



BACKGROUND

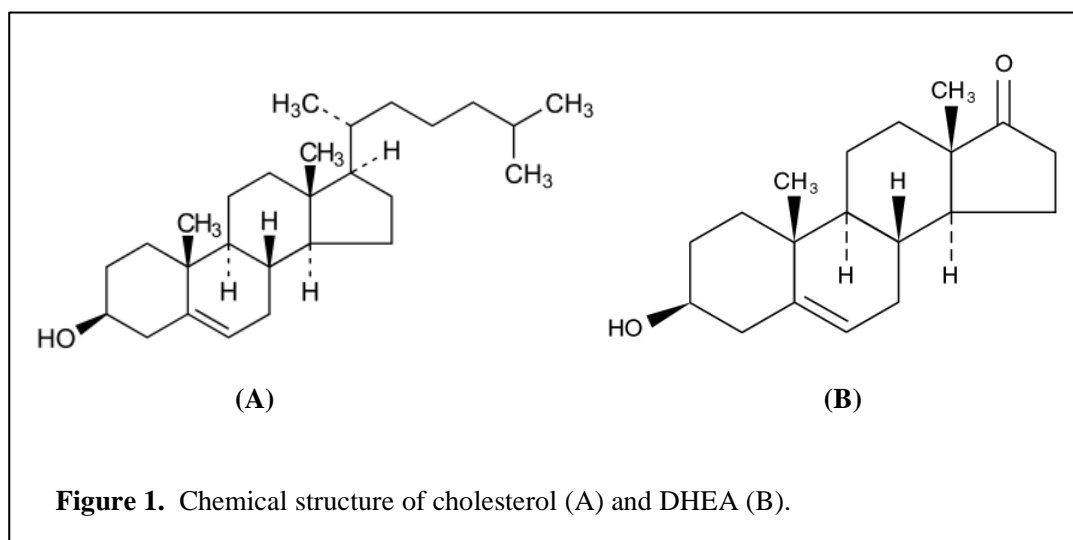
DHEA: The Basic Facts *Prepared by Andrew Shao, Ph.D., Vice President, Scientific & Regulatory Affairs*

Abstract

Dehydroepiandrosterone (DHEA) is a naturally occurring steroid hormone produced by the adrenal glands, whose levels decline rapidly with age. Under normal physiologic conditions, DHEA serves as an indirect precursor to estrogen and testosterone. Contrary to many media reports, DHEA is not an anabolic steroid, and its use is not associated with known side effects resulting from anabolic steroid abuse. Research from randomized, controlled trials has consistently shown that DHEA supplementation does not increase testosterone levels, enhance muscle mass or muscle strength in young, healthy adults. In contrast, a large body of continuously emerging research suggests that DHEA supplementation can restore levels that decline in the body with age, and provide other health benefits in older individuals or those with endocrine deficiencies.

DHEA is a steroid hormone

A *steroid* is defined as “any of numerous natural or synthetic compounds containing a 17-carbon 4-ring system and including the sterols and various hormones and glycosides” (1). Cholesterol is an example of a steroid, and is the basic structure from which all steroids are produced in the body. A *steroid hormone* is defined as “any of numerous hormones (as estrogen, testosterone, cortisone, and aldosterone) having the characteristic ring structure of steroids and formed in the body from cholesterol” (1). The active form of vitamin D that circulates in the body, known as calcitriol, is an example of a steroid hormone. DHEA (Figure 1), falls under both of these definitions, and is the most abundant steroid hormone precursor made by the body (2). It is produced by the body’s adrenal glands from cholesterol and levels peak in early adulthood and decline substantially with aging in both men and women (2). DHEA is present in the body in two pools: “free” DHEA and the major circulating form, “sulfated” DHEA, or DHEAS. Because of its distribution in two large pools, it has been described as a “buffer” hormone, serving to prevent excesses or deficits of other important steroid hormones (3). DHEA also affects multiple physiologic systems in the body, including the central nervous system, the vascular system, the immune system and glucose metabolism (4).



DHEA is not an anabolic steroid

DHEA is an adrenal steroid that serves as an indirect building block for other hormones and exerts very weak androgenic (testosterone-producing) and estrogenic (estrogen-producing) activity (Figure 2), depending on the body's need and hormone balance (5). Unlike androstenedione ("andro"), a direct precursor to testosterone, the fate of DHEA is subject to multiple biochemical pathways, and is not committed solely to testosterone production. This supports the assertion that DHEA serves as an effective buffer against excesses or deficits of estrogens and androgens (3, 6). Under normal physiologic conditions, such as those in young healthy adults, the conversion of DHEA to testosterone is tightly controlled by the body (5). Consistent with this point is the well-established finding that administration of DHEA to young, healthy adults does not influence testosterone levels (7-12).

An anabolic steroid is defined as "any of a group of usually synthetic hormones that increase constructive metabolism and are sometimes abused by athletes in training to increase temporarily the size of their muscles" (1). In contrast to exogenous testosterone, and its various synthetic derivatives, and contrary to countless media reports, DHEA is not an anabolic steroid hormone (13). Controlled clinical trials indicate that its use by young adults does not result in performance related gains (8-11, 14, 15), and is not associated with the myriad of side effects that accompany anabolic steroid abuse. Cardiovascular conditions such as hypertension, atherosclerosis, and blood clotting, liver conditions such as jaundice and hepatic carcinoma, tendon damage, reduced fertility and gynacomastia (in males), and also adverse psychiatric and behavioral effects are all known to result from anabolic steroid abuse (16, 17). DHEA does not exert such effects. Moreover, according to surveys of weightlifters and other athletes conducted by researchers at Harvard University, while andro and other hormone precursors are or have been used by athletes for performance enhancement, DHEA is rarely used for such purposes (18). Therefore, the proposition that DHEA is in any way comparable to illegal anabolic steroids is invalid and unfounded.

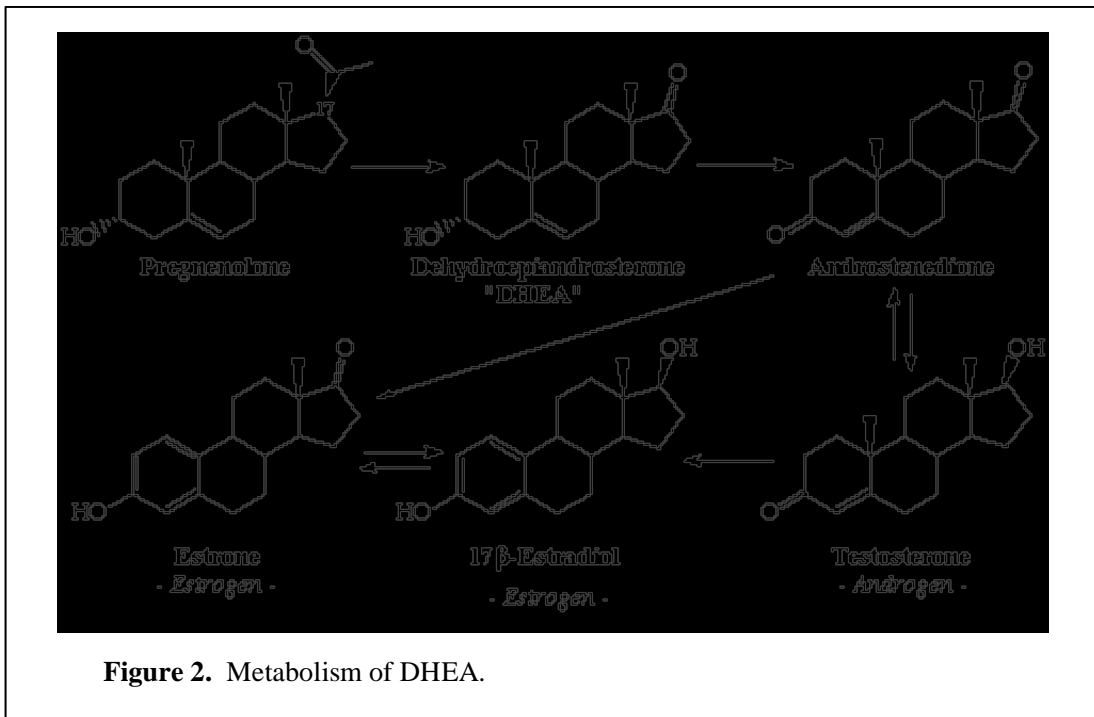


Figure 2. Metabolism of DHEA.

DHEA supplementation may benefit older people

DHEA levels start relatively low at birth, and gradually increase until puberty, when levels increase markedly, reaching a peak around 20 to 24 years of age. From there, serum and tissue DHEA levels decline at a rate of 2 to 3% per year, with a steep decline occurring around middle age. By age 75, humans exhibit 10 to 20% of young adult DHEA levels (4, 19, 20) (Figure 3). A number of review articles have summarized the available observational data showing that in older individuals serum DHEA levels are inversely related to incidence and prevalence of disease (21). Low levels of DHEA are associated with aging and cardiovascular disease in men (22), and an increased risk of premenopausal breast and ovarian cancer in women (23), impaired cognitive function (24), and compromised immune function (6). Results from controlled intervention studies indicate that DHEA supplementation may benefit older individuals. More than 50 published human studies show that supplementation in elderly and those with endocrine deficiencies can safely restore DHEA levels to those typical of healthy younger adults. Areas of emerging research showing a potential benefit from DHEA supplementation are shown in Table 1.

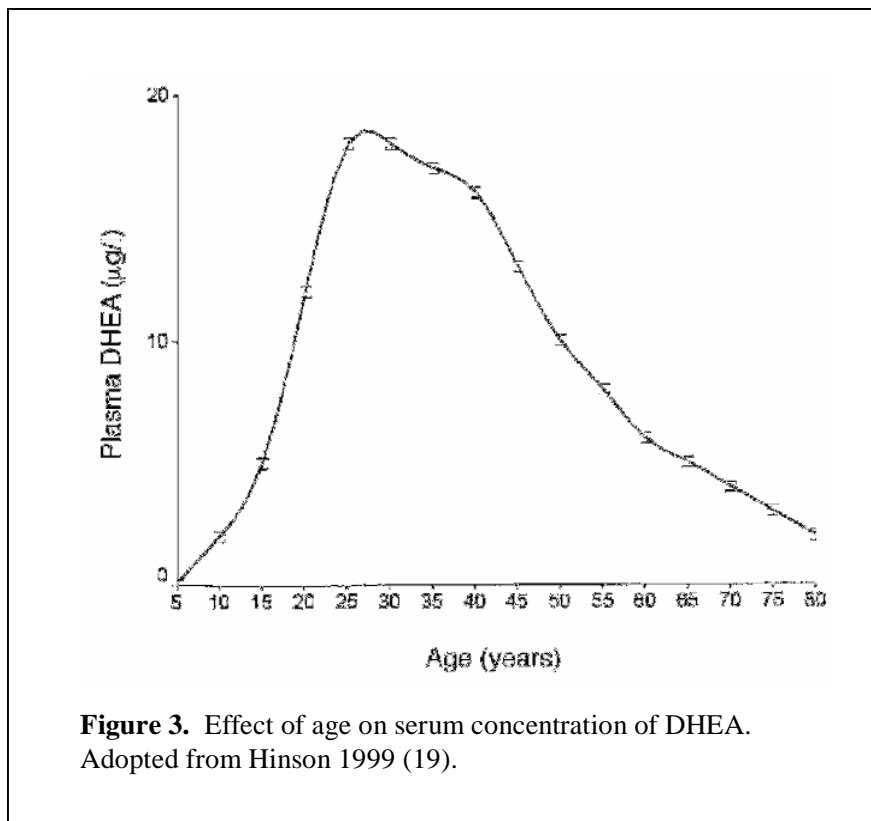


Table 1. Potential benefits from DHEA supplementation

| Function | Reference(s) |
|--|---------------------|
| Supporting immune function | (25, 26) |
| Maintaining cognitive function, elevating mood and sense of well-being | (27-35) |
| Improving sleep patterns | (36) |
| Peri- and postmenopausal support | (37, 38) |
| Reducing fat mass and maintaining lean body mass | (39-42) |
| Maintaining bone health | (41, 43-47) |
| Maintaining healthy lipid levels and overall cardiovascular health | (48-51) |
| Normalizing glucose metabolism | (40, 49, 51-53) |

Safety of DHEA as a dietary supplement

Controlled studies lasting between six months and a year at doses ranging from 25 to 200 mg daily have shown DHEA to be safe, with only some studies reporting transient and mild side effects (7, 40-42, 45, 51, 54, 55, 56, 57, 58). In randomized, controlled trials conducted in the elderly using 50 mg DHEA per day for six months, only mild facial acne is reported as the lone side effect (41, 57). In two of these studies, there were no changes in renal or liver biochemistry and no changes in prostate specific antigen (PSA) levels in the male subjects assigned to DHEA (40, 41). A recent two year trial conducted in elderly administered 75 mg DHEA/day concluded that there were no adverse effects (44). These findings are consistent with those from a multitude of shorter term trials incorporating a range of doses showing that DHEA supplementation is well tolerated.

Some studies have shown DHEA causes a slight decline in HDL (“good”) cholesterol (49, 59, 60), although the findings are not convincing. In one study, subjects ingested a supplement that in addition to DHEA, also contained many other active ingredients at various levels (59). Therefore, the effects observed over the course of the four week intervention cannot be attributed solely to DHEA. In another more recent study, while DHEA supplementation reduced HDL levels over a twelve week period, the total cholesterol-to-HDL cholesterol ratio, also an important indicator of cardiovascular health, was unchanged (49). Finally, the reduction of HDL does not appear to be consistent, with other studies finding no difference between DHEA compared to placebo (41, 42, 61), or even an increase in HDL associated with DHEA (51, 62). Additional studies are warranted to better define what effect, if any, DHEA supplementation has on HDL levels.

Conclusions

DHEA is a steroid hormone that plays an important role as an indirect intermediate to androgens and estrogens in the body. DHEA is not an anabolic steroid, its use is not associated with the anabolic and side effects that accompany anabolic steroid abuse, and the potential for DHEA abuse by athletes is remote. Emerging research continues to indicate that DHEA supplementation may be beneficial for older individuals or those with endocrine deficiencies.

References

1. MedlinePlus. Medical Dictionary. Bethesda, MD: National Library of Medicine and the National Institutes of Health, 2003.
2. Arlt W. Dehydroepiandrosterone and ageing. *Best Pract Res Clin Endocrinol Metab* 2004;18:363-80.
3. Regelson W, Loria R, Kalimi M. Hormonal intervention: "buffer hormones" or "state dependency". The role of dehydroepiandrosterone (DHEA), thyroid hormone, estrogen and hypophysectomy in aging. *Ann N Y Acad Sci* 1988;521:260-73.
4. Dharia S, Parker CR, Jr. Adrenal androgens and aging. *Semin Reprod Med* 2004;22:361-8.
5. Longcope C. Dehydroepiandrosterone metabolism. *J Endocrinol* 1996;150 Suppl:S125-7.
6. Regelson W, Loria R, Kalimi M. Dehydroepiandrosterone (DHEA)--the "mother steroid". I. Immunologic action. *Ann N Y Acad Sci* 1994;719:553-63.
7. Acacio BD, Stanczyk FZ, Mullin P, Saadat P, Jafarian N, Sokol RZ. Pharmacokinetics of dehydroepiandrosterone and its metabolites after long-term daily oral administration to healthy young men. *Fertil Steril* 2004;81:595-604.
8. Wallace MB, Lim J, Cutler A, Bucci L. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. *Med Sci Sports Exerc* 1999;31:1788-92.
9. Brown GA, Vukovich MD, Sharp RL, Reifenrath TA, Parsons KA, King DS. Effect of oral DHEA on serum testosterone and adaptations to resistance training in young men. *J Appl Physiol* 1999;87:2274-83.
10. Brown GA, Vukovich MD, Reifenrath TA, et al. Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. *Int J Sport Nutr Exerc Metab* 2000;10:340-59.
11. Welle S, Jozefowicz R, Statt M. Failure of dehydroepiandrosterone to influence energy and protein metabolism in humans. *J Clin Endocrinol Metab* 1990;71:1259-64.
12. Nestler JE, Barlascini CO, Clore JN, Blackard WG. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. *J Clin Endocrinol Metab* 1988;66:57-61.
13. Delbeke FT, Van Eenoo P, Van Thuyne W, Desmet N. Prohormones and sport. *J Steroid Biochem Mol Biol* 2002;83:245-51.
14. Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 2003;94:651-9.
15. Bahrke MS, Yesalis CE. Abuse of anabolic androgenic steroids and related substances in sport and exercise. *Curr Opin Pharmacol* 2004;4:614-20.
16. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004;34:513-54.
17. Mottram DR, George AJ. Anabolic steroids. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000;14:55-69.
18. Pope HG. Current state of DHEA in the marketplace. Washington, D.C.: Council for Responsible Nutrition, 2003.
19. Labrie F, Luu-The V, Labrie C, et al. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. *Endocr Rev* 2003;24:152-82.
20. Hinson JP, Raven PW. DHEA deficiency syndrome: a new term for old age? *J Endocrinol* 1999;163:1-5.
21. Watson RR, Huls A, Araghinikiam M, Chung S. Dehydroepiandrosterone and diseases of aging. *Drugs Aging* 1996;9:274-91.
22. Thijs L, Fagard R, Forette F, Nawrot T, Staessen JA. Are low dehydroepiandrosterone sulphate levels predictive for cardiovascular diseases? A review of prospective and retrospective studies. *Acta Cardiol* 2003;58:403-10.
23. Johnson MD, Bebb RA, Sirrs SM. Uses of DHEA in aging and other disease states. *Ageing Res Rev* 2002;1:29-41.
24. Ferrari E, Cravello L, Muzzoni B, et al. Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. *Eur J Endocrinol* 2001;144:319-29.
25. Degelau J, Guay D, Hallgren H. The effect of DHEAS on influenza vaccination in aging adults. *J Am Geriatr Soc* 1997;45:747-51.
26. Casson PR, Andersen RN, Herrod HG, et al. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993;169:1536-9.

27. Brooke AM, Kalingag LA, Miraki-Moud F, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006;91:3773-9.
28. Schmidt PJ, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry* 2005;62:154-62.
29. Nordmark G, Bengtsson C, Larsson A, Karlsson FA, Sturfelt G, Ronnblom L. Effects of dehydroepiandrosterone supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus. *Autoimmunity* 2005;38:531-40.
30. Alhaj HA, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. *Psychopharmacology (Berl)* 2006;188:541-51.
31. Genazzani AR, Inglese S, Lombardi I, et al. Long-term low-dose dehydroepiandrosterone replacement therapy in aging males with partial androgen deficiency. *Aging Male* 2004;7:133-43.
32. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry* 1999;45:1533-41.
33. Arlt W, Callies F, Allolio B. DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition. *Endocr Res* 2000;26:505-11.
34. Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999;341:1013-20.
35. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 1999;156:646-9.
36. Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. *Am J Physiol* 1995;268:E107-13.
37. Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol* 2000;14:342-63.
38. Stomati M, Rubino S, Spinetti A, et al. Endocrine, neuroendocrine and behavioral effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. *Gynecol Endocrinol* 1999;13:15-25.
39. Villareal DT, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. *Am J Physiol Endocrinol Metab* 2006;291:E1003-8.
40. Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial. *Jama* 2004;292:2243-8.
41. Villareal DT, Holloszy JO, Kohrt WM. Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. *Clin Endocrinol (Oxf)* 2000;53:561-8.
42. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)* 1998;49:421-32.
43. Jankowski CM, Gozansky WS, Schwartz RS, et al. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. *J Clin Endocrinol Metab* 2006;91:2986-93.
44. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006;355:1647-59.
45. Gordon CM, Grace E, Emans SJ, et al. Effects of oral dehydroepiandrosterone on bone density in young women with anorexia nervosa: a randomized trial. *J Clin Endocrinol Metab* 2002;87:4935-41.
46. Sun Y, Mao M, Sun L, Feng Y, Yang J, Shen P. Treatment of osteoporosis in men using dehydroepiandrosterone sulfate. *Chin Med J (Engl)* 2002;115:402-4.
47. Gordon CM, Grace E, Emans SJ, Goodman E, Crawford MH, Leboff MS. Changes in bone turnover markers and menstrual function after short-term oral DHEA in young women with anorexia nervosa. *J Bone Miner Res* 1999;14:136-45.
48. Martina V, Benso A, Gigliardi VR, et al. Short-term dehydroepiandrosterone treatment increases platelet cGMP production in elderly male subjects. *Clin Endocrinol (Oxf)* 2006;64:260-4.
49. Dhatariya K, Bigelow ML, Nair KS. Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005;54:765-9.
50. Libe R, Barbetta L, Dall'Asta C, et al. Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 2004;27:736-41.

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51. Lasco A, Frisina N, Morabito N, et al. Metabolic effects of dehydroepiandrosterone replacement therapy in postmenopausal women. *Eur J Endocrinol* 2001;145:457-61.
52. Brignardello E, Runzo C, Aragno M, et al. Dehydroepiandrosterone administration counteracts oxidative imbalance and advanced glycation end product formation in type 2 diabetic patients. *Diabetes Care* 2007;30:2922-7.
53. Bates GW, Jr., Egerman RS, Umstot ES, Buster JE, Casson PR. Dehydroepiandrosterone attenuates study-induced declines in insulin sensitivity in postmenopausal women. *Ann N Y Acad Sci* 1995;774:291-3.
54. Gurnell EM, Hunt PJ, Curran SE, et al. Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 2008;93:400-9.
55. Genazzani AD, Stomati M, Bernardi F, Pieri M, Rovati L, Genazzani AR. Long-term low-dose dehydroepiandrosterone oral supplementation in early and late postmenopausal women modulates endocrine parameters and synthesis of neuroactive steroids. *Fertil Steril* 2003;80:1495-501.
56. Percheron G, Hogrel JY, Denot-Ledunois S, et al. Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial. *Arch Intern Med* 2003;163:720-7.
57. Kahn AJ, Halloran B, Wolkowitz O, Brizendine L. Dehydroepiandrosterone supplementation and bone turnover in middle-aged to elderly men. *J Clin Endocrinol Metab* 2002;87:1544-9.
58. Genazzani AD, Stomati M, Strucchi C, Puccetti S, Luisi S, Genazzani AR. Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. *Fertil Steril* 2001;76:241-8.
59. Kohut ML, Thompson JR, Campbell J, et al. Ingestion of a dietary supplement containing dehydroepiandrosterone (DHEA) and androstenedione has minimal effect on immune function in middle-aged men. *J Am Coll Nutr* 2003;22:363-71.
60. Casson PR, Santoro N, Elkind-Hirsch K, et al. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril* 1998;70:107-10.
61. Barnhart KT, Freeman E, Grisso JA, et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab* 1999;84:3896-902.
62. Abbasi A, Duthie EH, Jr., Sheldahl L, et al. Association of dehydroepiandrosterone sulfate, body composition, and physical fitness in independent community-dwelling older men and women. *J Am Geriatr Soc* 1998;46:263-73.