Nutrition 31 (2015) 1295–1298

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Nutrition and food

A glance at…nutritional antioxidants and testosterone secretion

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ARTICLE INFO

Article history:
Received 24 April 2015
Accepted 23 May 2015

Keywords:
Low testosterone
Leydig cells
Oxidative stress
Antioxidants
Phosphatidylserine

The mitochondrial electron transfer system supplies the energy that drives testosterone synthesis, exposing Leydig cells to oxidative stress that can inhibit the synthesis and secretion of testosterone. Chronically elevated systemic oxidative stress and "low normal testosterone status" ("Leydig cell impairment," consistent with a mid-morning serum total testosterone concentration between 7 and 14 nmol/L) are becoming increasingly prevalent, particularly as men exceed middle age [1]. Low normal testosterone status is associated with physiological conditions that may include reductions in energy, motivation, initiative, self-confidence, concentration and memory, sleep quality, muscle bulk and strength, and skeletal integrity; diminished physical or work performance; feeling sad or blue; depressed mood or dysthymia; mild anemia; increased body fat and body mass index; systemic inflammation and oxidative stress; increased risk for developing any form of cardiovascular disease; increased risk for experiencing fatal or nonfatal cardiovascular events; and reduced life expectancy [1].

In contrast, reducing oxidative stress releases Leydig cells from oxidative inhibition and can increase testosterone synthesis in response to luteinizing hormone (LH). Increased consumption of dietary nutrients and phytonutrients with antioxidant properties can contribute safely to both oxidative stress reduction and enhanced androgenic status in otherwise healthy adult men. In this era of "60 is the new 40," the potential for maintaining healthy testosterone status through dietary oxidative stress reduction may become an important public health tactic [1].

Oxidative stress, Leydig cells, and testosterone secretion

Leydig cells are exposed to increased levels of oxidative stress during aging (demonstrated through studies of the Brown Norway rat, used extensively as a model for male reproductive aging [2,3]), after exposure to environmental prooxidants such as polychlorinated biphenyl (demonstrated through studies of cultured adult rat Leydig cells [4–6]), and when testosterone synthesis is stimulated in human Leydig cells [7–9] and in Leydig cells harvested from Brown Norway rats [10]. The aging-associated declines in testosterone production and circulating testosterone concentrations are at least in part the consequences of cumulative oxidative stress within Leydig cells [2,3,9,11]. In laboratory rats [2,3,9,11,12] and cultured mouse Leydig cells [13–17], oxidatively damaged Leydig cells and Leydig cells in aged testes experience suppression of antioxidant enzyme activities, reduced intracellular glutathione (GSH) content, accelerated lipid peroxidation and oxidative modification of DNA, and loss of the mitochondrial membrane potential required for testosterone synthesis. They exhibit reduced sensitivity to LH, fewer LH receptors expressed per cell, and impaired LH-induced activation of the steroidogenic acute regulatory protein (a component of a transmembrane multiprotein complex that catalyzes the import of cholesterol from the outer to the inner mitochondrial membrane, a rate-limiting step in steroid hormone synthesis [18]) [16,19–22]. Additionally, the activities of

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http://dx.doi.org/10.1016/j.nut.2015.05.019

several enzymes of the testosterone biosynthetic pathway (cytochrome P450 [CYP]11A1, 3β-hydroxysteroid dehydrogenase/$\Delta^5 \rightarrow \Delta^4$ isomerase [3β-HSD; HSD3B2], CYP17A1 hydroxylase, CYP17 A1lyase, 17β-HSD; HSD17B3) are reduced and testosterone synthesis is inhibited in aging rats [2,3,12], oxidatively damaged rat testes [23], oxidatively damaged cultured mouse Leydig cells [14,24], and oxidatively stressed adult human testes [25].

In contrast, a reduction in systemic oxidative stress in mice reduces oxidative stress within Leydig cells and increases the rate of testosterone secretion [26]. Consistent with the hypothesis that oxidative stress reduction may attenuate subnormal testosterone production, several nutritional antioxidants (e.g., the phytonutrients in pomegranates, vitamin C. Vitamin E, α-lipoic acid (ALA), zinc, selenium, and phosphatidylserine) have been observed to contribute to a reduction in systemic and local oxidative stress, stimulation or reversal of inhibition of testosterone synthesis, and enhancement of androgenic status.

Pomegranates

In adult rat, intraperitoneal injection of pomegranate polyphenols prevented carbon tetrachloride (CCl_4) inhibition of testicular glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), and LH-stimulated testosterone synthesis [27]. The consumption of the individual pomegranate polyphenol, ellagic acid, alone blocked adriamycin-induced testicular lipid peroxidation and inhibition of testosterone synthesis in young male rats [28].

Vitamin C

Oral vitamin C increases LH secretion by isolated pituitary cells in the absence of hypothalamic LH-releasing hormone and stimulates testosterone synthesis and increased serum total testosterone concentrations in otherwise unmanipulated healthy male rats [29–31]. Vitamin C supplementation prevents oxidative suppression of testosterone synthesis in animals exposed to cadmium [32], lead [33], cyclophosphamide [34–36], or arsenic trioxide [37], and upregulates testicular testosterone synthesis in these animals by stimulating the expression of HSD3B2 and HSD17B3 [32,37].

Vitamin E

Vitamin E (α-tocopherol) is the most powerful chain-breaking lipid-soluble dietary antioxidant [38], and attenuates oxidant-induced lipid peroxidation in adult male rat testes *in vivo* [39]. Dietary supplementation of male rats with vitamin E prevents the oxidative inhibition of testicular testosterone synthesis induced by exercise [40], cadmium [32,41,42], chromium VI [43], and sodium azide [44]. Dietary supplementation with vitamin E and vitamin C in combination prevents the oxidative inhibition of testosterone synthesis induced by arsenic trioxide in male mice [45].

Even in the absence of an increase in systemic or local oxidative stress, Leydig cell responsiveness to LH is proportional to vitamin E exposure [39] and supplemental vitamin E (483 mg/d for 8 wk) increased testosterone synthesis an average of 20% in healthy men [46].

ALA

Elevated oxidative stress caused by exposure to bisphenol-A inhibits the activities of Leydig cell GSH, GPx, GR, SOD, CAT, and HSD17B3; increases intracellular lipid peroxidation; and attenuates testosterone synthesis in adult rats [47] and in cultured rat Leydig cells [48]. In contrast, dietary supplementation with ALA has prevented or attenuated these detrimental effects on testosterone status [47].

Zinc

Chronically deficient zinc intake produces testosterone deficiency [49] and, in healthy men, the serum total testosterone concentration is directly correlated with dietary zinc intake [49]. In addition to its other beneficial effects [50–54], increased dietary zinc intake can stimulate testosterone synthesis in men [55] and improve testosterone status [49].

Selenium

In laboratory animals, dietary selenium deficiency impairs testosterone synthesis in response to LH [56]. Conversely, supplemental selenium attenuates or prevents the inhibition of testosterone synthesis caused by exposure to several oxidants, including cadmium [57,58], sodium azide [44], or di(2-ethylhexyl)phthalate [59].

Phosphatidylserine

Testicular cells are enriched in phosphatidylserine [60] and require phosphatidylserine for testosterone synthesis [61]. In Leydig cells, phosphatidylserine induces the translocation of cytosolic Akt (protein kinase B) to the plasma membrane and interacts directly with Akt to alter its conformation and allow it to be activated via phosphorylation by mammalian target of rapamycin-2 [62]. Phosphatidylserine-dependent activation of Akt is followed by Akt activation of protein kinase C [62,63], which participates in signaling pathways that culminate in testosterone synthesis through the primary "Δ^5" pathway (pregnenolone → 17α-hydroxypregnenolone → dehydroepiandrosterone → androstenedione → testosterone). Phosphatidylserine also stimulates the isomerase activity of HSD3B2 in the testes, increasing testosterone synthesis through the alternate "Δ^4"pathway (pregnenolone → progesterone → androstenedione → testosterone) [61,63]. By participating in the initiation of androgenic signaling cascades and through direct stimulation of the rate-limiting HSD3B2 enzyme, dietary phosphatidylserine directly influences testosterone status [61–63].

For example, in a double-blind, randomized placebo-controlled study, healthy men with initially "desirable" resting plasma free testosterone concentrations and participating in a prescribed exercise regimen added 600 mg of phosphatidylserine to their daily diets for 10 d [64]. Supplemental phosphatidylserine produced a 60% greater increase in resting plasma free testosterone concentration than was produced by placebo.

Conclusions

Human aging often is accompanied by excessive endogenous and exogenous oxidative stress and enhanced oxidative damage within Leydig cells. Oxidatively damaged Leydig cells exhibit decreased responsiveness to LH and impaired testosterone synthesis. Conversely, antioxidant defenses that can be augmented by dietary supplementation with specific antioxidant nutrients can reduce cell-wide oxidative damage, support redox balance within Leydig cells, release Leydig cells from oxidative inhibition of testosterone synthesis, increase the rate of testosterone