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How to cite

GENAZZANI, A R, PLUCHINO, Nicola. DHEA replacement for postmenopausal women: have we been looking in the right direction? In: Climacteric, 2015, vol. 18, n° 5, p. 669–671. doi: 10.3109/13697137.2015.1042337

This publication URL: https://archive-ouverte.unige.ch/unige:89555
Publication DOI: 10.3109/13697137.2015.1042337

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

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To cite this article: A. R. Genazzani & N. Pluchino (2015) DHEA replacement for postmenopausal women: have we been looking in the right direction?, Climacteric, 18:5, 669-671, DOI: 10.3109/13697137.2015.1042337

To link to this article: http://dx.doi.org/10.3109/13697137.2015.1042337

Published online: 11 May 2015.

CLIMACTERIC 2015;18:669–671

Invited Editorial

DHEA replacement for postmenopausal women: have we been looking in the right direction?

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Key words: DEHYDROEPIANDROSTERONE, DEHYDROEPIANDROSTERONE SULFATE, HORMONE THERAPY, POSTMENOPAUSE

ABSTRACT

Dehydroepiandrosterone (DHEA) and its sulfate represent the most abundant sex steroid in humans. In addition to age-related reduction, serum DHEA shows large interindividual variability. Although cross-sectional studies suggest that lower levels are associated with cardiovascular, cognitive and sexual impairment in women, clinical trials of oral DHEA replacement have failed to show benefits. However, current evidence is too imprecise to draw definite conclusions.

Almost 20 years after the statement by Étienne-Émile Baulieu about dehydroepiandrosterone (DHEA) as a fountain of youth[1], DHEA is still the hormone of controversy. The controversy relates to the spectrum of women who would benefit from DHEA therapy, the dose of treatment and the route of administration. Almost 20 years of basic science and translational studies coupled with cross-sectional, observational and randomized, controlled trials evaluating the role of DHEA in brain function, sexuality, cardiovascular health and metabolic syndrome show that the *evidence* is too imprecise[2]. Have we been looking in the *right direction?*

DHEA serves as a precursor for estrogens and androgens from fetal life to postmenopause, and many people believe that DHEA is merely an inactive precursor pool for the formation of bioactive steroid hormones. On the contrary, DHEA also acts in its own right through dedicated receptors. In the brain, DHEA is a neurosteroid that acts as a modulator of neurotransmitter receptors, such as gamma aminobutyric acid type A, *N*-methyl-D-aspartate, and sigma-1 receptors. In addition, DHEA or DHEA sulfate (DHEAS) may also have effects through its more immediate metabolites, such as 7α-hydroxy-DHEA. Higher concentrations of DHEA are found in brain in comparison with plasma values, with a brain-to-plasma ratio of ~6.5 (see reference 3 for review). *In vitro* and *in vivo* specific effects involve neuroprotection, neurite growth, neurogenesis and neuronal survival, apoptosis, catecholamine synthesis and secretion, as well as antioxidant, anti-inflammatory and antiglucocorticoid effects[3]. Although DHEA is not produced by rat adrenal glands, high DHEA levels in rat brain derive from local synthesis, supporting the biological plausibility of preclinical neuroendocrine studies[3,4].

In human vessels, DHEA binds with high affinity to the endothelial cell membrane, and it is not displaced by structurally related steroids. Binding of DHEA to the cell membrane is coupled to recruitment of G proteins such as G{alpha}i2 and G{alpha}i3 that mediate the rapid activation of intracellular signaling cascades[5].

DHEAS represent the most abundant sex steroid in plasma in humans (more than 1000 times higher than estradiol and testosterone levels)[6–8]. In addition to age-related reduction, serum DHEA shows large interindividual variability. With a mean ± standard deviation concentration of 2.03 ± 1.33 ng/ml, serum DHEA in intact postmenopausal women is particularly variable, with 5th and 95th centiles at 0.55 and 4.34 ng/ml, respectively, for a 7.9-fold difference[8]. In addition to being decreased, on average, by approximately 60% at the time of menopause compared with the maximal values found at the age of 30 years, the 5th and 95th centiles of serum DHEA

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INVITED EDITORIAL

DOI: 10.3109/13697137.2015.1042337

Received 13-04-2015
Accepted 14-04-2015

and its metabolites vary by 8- to 12-fold in 42–74-year-old postmenopausal women[8]. This large difference between low and high serum DHEA levels has a major clinical impact and underlies some biological explanations for divergent results coming from recent cross-sectional studies and interventional trials.

Specifically, among postmenopausal women with coronary risk factors undergoing coronary angiography, lower DHEAS levels were linked with higher mortality from cardiovascular disease and all-cause mortality. Similarly, women with lower DHEAS levels show increased risk of ischemic stroke and reduced flow-mediated dilation of the brachial artery compared to women with normal DHEAS plasma values[9,10]. Higher endogenous DHEAS levels are independently and favorably associated with executive function, concentration, and working memory[11]. Women showing low scores of some domains of female sexual function have higher odds of having a serum DHEAS level below the 10th percentile for the corresponding age[12].

Whether cross-sectional studies support the hypothesis that lower DHEA values might be associated with measures of accelerating aging process and disease, randomized, controlled trials (RCTs) are not fully designed to look in the *right direction*. Interestingly, quite all RCT studies analyzed in two recent reviews[2,13] about the use of DHEA in postmenopausal women do not consider basal level of DHEA/S. In addition, studies differ in the age of enrolled women (45–70 years), dose of treatment (50–1600 mg) and duration of treatment (1–24 months). As a consequence, the evidence is too imprecise or inclusive.

Considering the hormonal basal level is crucial for any replacement therapy. This is specifically mandatory in the case of DHEAS, where age-related decline may be associated with high individual variability. This is also decisive for defining the spectrum of women who would benefit from DHEA therapy and to examine potential side-effects due to hyperandrogenism.

As a consequence, we have previously demonstrated that 1-year treatment, using administration of 10 mg DHEA daily in symptomatic postmenopausal women with lower (5th percentile) baseline DHEAS levels, improved climacteric and sexual symptoms and directly reversed some age-related changes in adrenal enzymatic pathways, including adrenal DHEA and progesterone synthesis[14–17].

In addition, before drawing definitive conclusions on DHEA *replacement* therapy, further aspects need to be better investigated, such as the genetics of DHEA intracrinology and adrenal aging as well their relation with climacteric symptoms. Interindividual variability and its modification after oral treatment may represent a key factor for understanding potential applications.

DHEA replacement therapy is not a panacea for all women. Twenty years of research has the merit to show that DHEA *replacement* therapy must be individualized in women who could benefit from its *replacement*. We recently proclaimed the need to move forward beyond the lack of evidence on DHEA therapy to reconcile basic science with clinical studies[17]. After 20 years, we now hope we are going in the right direction.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Source of funding Nil.

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