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Review

DHEA and mortality: What is the nature of the association?

Claes Ohlsson[a], Liesbeth Vandenput[a], Åsa Tivesten[b,*]

[a] Centre for Bone and Arthritis Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[b] Wallenberg Laboratory for Cardiovascular and Metabolic Research, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Bruna Stråket 16, S-413 45 Gothenburg, Sweden

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ABSTRACT

Although very little is known about the importance of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) in human physiology and pathophysiology, emerging observations imply pivotal roles of DHEA/-S. One such observation is the association between serum DHEA/-S levels and mortality risk. In this review, we focus on the literature addressing DHEA/-S and mortality with the aim to describe and discuss patterns and potential underlying mechanisms. Although the literature reports somewhat inconsistent results, we conclude that several larger population-based studies support an association between low DHEA/-S and risk of death, at least in elderly men. In women, the association may not be present; alternatively, there may be a U-shaped association. In men, most available evidence suggests an association with cardiovascular (CV) mortality rather than cancer mortality. Further, there are biologically plausible mechanisms for an effect of DHEA/-S on the development of CV disease. On the other hand, there is also strong evidence supporting that any disease may lower DHEA/-S. Thus, the cause-effect relation of this association is less clear. Future studies may employ a mendelian randomization approach using genetic determinants of DHEA-S levels as predictors of clinical outcomes, to delineate the true nature of the association between DHEA/-S and mortality.

Contents

Abbreviations: DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; CV, cardiovascular; IHD, ischemic heart disease; AI, adrenal insufficiency; GWAS, genome-wide association study.

* Corresponding author. Tel.: +46 31 342 29 13; fax: +46 31 82 37 62.
E-mail addresses: claes.ohlsson@medic.gu.se (C. Ohlsson), liesbeth.vandenput@medic.gu.se (L. Vandenput), asa.tivesten@medic.gu.se (Å. Tivesten).

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1. Introduction

Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone in human blood and is present in serum mainly as a sulfate ester (DHEA-S) [1,2]. In this review, the term DHEA will be used for the unconjugated form of the hormone, DHEA-S denotes the sulfated form, and DHEA/-S denotes any or unspecified form of the hormone.

DHEA/-S levels decline dramatically with age [3], but the mechanism(s) underlying this decline and its consequences for health are unclear. The potential importance of DHEA/-S in age-related disorders has received a larger interest among the lay public than in the scientific community, and there is a widespread, non-supervised use of DHEA/-S as a dietary supplement for elderly people, particularly in the US [4]. Thus, the public interest in this endogenous substance is far ahead of scientific evidence and understanding.

Although very little is known about the importance of DHEA/-S in human physiology and pathophysiology, emerging observations imply pivotal roles of DHEA/-S. One such observation is the association between DHEA/-S levels and mortality risk. In this review, we focus on the literature addressing DHEA/-S and mortality with the aim to describe and discuss patterns and potential underlying mechanisms.

2. Describing the association

There are numerous studies, with different study designs, that have addressed the potential association between DHEA/-S and mortality risk. In Table 1 we list the larger prospective population-based cohort studies on all-cause mortality published to date [5–15]. Besides these studies, there are studies using other endpoints, designs, specific patient cohorts etcetera that will not be systematically listed in this review, but may be highlighted if they illustrate particular aspects outlined below. Besides mortality risk, an association between DHEA-S and longevity in men has been reported in at least one community-based cohort study [16].

2.1. Certain aspects: Consistency, power and hormone assays

The population-based studies that addressed the association between DHEA/-S levels and future all-cause mortality show somewhat inconsistent findings (Table 1). In this context, two major features of positive versus negative studies can be distinguished. Firstly, it may be a matter of power of the study; the two largest studies both show clear associations, such that the lowest DHEA/-S levels (lowest quartile) are associated with increased mortality risk in elderly men [9,13]. By contrast, some smaller studies do not find this association [8,12,14,15]. Secondly, as will be discussed further below, there may be an important sex difference such that the association is found in men but not in women [5–7,9].

Another important aspect may be the quality of the hormone measurements. Although DHEA-S levels are high in human blood, low sensitivity and precision of immunoassays may result in incorrect measurements in subjects with low levels of DHEA/-S [17,18]. The methods of choice for the measurement of sex hormones, including adrenal steroids, are mass spectrometry-based

Table 1
Prospective population-based cohort studies on DHEA/-S and all-cause mortality.

Reference	Cohort age at baseline	Follow-up time[a]	Association with mortality	Comments
Barrett-Connor et al. [5]	Rancho-Bernardo 50–79 yrs *n* = 242 ♂	12 yrs	↑ all-cause and CV mortality with lower DHEA-S (♂)	• No similar association in an extended cohort with 19-yr follow-up [58]
Barrett-Connor et al. [6]	Rancho-Bernardo 60–79 yrs *n* = 289 ♀	12 yrs	↔ (DHEA-S vs all-cause and CV mortality; ♀)	• No association in an extended cohort with 19-yr follow-up [59]
Berr et al. [7]	PAQUID >65 yrs *n* = 266 ♂, 356 ♀	2–4 yrs	↑ all-cause mortality with lower DHEA-S in ♂ ↔ in ♀	• Similar results in 8-yr follow-up [19]
Tilvis et al. [8]	Helsinki Aging Study 75–85 yrs *n* = 150 ♂, 421 ♀	5 yrs	↔ (DHEA-S vs all-cause and CV mortality)	
Trivedi et al. [9]	Cambridge General Practice Study 65–76 yrs *n* = 963 ♂, 1171 ♀	7.4 yrs	↑ all-cause and CV mortality with lower DHEA-S in ♂ ↔ in ♀	• U-shaped trend in ♀
Glei et al. [10]	Taiwanese cohort 54–91 yrs *n* = 963 ♂ + ♀	3 yrs	(↑) all-cause mortality with lower DHEA-S, ♂ + ♀ pooled	• No sex-specific analysis
Maggio et al. [11]	InCHIANTI 65–92 yrs *n* = 410 ♂	6 yrs	↑ all-cause mortality with lower DHEA-S (♂)	
Cappola et al. [12]	Cardiovascular Health Study >65 yrs *n* = 466 ♂, 484 ♀	Up to 17 yrs	↔ (DHEA-S vs all-cause mortality, ♂ and ♂ + ♀ pooled)	• Trajectories, but not baseline levels, of DHEA-S predicted all-cause mortality • U-shaped trend with baseline levels in ♀
Ohlsson et al. [13]	MrOS Study in Sweden 69–81 yrs *n* = 2644 ♂	4.5 yrs	↑ all-cause and CV mortality with lower DHEA and DHEA-S (♂)	• Association with CV, but not cancer mortality • Mass spectrometry-based assays • Similar results with DHEA and DHEA-S
Forti et al. [14]	Conselice Study of Brain Aging >65 yrs *n* = 416 ♂, 504 ♀	8 yrs	↔ (DHEA-S vs all-cause mortality; ♂ = ♀)	
Haring et al. [15]	Framingham 69–81 yrs *n* = 254 ♂	5 and 10 yrs	↔ (DHEA-S vs all-cause and CV mortality; ♂)	• Neither trajectories nor baseline levels of DHEA-S predicted mortality

CV, cardiovascular.
[a] As defined by the authors.