening to ascertain their plasma testosterone levels. Signs and symptoms were also checked against a pre-defined chart prepared by us.

Before the study, 105 participants had testosterone levels between 180 to 200ng/dL while the remaining 15 had levels even lower than that. Varying degrees of signs and symptoms were present in all 120 participants; these have been outlined in Table 2.

Table 1: Testosterone levels before commencement of study.

Testosterone levels	No. of participants reported
180-200 ng/dL	105
<180 ng/dL	15

Table 2: Signs and symptoms before commencement of study.

Symptoms/signs	No. of participants reported	
	Test Group	Control Group
Reduced libido	60	60
Erectile dysfunction	39	38
Reduced muscle mass	45	47
Depressed mood	52	49
Decreased energy levels	49	38
Poor concentration & memory	38	49
Sleep disturbances	45	48
Increased body fat and BMI	58	55

After supplementing with either AlphaViril™ or placebo for a period of 12 weeks, plasma testosterone levels and signs and symptoms were again checked.

As seen in Table 3 below, all 60 test participants reported improved testosterone levels in their blood: a staggering 80% of hypogonadal men supplemented with AlphaViril™ over 12 weeks had their testosterone levels rise from below 200ng/dL to above 350 ng/dL.

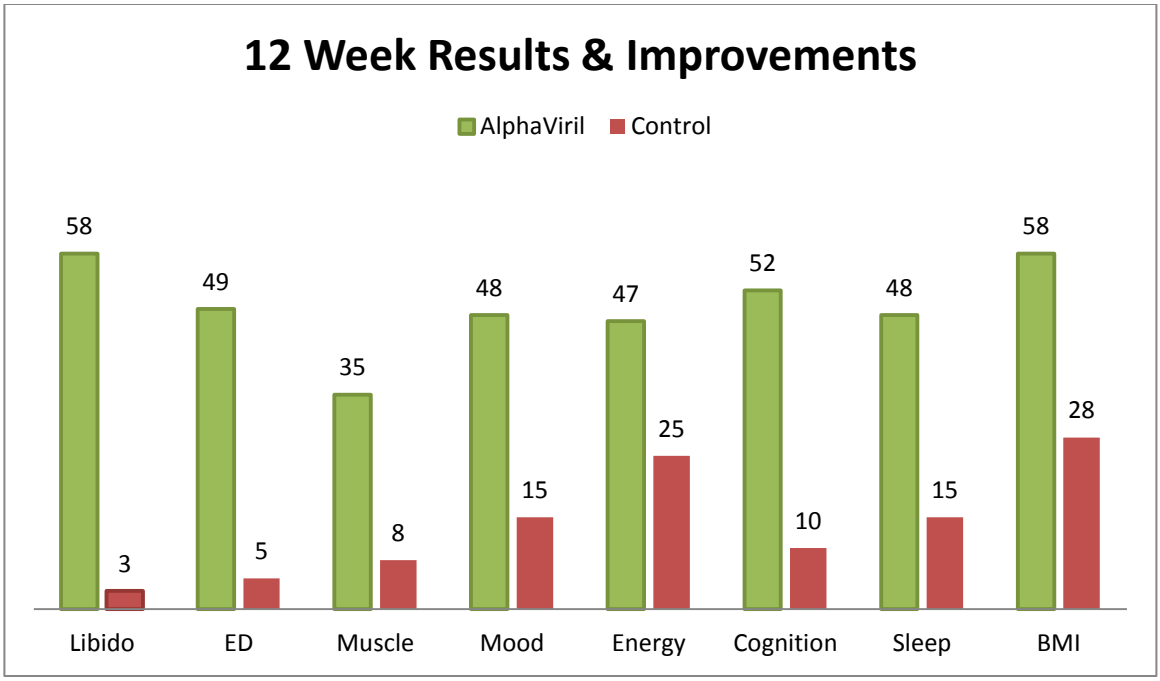
Table 3: Testosterone levels at the end of week 12, of supplementation with AlphaViril™

Testosterone levels	No. of participants reported	
	Test Group	Control Group
<200 ng/dL	0	52
200-350 ng/dL	12	8
351-500ng/dL	16	0
>501 ng/dL	32	0

Similar to improved plasma testosterone levels, signs and symptoms associated with hypogonadism also showed improvement after supplementation with AlphaViril™. .

Table 4: Signs and symptoms at the end of week 12 of supplementation with AlphaViril™

Symptoms/signs	No. of participants reported	
	Test Group	Control Group
Improved libido	58	3
Improvement in Erectile dysfunction	49	5
Improved muscle mass	35	8
Elevated mood	48	15
Increased energy levels	47	25
Improved concentration & memory	52	10
Improved sleep patterns	48	15
Improved body composition	58	28



Almost 97% of men showed improved libido, and body composition. While 80-82% showed improved and longer maintained erections, elevated moods, increased vigor and energy levels and better sleep patterns.

In the control group, a dismal 5-8% of men showed improved libido, erections and sexual performance. 45% of control participants showed improved energy levels and body composition – these were attributed to exercise sessions and healthier food choices made by these individuals.

No adverse reactions were reported by participants from the test group. 2 participants from the control group did report mild gastrointestinal discomfort at the beginning of the study. These were attributed to apprehension on the part of the individuals.

DISCUSSION

Although in dire need of it, according to an estimate, 35% of hypogonadal men in the US do not receive testosterone replacement therapy treatment. This is because of the misconception (on the part of the physician) that it might lead to prostate cancer (Gooren et al., 2007; Dandona & Rosenberg, 2010).

To compound the problem, almost one-third of doctors all over the world consider testosterone replacement therapy fraught with risks (Dandona & Rosenberg, 2010).

Testosterone and benign prostatic hyperplasia.

Benign prostatic hyperplasia (BPH) is clinically defined as benign enlargement of the prostatic gland leading to compression of the urethra. Symptoms vary from slight to significant blockage of urinary passage and may

severe impact quality of life (Roehrborn, 2011; Nicholson & Ricke, 2011).

Although androgens have been blamed traditionally for causing BPH (White, 1895; Huggins & Hodges, 2002; Stone & Clejan, 1991; Wendel, Brannen, Putong, & Grayhack, 1972), recent research suggests otherwise (Morales, 2002; Davies & Eaton, 1991). Supplementing men with androgens (or using androgen-boosting supplements) does not seem to increase the risk of either BPH or LUTS - lower urinary tract symptoms (Morales, 2002; Davies & Eaton, 1991).

Some researchers also observe that since risk of BPH increases with advancing age when androgens levels decrease, BPH is not likely to be caused by androgens (Nicholson & Ricke, 2011). Androgens in fact may be responsible for reducing the size of hyperplasic prostate glands.

More recently, there is a new school of thought that suggests that estrogens may be more directly linked to BPH (and prostatic cancer) than androgens.

As men age, their androgen levels drop while estrogens levels remain constant or even rise. The increased estrogen to androgen ratio has been shown to coincide with the development of BPH.

Aromatization of circulating testosterone in fat and muscle is mainly responsible for production of estradiol-17β, the most physiologically active estrogen in men; a small amount (20%) is produced by the Leydig cells of the testes (Vermeulen, Kaufman, Goemaere, & van, I, 2002).

Prostate is an important target organ for estrogens and loss of aromatase activity and decreased conversion of testosterone to estrogen has been shown to be associated with reduced estrogen-induced proliferation (Ellem & Risbridger, 2009).

Fear Psychosis Associated With Testosterone Replacement Therapy

This fear of risks associated with testosterone – chiefly development of BPH in middle-aged men – has led to skepticism for use of other alternative treatments as well – especially supplements to boost testosterone levels.

However, as shown above, much of this fear is unwarranted. Moreover, testosterone levels in men with and without prostate cancer do not vary much (Raynaud, 2006; Rhoden & Morgentaler, 2004). Testosterone, therefore, is not very likely to be the offending cause.

Furthermore, most of these adverse effects are attributed to testosterone replacement therapy and not to the so called 'secretogogues' of testosterone. AlphaViril™ contains – as described below – herbal ingredients which circumvent the risks associated with injectable testosterone.

Contents of AlphaViril™

The libido enhancing/testosterone boosting complex of AlphaViril™ contains *Avena sativa, Tongkat Ali* extract and *Maca* root. Together, these have been proven to increase appetite, elevate mood and increase virility. *Avena sativa* extract, derived from wild oats, in particular is known to boost testosterone secretion in men.

Although it is unclear how *Avena sativa* increases testosterone levels in blood, it is suspected that stimulation of luteinizing hormone (LH) levels may be its mechanism of action. Terrestris Tribulis and Stinging Nettle extract, likewise, work in a similar manner – by boosting LH levels. Additionally, they also free

testosterone that is bound to SHBG in the plasma.

Nitric oxide is a phosphodiesterase-5 inhibitor which causes vascular dilatation. Resultant increase in blood flow to the penis forms the basis of improvement in erections. Additionally, increased blood flow to exercising muscles improves post-exercise recovery and overall body composition. This translates into more muscle strength, vigor and vitality.

Other constituents like Vitex agnus cactus, L-Arginine AKG, DIM (diindolylmethane), Eurycoma, and Icarrin also help improve and regulate testosterone levels, while reducing negative sexual hormones – estradiol and prolactin. Additionally, clinically proven combination of Zinc Picolinate, Copper Oxide, Selenium and Vitamin D3 is also being utilized in the AlphaViril™ formula – which further explains the improved results of this study.

CONCLUSION

The results of this investigation suggest that the contents of AlphaViril^{TM} may work synergistically to improve testosterone levels in hypogonadal middle-aged men. Improved libido, enhanced sexual and exercise performance and relief from signs and symptoms of hypogonadism are some of the health benefits that can be achieved through the use of this herbal preparation.

Additionally, since improved testosterone blood profile reduces the risk of obesity, the risk of developing metabolic diseases in later life is reduced drastically. Also, since testosterone deficiency amounts to bone rarefaction, needless to say that restoration of testosterone levels will decrease the chances of osteoporosis during 'andropause' and hence the risk of spontaneous fractures in later life.

None of the herbal products contained in AlphaViril^{TM} are associated with the risk of developing prostate cancer, causing deranged blood lipid profiles or shrinkage of testes (as is thought to occur with testosterone replacement therapy).

Since most clinicians are skeptical to administer testosterone therapy to hypogonadal men – despite evidence of its effectiveness – availability of herbal secretogogues to elevate testosterone levels seem to an exciting therapeutic advancement.

FURTHER RESEARCH

Larger clinical trials to ascertain safety of use of AlphaViril^{TM} in younger, hypogonadal men are recommended by us.

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