IMMUNOMODULATORY EFFECTS OF ZINC AND DHEA ON THE TH-1 IMMUNE RESPONSE IN RATS INFECTED WITH TRYPANOSOMA CRUZI.

Chagas’ disease is considered the sixth most important neglected tropical disease worldwide. Considerable knowledge has been accumulated concerning the role of zinc on cellular immunity. The steroid hormone dehydroepiandrosterone (DHEA) is also known to modulate the immune system. The aims of this paper were to investigate a possible synchronization of their effects on cytokines and NO production and the resistance to Trypanosoma cruzi during the acute phase of infection. It was found that zinc, DHEA or zinc and DHEA supplementation enhanced the immune response, as evidenced by a significant reduction in parasitemia levels. Zinc and DHEA supplementation exerted additive effects on the immune response by elevation of macrophage counts, and by increasing concentrations of IFN-gamma and NO.

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THE SEX STEROID PRECURSOR DHEA ACCELERATES CUTANEOUS WOUND HEALING VIA THE ESTROGEN RECEPTORS.

Age-related impaired wound healing states lead to substantial morbidity and cost, with treatment in the USA resulting in an expenditure of over $9 billion per annum. Dehydroepiandrosterone (DHEA) is a ubiquitous adrenal hormone with immunomodulatory properties whose levels decline significantly with advanced age in humans. Conversion of DHEA locally to downstream steroid hormones leads to estrogenic and/or androgenic effects which may be important in age-related skin homeostasis, and which would avoid systemic adverse effects related to estrogen. We report that systemic DHEA levels are strongly associated with protection against chronic venous ulceration in humans. DHEA accelerated impaired healing in an impaired healing model (mice rendered hypogonadal) associated with increased matrix deposition and dampens the exaggerated inflammatory response. Such effects were mediated by local conversion of DHEA to estrogen, acting through the estrogen receptor, and vitro studies suggest a direct effect on specific pro-inflammatory cytokine production by macrophages via mitogen activated kinase (MAP) and phosphatidylinositol 3 (PI3) kinase pathways. In addition, we show that local injection of DHEA accelerates impaired healing in an ageing mouse colony. We suggest that exogenous application of DHEA accelerates impaired wound repair, results which may be applicable to the prophylaxis and treatment of human impaired wound healing states.


ORAL ADMINISTRATION OF DEHYDROEPIANDROSTERONE-SULFATE (DHEAS) INCREASES IN VITRO LYMPHOCYTE FUNCTION AND IMPROVES IN VIVO RESPONSE OF PIGS TO IMMUNIZATION AGAINST KEYHOLE LIMPET HEMOCYANIN (KLH) AND OVALBUMIN.

The present study tested the hypothesis that the oral administration of DHEAS enhances the in vitro and the in vivo immune response of young pigs. Crossbred, female pigs (80 days of age; 49+/2 kg) were separated into two treatment groups.
DEHYDROEPIANDROSTERONE: A MODULATOR OF CELLULAR IMMUNITY AND HEAT SHOCK PROTEIN 70 PRODUCTION DURING POLYMICROBIAL SEPSIS.

OBJECTIVE: DHEA is an immunomodulatory steroid hormone that improves survival during systemic inflammation. A DHEA-induced modulation of heat shock protein response may be an alternative mechanism contributing to the beneficial effects of this hormone. We investigated the effect of DHEA administration on survival, cellular immune functions, and HSP-70 production in septic mice. DESIGN AND SETTING: Randomized animal study, level I trauma center, university research laboratory. SUBJECTS: Male NMRI mice. INTERVENTIONS: Mice were subjected to sham operation (laparotomy, LAP) or sepsis (cecal ligation and puncture, CLP) with or without administration of either saline 0.9% (LAP, CLP) or 20 mg/kg DHEA subcutaneously (LAP/DHEA, CLP/DHEA). Survival was monitored over a 48-h period. Splenocyte apoptosis rate (AnnexinV binding), splenocyte proliferation ([3H]thymidine incorporation), TNF-alpha plasma concentration (ELISA), and HSP-70 concentration (ELISA) in tissue extracts from liver, lung, and spleen were monitored 48 h after onset of sepsis. RESULTS: DHEA administration improved the survival of septic mice (78% vs. 50%). This effect was paralleled by increased splenocyte proliferation, decreased cellular apoptosis rate of splenocytes, and attenuation of TNF-alpha release. Furthermore, an increased HSP-70 concentration was observed in lungs and spleens of DHEA-treated septic animals. CONCLUSIONS: DHEA-treatment decreased the mortality rate of septic mice. This was accompanied by improved cellular immune functions and an augmented heat shock response (HSP-70) of lungs and spleens. Further studies are required to demonstrate a direct relationship between the improved survival and the observed alterations in the immune system in DHEA-treated animals.

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MECHANISM OF ACTION OF ANTI-AGING DHEA-S AND THE REPLACEMENT OF DHEA-S.

The plasma ACTH and cortisol levels do not change during aging. On the other hand, the plasma dehydroepiandrosterone sulfate (DHEA-S) changes remarkably during aging. Before puberty, the plasma DHEA-S level both in males and females is very low, however, it rapidly increases at puberty, and thereafter significantly decreases both linearly and age-dependently. Cytochrome P450c17 has two enzyme activities, 17-alpha-hydroxylase and 17,20-lyase. Cortisol is synthesized by 17-alpha-hydroxylase, and DHEA is synthesized by 17,20-lyase. The mechanism of dissociation of cortisol and DHEA synthesis in aging depends on another regulator of 17,20-lyase of cytochrome P450c17 such as cytochrome P450 reductase. We demonstrated significant decrease in cytochrome P450 reductase activity in bovine aged adrenal glands. We clarified the beneficial effects of DHEA as an anti-aging steroid based on both in vitro and in vivo experiments, such as the stimulatory effect of immune system, anti-diabetes mellitus, anti-atherosclerosis, anti-dementia (neurosteroid), anti-obesity and anti-osteoporosis. It is very important to identify the mechanism of action of DHEA. We clarified the conversion of DHEA to estrone by cytochrome P450 aromatase in primary cultured human osteoblasts. We identified high affinity of DHEA binding with K(d)=6.6 nM in antigen and DHEA stimulated human T lymphocytes. We searched for the target genes that are specifically induced in activated T lymphocytes in the presence of DHEA by subtractive hybridization screening for differentially expressed transcripts. The double blind, randomized human replacement therapies utilizing DHEA are also reviewed.

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IMPACT OF DHEA(S) AND CORTISOL ON IMMUNE FUNCTION IN AGING: A BRIEF REVIEW.

A decline in the human immune system that occurs with aging is known as immunosenescence. Several factors are involved in the process, including reduced neutrophil function and cytotoxic capacity of natural killer (NK) cells, thymus atrophy and reduced naïve T cell number, and lowered B cell antibody production in response to antigen. The endocrine system, specifically the hypothalamus-pituitary-adrenal axis, plays an important role in modulating immune function. With aging an imbalance occurs...
DEHYDROEPIANDROSTERONE REPLACEMENT THERAPY IN OLDER ADULTS: 1- AND 2-Y EFFECTS ON BONE.

BACKGROUND: Age-related reductions in serum dehydroepiandrosterone (DHEA) concentrations may be involved in bone mineral density (BMD) losses. OBJECTIVE: The objective was to determine whether DHEA supplementation in older adults improves BMD when co-administered with vitamin D and calcium. DESIGN: In year 1, a randomized trial was conducted in which men (n = 55) and women (n = 58) aged 65-75 y took 50 mg/d oral DHEA supplements or placebo. In year 2, all participants took open-label DHEA (50 mg/d). During both years, all participants received vitamin D (16 microg/d) and calcium (700 mg/d) supplements. BMD was measured by using dual-energy X-ray absorptiometry. Concentrations of hormones and bone turnover markers were measured in serum. RESULTS: In men, no difference between groups occurred in any BMD measures or in bone turnover markers during year 1 or year 2. The free testosterone index and estradiol increased in the DHEA group only. In women, spine BMD increased by 1.7 +/- 0.6% (P = 0.0003) during year 1 and by 3.6 +/- 0.7% after 2 y of supplementation in the DHEA group; however, in the placebo group, spine BMD was unchanged during year 1 but increased to 2.6 +/- 0.9% above baseline during year 2 after the crossover to DHEA. Hip BMD did not change. Testosterone, estradiol, and insulin-like growth factor 1 increased in the DHEA group only. In both groups, serum concentrations of bone turnover markers decreased during year 1 and remained low during year 2, but did not differ between groups. CONCLUSION: DHEA supplementation in older women, but not in men, improves spine BMD when co-administered with vitamin D and calcium.

EFFECT OF DEHYDROEPIANDROSTERONE SUPPLEMENTATION ON BONE MINERAL DENSITY, BONE MARKERS, AND BODY COMPOSITION IN OLDER ADULTS: THE DAWN TRIAL.

SUMMARY: We present results of a randomized, placebo-controlled trial to examine the effect of 50 mg daily oral DHEA supplementation for one year on bone mineral density (BMD), bone metabolism and body composition in 225 healthy adults aged 55 to 85 years. INTRODUCTION: Dehydroepiandrosterone (DHEA) levels decline dramatically with age, concurrent with the onset of osteoporosis, suggesting a role for DHEA supplementation in preventing age-related bone loss. METHODS: We conducted a randomized, placebo-controlled trial to examine the effect of 50 mg daily oral DHEA supplementation for one year on bone mineral density (BMD), bone metabolism and body composition in 225 healthy adults aged 55 to 85 years. RESULTS: DHEA treatment increased serum DHEA and DHEA sulfate levels to concentrations seen in young adults. Testosterone, estradiol and insulin-like growth factor (IGF-1) levels increased in women (all p < 0.001), but not men, receiving DHEA. Serum C-terminal telopeptide of type-1 collagen levels decreased in women (p = 0.03), but not men, whereas bone-specific alkaline phosphatase levels were not significantly altered in either sex. After 12 months, there was a positive effect of DHEA on lumbar spine BMD in women (p = 0.03), but no effect was observed for hip, femoral neck or total body BMD, and no significant changes were observed at any site among men. Body composition was not affected by DHEA treatment in either sex. CONCLUSION: Among older healthy adults, daily administration of 50 mg of DHEA has a modest and selective beneficial effect on BMD and bone resorption in women, but provides no bone benefit for men.

DEHYDROEPIANDROSTERONE (DHEA), DHEA SULFATE, AND AGING: CONTRIBUTION OF THE DHEAGE STUDY TO A SOCIOMEDICAL ISSUE.

The secretion and the blood levels of the adrenal steroid dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decrease profoundly with age, and the question is posed whether administration of the steroid to compensate for the decline counteracts defects associated with aging. The commercial availability of DHEA outside the regular pharmaceutical-medical network in the United States creates a real public health problem that may be resolved only by appropriate long-term clinical trials in elderly men and women. Two hundred and eighty healthy individuals (women and men 60-79 years old) were given DHEA, 50 mg, or placebo, orally, daily for a year in a double-blind, placebo-controlled study. No potentially harmful accumulation of DHEAS and active steroids was recorded. Besides the reestablishment of a “young” concentration of DHEAS, a small increase of testosterone and estradiol was noted, particularly in women, and may be involved in the significantly demonstrated physiological-clinical manifestations here reported. Bone turnover improved selectively in women >70 years old, as assessed by the dual-energy x-ray absorptiometry (DEXA) technique and the decrease of osteoclastic activity. A significant increase in most libido parameters was also found in women. Improvement of the skin status was observed, particularly in women, in terms of hydration, epidermal thickness, sebum production, and pigmentation. A number of biological indices confirmed the lack of harmful consequences of this 50 mg/day DHEA administration over one year, also indicating that this kind of replacement therapy normalized some effects of aging, but does not create “supermen/women” (doping).
INCREASES IN BONE MINERAL DENSITY IN RESPONSE TO ORAL DEHYDROEPIANDROSTERONE REPLACEMENT IN OLDER ADULTS APPEAR TO BE MEDIATED BY SERUM ESTROGENS.

CONTEXT: The mechanisms by which dehydroepiandrosterone (DHEA) replacement increases bone mineral density (BMD) in older adults are not known. Objective: The aims were to determine the effects of DHEA therapy on changes in sex hormones and IGF-I and their associations with changes in BMD. DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blinded, placebo-controlled trial was conducted at an academic research institution. Participants were 58 women and 61 men, aged 60-88 yr, with low serum DHEA sulfate (DHEAS) levels. INTERVENTION: The intervention was oral DHEA 50 mg/d or placebo for 12 months. MAIN OUTCOME MEASURES: BMD and serum DHEAS, testosterone, estradiol (E(2)), estrone (E(1)), SHBG, IGF-I, and IGF binding protein 3 were measured before and after intervention. Free testosterone and estrogen (FEI) indices were calculated. RESULTS: The average changes in hip and spine BMD (DHEA vs. placebo) ranged from 1.1 to 1.6%. Compared with placebo, DHEA replacement increased serum DHEAS, testosterone, free testosterone index, E(1), E(2), FEI, and IGF-I (all P < 0.001) and decreased SHBG (P = 0.02) in women and, in men, increased DHEAS, E(1), FEI (all P < 0.001), and E(2) (P = 0.02) and decreased SHBG (P = 0.037). The changes in total and regional hip BMD were associated with 12-month E(2) (all P <0.001) and FEI (all P <0.013). The effects of DHEA treatment were eliminated by adjustment for 12-month E(2). CONCLUSIONS: The significant increases in hip BMD in older adults undergoing DHEA replacement were mediated primarily by increases in serum E(2) rather than direct effects of DHEAS.

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