



Buriti (*Mauritia Flexuosa*) Pulp and Oil as an Adjuvant in Testosterone Replacement Therapy



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Abstract

Aging is a physiologic and multi factorial process and oxidative stress plays a major role in it. It is expected, as men age, the decline of testosterone levels and that some develop hypogonadism. Hypogonadal men have a lower antioxidant capacity than normogonadal ones, and therefore are more exposed to oxidative stress damage. Testosterone replacement therapy (TRT) has been widely used to ameliorate the symptoms inherent to testosterone deficiency. The use of androgenic hormones in the United States has more than tripled over a ten-year period (2001 to 2011), although the harm and benefits of this therapy are not fully consolidated in the literature. This minireview proposes the use of Buriti, an Amazonian fruit rich in oleic acid, beta-carotene, vitamin E, tocopherols and many other nutrients, as adjuvant in TRT. As a potential phytoterapeutic, Buriti may potentialize beneficial effects of TRT as well as lessen its deleterious effects.

Keywords: Antioxidative therapy; Amazonian fruit; Testosterone-replacement-therapy

Introduction

Hypogonadism and testosterone replacement therapy

There is a continuing gain in life expectancy in the Western population; a man born in Canada in 2016 will live slightly more than a man born in the United States of America in the 1930s [1]. The increase in the life expectancy of Brazilian people is also evident: over a period of 10 years, it has gone from 71 to 75 years of age [2]. Through this increase, the prevalence of chronic non-communicable diseases (CNCD) also increased. In 2007 the morbidity and mortality rate in Brazil due to these causes was 540 deaths per 100 thousand inhabitants, being cardiovascular diseases, cancer, chronic respiratory disease and diabetes mellitus the most representative pathologies in the deaths [3].

It is well stabilized in the academic field that ageing process in males is associated with decrease of serum testosterone levels, increase of sex hormone-binding globulin (SHBG) concentration and decrease in free testosterone [4,5]. The clinical consequences of declining serum testosterone levels with age are not known, however, it is possible to create several parallels between the physiological process of aging and hypogonadism suggesting that this decrease may be the cause for the effects of aging in man. Hypogonadism is a term that refers to a decrease in sperm

production and/or testosterone production (the two major functions of the testes). If these dysfunctions result from a disease of the testes, primary hypogonadism is configured; however, it is called secondary hypogonadism when gonadal dysfunction results from a problem in the hypothalamus [6].

This condition can be from a congenital or acquired cause. Among the primary causes of hypogonadism are: klinefelter syndrome and other chromosomal abnormalities, mutations in FSH and LH receptor genes, cryptorchidism, varicocele, disorders of androgen synthesis, radiation, ketoconazole, glucocorticoids, trauma, testicular torsion, autoimmune damage, and many others. Among secondary causes are: kallmann syndrome, leptin or leptin receptor mutation, prader-willi syndrome, hyperprolactinemia, gonadal steroid administration, glucocorticoids, opiates, diabetes mellitus, trauma, tumors, pituitary apoplexy, surgery in the sellar region, and others [7-10].

Evaluating 2966 men between 40 and 79 years of age, with low serum testosterone levels for no apparent cause besides aging, the EMAS study [4] showed that only a small percentage of these men (2.1%) had typical signs of hypogonadism. Therefore, although suppressed serum testosterone is common in old men, only a small

fraction of them develop a genuine set of signs and symptoms associated with it. This syndrome is most known as Late-onset hypogonadism (LOH) [11]. The most common symptoms of LOH are: erectile dysfunction, loss of libido, deterioration of cognitive abilities, irritability, depression, loss of bone and muscle mass and physical strength [12,13]. Testosterone replacement therapy (TRT) has been used to attenuate these symptoms.

The use of androgen hormones more than tripled in the United States, from 0.81% in 2001 to 2.91%, mainly among men over 40 years old [13,14]. Handelsman [15], researching the prescription of TT in 41 countries, noted that this may indicate a worldwide trend and that the use of this drug has increased in all countries. This is worrying, since the harm and benefits of TRT are not well established in the literature. There are some potential undesirable and adverse effects related to TRT: worsening of apnea [16]; reduction of HDL-cholesterol levels [17]; erythrocytosis, particularly with testosterone ester injections [17,18]; venous thromboembolism as a consequence of erythrocytosis because the risk of venous thromboembolic disease is directly related to hematocrit [19] and skin rash (by the patch Androderm) [20,21]. Prostate cancer is considered testosterone-dependent [22,23], so there is a concern in the academic arena regarding the possibility of increased risk of cancer in patients undergoing TRT. Although TRT has been shown to increase prostate volume as well as PSA [23-25], a meta-analysis [17] of 51 randomized trials of testosterone therapy in men showed no significant increase in the incidence of prostate cancer.

The association between TRT and cardiovascular risk is still a subject of great academic debate. Analyzing subclinical atherosclerosis in older men, a trial [26] showed no significant difference between carotid intima-media thickness and coronary artery calcium scores from the TRT to the placebo group. None

the less, authors [27-30] agree that more studies are needed to establish cardiovascular safety. A randomized trial of testosterone therapy in older men with sarcopenia [31] was stopped early, due to cardiovascular-related adverse events. A retrospective cohort study with 8709 men aged from 60 to 64 years old [32] showed that men undergoing TRT are more likely to present cardiovascular events than those who are not. Borst et al. [33] also found in their studies that oral TRT significantly increased the risk of heart diseases.

The Amazonian biodiversity concentrates the largest flora on the planet, although its potential is still little explored. In this diversity it was possible to find Buriti: a hard fruit with a scaly appearance and a reddish color (Figure 1). The Buriti Palm (*Mauritia flexuosa*) is a native Brazilian palm that grows periodically in flooded areas, along the rivers, forests and savannas [34] (Figure 1). The bioactive compounds in the most promising foods are prebiotics, sulfuric and nitrogen compounds, antioxidant vitamins and minerals, phenolic compounds, unsaturated fatty acids and fibers [35]. In the buriti fruit, oleic acid (73.3 and 78.73%), palmitic acid (17.34 and 19.2%), linoleic acid (2.4 and 3.93%), linolenic acid (2, 2%), stearic acid (2.0%) and myristic acid (0.1%). Some analyzes of buriti oil showed traces of palmitoleic acid [36]. In addition, buriti oil has high levels of β -carotene (2150 and 2251 μ g/g) and vitamin E or tocopherol (1750 and 1760ppm). It also has vitamin C (26mg), calcium (113mg), phosphorus (19mg) and iron (3.5mg). In its pulp can also be found vitamin B1 or thiamine (0.03mg), vitamin B2 or riboflavin (0.23mg) and vitamin B3 or niacin [37]. Costa et al [38] analyzing phytosterols and tocopherols of pulps and seeds of eight Brazilian fruits concluded that Buriti pulp presented high concentration of α -tocopherol (346.71 μ g/100g), reinforcing the hypothesis that amazonian fruits may have great potential for as an alternative source of bioactive compounds. Buriti oil has aroused interest due to its nutritional composition, which in addition to nourishing promote health benefits to consumers [39].

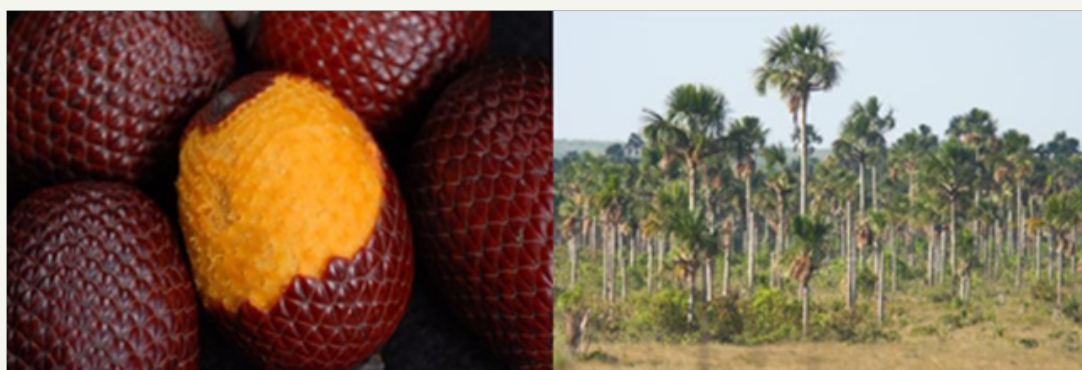


Figure 1: Buriti fruit (in the left) and Buriti palm trees (in the right).

Discussion

Aging is a physiologic and multi-factorial process and there are many theories about it, but many authors agree that oxidative stress plays a major role in it [40-52]. The hypothesis of Free Radical Theory of Aging was first described in 1956 by Harman

[40] and then it was modified [53] in 1972. Nowadays, the modern version is The Oxidative Stress Theory [44]. Oxidative Stress has been associated to many aging-related diseases, and it was observed that hypogonadal men has less total antioxidant capacity (TAC) than the normogonadal ones [54]. It is reasonable to assume that this particular group of men (hypogonadal) are more exposed

to oxidative stress (OS), being hypogonadism symptoms, in some degree, related to OS. Erectile dysfunction is associated with OS caused by dysfunction of antioxidant enzymes and excessive production of free radicals such as superoxide, hydrogen peroxide and hydroxyl radicals [55-57]. Zhang et al. [55], in their study, found a possible protective role of dietary antioxidants against erectile dysfunction. Kazem et al. [56] in an animal model with rabbits evidenced that long-term use of pomegranate juice (an antioxidant beverage) was capable of decreasing erectile dysfunction. Analyzing 350 men, between 18 and 40 years of age, one study [57] found that the group diagnosed with erectile dysfunction had lower dietary intake of antioxidants than the control group. This same study further showed that consumption of 50mg/day of flavonoids was able to reduce the risk of erectile dysfunction by 32%.

It has been already explained that OS contributes to the neuro-degeneration process [46,47,49,58]. Chronic testosterone supplementation, in an animal model with rats, presented a neuro-protective effect; resulted in the reduction of oxidative stress by increasing the expression of antioxidant substances in the cerebral parenchyma [59]. On the other hand, other studies demonstrate that the neuroprotective effects of TRT are dependent to the OS intensity; it has neuro-protective effect on low OS scenario [45,60,61] but can exacerbate OS damage in high OS state [45,62]. It has been already shown that hypotestosteronemia is related to increase of cardiovascular risk [63] such as OS itself [48]. Rita Tostes et al. [64] argues that the possible protective effect of TRT on the cardiovascular system is far from being elucidated; in her study she argues that TRT has both antioxidant and pro-oxidant effects on cardiovascular system. Borst et al. [33] found that oral TRT produces significant cardiovascular risk in opposition to parenteral and transdermal TRT that doesn't.

Therefore, the pro-oxidative state is related to most of the problems inherent to aging and testosterone deficiency. We propose the use of Buriti as an adjuvant in TRT due to its great antioxidant potential. There is the possibility of this fruit acting in synergy with testosterone in the genesis of an anti-oxidative state, especially in patients with hypogonadism who present erectile dysfunction. It may also be used as a pre-treatment for those patients with hypogonadism who have a higher state of oxidative stress (eg: advanced age, metabolic syndrome, sedentary lifestyle, etc.) or risk of neurodegenerative disease (eg: alzheimer's and dementia).

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