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

Review

DHEA and mortality – what is the nature of the association?

Claes Ohlsson[1], Liesbeth Vandenput[1], Åsa Tivesten[2]

[1]Centre for Bone and Arthritis Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Wallenberg Laboratory for Cardiovascular and Metabolic Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

E-mail addresses: claes.ohlsson@medic.gu.se; liesbeth.vandenput@medic.gu.se; asa.tivesten@medic.gu.se

Corresponding author: Åsa Tivesten, Wallenberg Laboratory for Cardiovascular and Metabolic Research, Bruna Stråket 16, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden. Telephone +46 31 342 29 13, Fax +46 31 82 37 62, E-mail: asa.tivesten@medic.gu.se

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

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.

Keywords: dehydroepiandrosterone, dehydroepiandrosterone sulfate, mortality

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 methods [18]. We used mass spectrometry-based assays for DHEA and DHEA-S assessment in the MrOS Sweden study, demonstrating an association between DHEA and DHEA-S levels and mortality in elderly men [13].

Looking at the published population-based prospective studies, certain patterns can be distinguished. Because these may give important clues to the underlying mechanisms, they are discussed in more detail below.

2.2. Age heterogeneity

Across all populations, there is a dramatic decline in DHEA-S with increasing age [3]. Previous data suggest that this decline is lost among non-survivors, in which DHEA-S levels are at a constant, low level over the age span of 50-75 years, as compared with survivors [5]. In the MrOS Sweden study, low DHEA and DHEA-S predicted increased mortality risk only among older men aged 69-75 years, but not among men above 75 years of age [13]. Age heterogeneity was also evident in another study [19], in which DHEA-S was a predictor of mortality in men aged 65-69 years, but not 70-74 or >75 years. Because DHEA/-S levels are very low even in the relatively healthier oldest old, it may be speculated that it thereby loses its predictive information with increasing age, as the relative differences turn smaller.

2.3. Sex difference

Several cohorts that analyzed women and men separately report that there is an association in men but not women [5-7, 9]. Accordingly, Enomoto et al. reported an association between DHEA-S and longevity in men but not women [16]. There are some indications that an association may be present in women, but that the association is different and more U-shaped. For example, in two studies [9, 12] there were non-significant U-shaped trends between DHEA-S levels and all-cause mortality risk in women. Supporting the notion that women with either low or high DHEA-S levels are at increased risk, Cappola et al found that disabled older women in both the top and bottom DHEA-S quartiles had a more than 2-fold higher 5-year mortality than those in the middle quartiles [20].

2.4. Cause-specific mortality

In trying to understand the nature of the association between DHEA/-S and mortality, crucial information should come from analyses of underlying death causes. Unfortunately,

because many of the published studies are relatively small, they do not allow further analysis of cause-specific mortality.

A few population-based studies have studied both all-cause mortality as well as cardiovascular (CV) mortality, and in these studies DHEA status was associated with both [5, 9, 13]. Thus, these results are in line with CV disease/death as an important driver underlying the association between DHEA/-S and mortality. Accordingly, in the MrOS Sweden cohort, there was also a very strong association between DHEA/-S and the ischemic heart disease (IHD) subgroup of CV deaths in men [13]. The Massachusetts Male Aging Study found no significant association between low DHEA/-S and the 9-year IHD mortality among 1709 men aged 40-70 years, but did find an association between low DHEA/-S and combined fatal and non-fatal IHD events [21]. However, another population-based study reported no association between DHEA-S levels and incident CVD in 2084 middle-aged men with a mean age of 55 years [22]. Thus, data are somewhat conflicting and there is a need for large population-based studies addressing the potential association between DHEA/-S and CV outcomes.

The other major group of death causes, cancer deaths, are even less studied. In the MrOS Sweden study, we found no association between DHEA/-S levels and cancer mortality in men [13]. However, among male US army veterans, higher DHEA-S levels were associated with reduced risk of death from cancer while there was no association between DHEA-S and CV mortality [23]. Interestingly, we found an association between non-cancer, non-CV deaths and low DHEA/-S levels in the MrOS Sweden study [13]. Taken together, most available data on cause-specific mortality suggest an association between DHEA/-S and CV death, but an association with other death causes cannot be precluded.

3. Potential underlying mechanisms

From the available evidence we can state that there is an association between low DHEA/-S and risk of death, at least in elderly men over approximately 65 years of age. The next question that arises is the one about causality, i.e. is relatively higher DHEA/-S only a marker of better general health or does it have some kind of protective effect? Below we discuss some potential explanations and mechanisms, citing references selected from a relatively rich literature.

3.1. Reverse causality?

Any systemic disease may lower DHEA/-S [24] and DHEA/-S levels decrease rapidly during critical illness [25]. Intuitively, it seems appropriate that the body shuts down anabolic signals, such as DHEA/-S, in severe disease and instead directs energy fuel to an activated immune system to combat the disease/infection [24].

The impact of disease and general poor health on DHEA/-S is evidently a plausible explanation for the association between DHEA/-S status and mortality risk. Thus, there is potentially reverse causality such that low DHEA/-S is a result rather than a cause of disease and death risk. Adjustment for and exclusion of subjects with baseline disease have been performed in many studies, but there may be residual confounding in the analyses. As those who have poor general health (of any cause) at baseline are more likely to die soon after the baseline examination, we excluded the first three years of follow-up in an exploratory analysis of the MrOS Sweden cohort in an effort to reduce the impact of reverse causality [13]. Importantly, we found that the association between DHEA/-S and mortality in this male cohort was unchanged following this exclusion. Although similar analyses have not been performed in other studies, this finding argues against confounding by comorbidity as a sole explanation for the association.

3.2. Causality?

It is obvious that reverse causality is a major issue to consider in this context. On the other hand, there are also data to support a causal association between DHEA/-S levels and disease/death.

3.2.1. Disorders of adrenal hormone production and mortality

Low DHEA/-S levels may derive from diseases of the sex hormone system such as primary adrenal insufficiency (AI; Addison´s disease) or secondary AI due to hypopituitarism. Due to current lack of evidence of benefit, DHEA replacement is not undertaken routinely in clinical practice in patients with AI [26]. If low DHEA/-S is causally associated with increased mortality, we thus would expect increased mortality risk in these patient groups. Indeed, patients with primary AI continue to have increased mortality, mainly from CV and infectious diseases, despite treatment and monitoring [26-28]. Further, patients with secondary AI have an increased mortality mainly due to CV disease [26]. In both these patient groups multiple hormone deficiencies and suboptimal substitution of other hormones may potentially explain the increased mortality. However, unsupplemented DHEA/-S deficiency should be included on that list, and the reduced life expectancy among these patient groups supports the notion that DHEA/-S may confer some kind of protection.

3.2.2. Biologically plausible mechanisms

The presence of a biologically plausible mechanism for an observed association generally strengthens the idea of causality. The fact that studies show an association between low DHEA/-S and CV mortality particularly raises the question whether DHEA/-S has an impact on pathways that modulate the development of CV disease. Indeed, there is relatively ample evidence supporting this notion. For example, experimental *in vitro* and rodent studies

suggest that DHEA/-S may modulate lipid/glucose metabolism, systemic inflammation and vascular biology via different mechanisms, such as PPARα activation, activation of a G protein-coupled receptor or conversion to estradiol, testosterone or other downstream DHEA metabolites [1, 2, 29, 30]. Another mechanism of potential importance is the effect of DHEA/-S to counteract glucocorticoid action [2, 31]. Importantly, because adult rodents do not produce DHEA/-S due to lack of expression of the enzyme CYP17 in the adrenals [32], results from rodent or *in vitro* studies may not necessarily translate to the human setting. Given the biological activity of testosterone and estradiol and that both low serum testosterone and estradiol may predict mortality in elderly men [33-35], the function of DHEA/-S as an alternate source of androgens and estrogens locally in tissues [3] is perhaps one of the most plausible pathways for DHEA/-S actions in humans.

Traditional CV risk factors. DHEA/-S production has been suggested to be of importance for body composition as well as insulin sensitivity and lipid profile [3, 4, 36]. However, four longer (6 months-2 years) trials of DHEA therapy in elderly persons show conflicting results on the effects on body composition and insulin action [37-41].

Vascular biology and atherogenesis. Several studies support direct actions of DHEA/-S on the vascular wall, e.g. on endothelial function/regeneration [2, 42-44], proliferation of vascular smooth muscle cells and vascular remodeling [29, 45, 46]. Further, experimental studies suggest that DHEA/-S may reduce vascular inflammation [47-49]. Several of these mechanisms may contribute to an anti-atherogenic effect that has been described in rodents [50]. Short-term trials on the effect of DHEA therapy on vascular endothelial function in humans have reported both improvement [44, 51] and no effect [52, 53].

Immune functions. DHEA/-S is a modulator of immune functions, which is assumingly very important, yet poorly understood [48, 49, 54, 55]. Given the involvement of the immune system in any acute (or chronic) disease, including cancer, atherosclerosis, and infectious

diseases, further understanding of these effects may provide important clues to the DHEA/-S-mortality association.

"Ageing" mechanisms, oxidative stress and PPARα activation. In the first genome-wide association study (GWAS) of genetic variants associated with serum DHEA-S levels, eight independent single nucleotide polymorphisms were identified [56]. Interestingly, the related genes have various associations with steroid hormone metabolism as well as co-morbidities of ageing including type 2 diabetes, lymphoma, actin filament assembly, drug and xenobiotic metabolism, and zinc fingers - suggesting a wider functional role for DHEA-S than previously thought [56]. Further, data indicate that DHEA/-S may reduce oxidative stress [47, 57]. Notably, DHEA/-S has been shown to be an efficient activator of PPARα [2, 47, 57], which may constitute a possible mechanism for its function as a modulator of immune functions [48, 49, 54] and oxidative stress [47, 57] as well as atherosclerosis [50].

4. Conclusions

Given the decline in DHEA/-S levels with increasing age in both men and women, the potential association between lower DHEA/-S and increased mortality risk is intriguing. Although the literature reports somewhat inconsistent results, we conclude that several larger population-based studies support such an association in men. In women, the association may not be present; alternatively, there may be a U-shaped association, yielding negative findings in studies using smaller cohorts of women and conventional analyses assuming a linear association. In men, most available evidence suggest an association with 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. Possibly, there may be both causality and reverse causality and a vicious circle of disease lowering DHEA/-S that in turn aggravates disease and mortality risk.

5. Future perspectives

How can we gain more insight into the true nature of the association between endogenous DHEA/-S levels and risk of death? The classical solution to the question of causality is to use genetics and a mendelian randomization approach. For this purpose, information from the GWAS of DHEA-S levels may be employed [56], studying a genetic score for DHEA-S levels as a predictor of clinical outcome. This approach will require very large cohorts and research resources. There are pitfalls in this approach as well, as the DHEA-S GWAS may have captured general disease susceptibility genes rather than specific DHEA-S regulators.

Although there are many interesting studies on DHEA/-S actions in rodents, these results must be interpreted with caution, due to the natural lack of DHEA/-S in adults rodents [32]. Instead, we are obliged to studies in humans and primates and it is here we should put our major research efforts in this exciting research field. Further, for the assessment of all sex steroid levels, we should use mass spectrometry-based methods, which soon will become a requirement for publication of sex hormone research in leading journals, also for adrenal steroids [18].

A pivotal question is whether exogenous DHEA may affect e.g. CV outcomes and death in placebo-controlled trials. This would be the ultimate proof of the existence and clinical relevance of a DHEA/-S deficiency syndrome that requires monitoring and treatment. To date, smaller trials of DHEA therapy in elderly persons show conflicting results, e.g. on CV risk factors [37-41]. Further, it is unlikely that these studies combined would yield sufficient power for a meta-analysis regarding mortality or CV events. Notably, most of these trials did

not select persons with DHEA/-S deficiency, so new and larger trials of DHEA therapy in patients with AI and/or elderly subjects with the lowest DHEA/-S levels may be motivated. Importantly, as long as we do not understand the intermediates between DHEA/-S and mortality risk, it may be problematic to let results on any of these intermediates prevent future investments into larger clinical trials.

Grant support

The authors' own work in this review was supported by the Swedish Research Council, the Swedish Foundation for Strategic Research, The Avtal om Läkarutbildning och Forskning research grant in Gothenburg, the Swedish Heart-Lung Foundation, the Marianne and Marcus Wallenberg Foundation, the Lundberg Foundation, the Torsten and Ragnar Söderberg´s Foundation, the Petrus and Augusta Hedlunds Foundation, AFA Insurance and the Novo Nordisk Foundation.

Disclosure

The authors have nothing to disclose.

Conflict of interest

The authors declare no competing interests.

References

[1] A.M. Traish, H.P. Kang, F. Saad, A.T. Guay, Dehydroepiandrosterone (DHEA)--a precursor steroid or an active hormone in human physiology, J Sex Med 8(11) (2011) 2960-2982; quiz 2983.

[2] S.J. Webb, T.E. Geoghegan, R.A. Prough, K.K. Michael Miller, The biological actions of dehydroepiandrosterone involves multiple receptors, Drug Metab Rev 38(1-2) (2006) 89-116.

[3] F. Labrie, V. Luu-The, A. Belanger, S.X. Lin, J. Simard, G. Pelletier, C. Labrie, Is dehydroepiandrosterone a hormone?, J Endocrinol 187(2) (2005) 169-196.

[4] S. Bhagra, T.B. Nippoldt, K.S. Nair, Dehydroepiandrosterone in adrenal insufficiency and ageing, Curr Opin Endocrinol Diabetes Obes 15(3) (2008) 239-243.

[5] E. Barrett-Connor, K.T. Khaw, S.S. Yen, A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease, N Engl J Med 315(24) (1986) 1519-1524.

[6] E. Barrett-Connor, K.T. Khaw, Absence of an inverse relation of dehydroepiandrosterone sulfate with cardiovascular mortality in postmenopausal women, N Engl J Med 317(11) (1987) 711.

[7] C. Berr, S. Lafont, B. Debuire, J.F. Dartigues, E.E. Baulieu, Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study, Proc Natl Acad Sci U S A 93(23) (1996) 13410-13415.

[8] R.S. Tilvis, M. Kahonen, M. Harkonen, Dehydroepiandrosterone sulfate, diseases and mortality in a general aged population, Aging (Milano) 11(1) (1999) 30-34.

[9] D.P. Trivedi, K.T. Khaw, Dehydroepiandrosterone sulfate and mortality in elderly men and women, J Clin Endocrinol Metab 86(9) (2001) 4171-4177.

[10] D.A. Glei, N. Goldman, Dehydroepiandrosterone sulfate (DHEAS) and risk for mortality among older Taiwanese, Ann Epidemiol 16(7) (2006) 510-515.

[11] M. Maggio, F. Lauretani, G.P. Ceda, S. Bandinelli, S.M. Ling, E.J. Metter, A. Artoni, L. Carassale, A. Cazzato, G. Ceresini, J.M. Guralnik, S. Basaria, G. Valenti, L. Ferrucci, Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study, Arch Intern Med 167(20) (2007) 2249-2254.

[12] A.R. Cappola, E.S. O'Meara, W. Guo, T.M. Bartz, L.P. Fried, A.B. Newman, Trajectories of dehydroepiandrosterone sulfate predict mortality in older adults: the cardiovascular health study, J Gerontol A Biol Sci Med Sci 64(12) (2009) 1268-1274.

[13] C. Ohlsson, F. Labrie, E. Barrett-Connor, M.K. Karlsson, O. Ljunggren, L. Vandenput, D. Mellstrom, A. Tivesten, Low serum levels of dehydroepiandrosterone sulfate predict all-cause and cardiovascular mortality in elderly Swedish men, J Clin Endocrinol Metab 95(9) (2010) 4406-4414.

[14] P. Forti, B. Maltoni, V. Olivelli, G.L. Pirazzoli, G. Ravaglia, M. Zoli, Serum dehydroepiandrosterone sulfate and adverse health outcomes in older men and women, Rejuvenation Res 15(4) (2012) 349-358.

[15] R. Haring, Z. Teng, V. Xanthakis, A. Coviello, L. Sullivan, S. Bhasin, J.M. Murabito, H. Wallaschofski, R.S. Vasan, Association of sex steroids, gonadotrophins, and their trajectories with clinical cardiovascular disease and all-cause mortality in elderly men from the Framingham Heart Study, Clin Endocrinol (Oxf) 78(4) (2013) 629-634.

[16] M. Enomoto, H. Adachi, A. Fukami, K. Furuki, A. Satoh, M. Otsuka, S. Kumagae, Y. Nanjo, Y. Shigetoh, T. Imaizumi, Serum dehydroepiandrosterone sulfate levels predict longevity in men: 27-year follow-up study in a community-based cohort (Tanushimaru study), J Am Geriatr Soc 56(6) (2008) 994-998.

[17] C. Wang, D.H. Catlin, L.M. Demers, B. Starcevic, R.S. Swerdloff, Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry, J Clin Endocrinol Metab 89(2) (2004) 534-543.

[18] D.J. Handelsman, L. Wartofsky, Requirement for mass spectrometry sex steroid assays in the Journal of Clinical Endocrinology and Metabolism, J Clin Endocrinol Metab 98(10) (2013) 3971-3973.
[19] L. Mazat, S. Lafont, C. Berr, B. Debuire, J.F. Tessier, J.F. Dartigues, E.E. Baulieu, Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality, Proc Natl Acad Sci U S A 98(14) (2001) 8145-8150.
[20] A.R. Cappola, Q.L. Xue, J.D. Walston, S.X. Leng, L. Ferrucci, J. Guralnik, L.P. Fried, DHEAS levels and mortality in disabled older women: the Women's Health and Aging Study I, J Gerontol A Biol Sci Med Sci 61(9) (2006) 957-962.
[21] H.A. Feldman, C.B. Johannes, A.B. Araujo, B.A. Mohr, C. Longcope, J.B. McKinlay, Low dehydroepiandrosterone and ischemic heart disease in middle-aged men: prospective results from the Massachusetts Male Aging Study, Am J Epidemiol 153(1) (2001) 79-89.
[22] J. Arnlov, M.J. Pencina, S. Amin, B.H. Nam, E.J. Benjamin, J.M. Murabito, T.J. Wang, P.E. Knapp, R.B. D'Agostino, Sr., S. Bhasin, R.S. Vasan, Endogenous sex hormones and cardiovascular disease incidence in men, Ann Intern Med 145(3) (2006) 176-184.
[23] A.C. Phillips, D. Carroll, C.R. Gale, J.M. Lord, W. Arlt, G.D. Batty, Cortisol, DHEA sulphate, their ratio, and all-cause and cause-specific mortality in the Vietnam Experience Study, Eur J Endocrinol 163(2) (2010) 285-292.
[24] R.H. Straub, M. Cutolo, F. Buttgereit, G. Pongratz, Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases, J Intern Med 267(6) (2010) 543-560.
[25] C. Marx, S. Petros, S.R. Bornstein, M. Weise, M. Wendt, M. Menschikowski, L. Engelmann, G. Hoffken, Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: diverse time course of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol, Crit Care Med 31(5) (2003) 1382-1388.
[26] A. Grossman, G. Johannsson, M. Quinkler, P. Zelissen, Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: clinical insights from across Europe, Eur J Endocrinol 169(6) (2013) R165-175.
[27] R. Bergthorsdottir, M. Leonsson-Zachrisson, A. Oden, G. Johannsson, Premature mortality in patients with Addison's disease: a population-based study, J Clin Endocrinol Metab 91(12) (2006) 4849-4853.
[28] S. Bensing, L. Brandt, F. Tabaroj, O. Sjoberg, B. Nilsson, A. Ekbom, P. Blomqvist, O. Kampe, Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency, Clin Endocrinol (Oxf) 69(5) (2008) 697-704.
[29] S. Bonnet, R. Paulin, G. Sutendra, P. Dromparis, M. Roy, K.O. Watson, J. Nagendran, A. Haromy, J.R. Dyck, E.D. Michelakis, Dehydroepiandrosterone reverses systemic vascular remodeling through the inhibition of the Akt/GSK3-{beta}/NFAT axis, Circulation 120(13) (2009) 1231-1240.
[30] J.P. Camporez, E.H. Akamine, A.P. Davel, C.R. Franci, L.V. Rossoni, C.R. Carvalho, Dehydroepiandrosterone protects against oxidative stress-induced endothelial dysfunction in ovariectomized rats, J Physiol 589(Pt 10) (2011) 2585-2596.
[31] M. Kalimi, Y. Shafagoj, R. Loria, D. Padgett, W. Regelson, Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA), Mol Cell Biochem 131(2) (1994) 99-104.
[32] A.H. Payne, D.B. Hales, Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones, Endocr Rev 25(6) (2004) 947-970.
[33] A. Tivesten, L. Vandenput, F. Labrie, M.K. Karlsson, O. Ljunggren, D. Mellstrom, C. Ohlsson, Low serum testosterone and estradiol predict mortality in elderly men, J Clin Endocrinol Metab 94(7) (2009) 2482-2488.
[34] C. Ohlsson, E. Barrett-Connor, S. Bhasin, E. Orwoll, F. Labrie, M.K. Karlsson, O. Ljunggren, L. Vandenput, D. Mellstrom, A. Tivesten, High serum testosterone is associated with

reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden, J Am Coll Cardiol 58(16) (2011) 1674-1681.
[35] J.S. Finkelstein, H. Lee, S.A. Burnett-Bowie, J.C. Pallais, E.W. Yu, L.F. Borges, B.F. Jones, C.V. Barry, K.E. Wulczyn, B.J. Thomas, B.Z. Leder, Gonadal steroids and body composition, strength, and sexual function in men, N Engl J Med 369(11) (2013) 1011-1022.
[36] A. Tchernof, F. Labrie, Dehydroepiandrosterone, obesity and cardiovascular disease risk: a review of human studies, Eur J Endocrinol 151(1) (2004) 1-14.
[37] D.T. Villareal, J.O. Holloszy, Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial, Jama 292(18) (2004) 2243-2248.
[38] K.S. Nair, R.A. Rizza, P. O'Brien, K. Dhatariya, K.R. Short, A. Nehra, J.L. Vittone, G.G. Klee, A. Basu, R. Basu, C. Cobelli, G. Toffolo, C. Dalla Man, D.J. Tindall, L.J. Melton, 3rd, G.E. Smith, S. Khosla, M.D. Jensen, DHEA in elderly women and DHEA or testosterone in elderly men, N Engl J Med 355(16) (2006) 1647-1659.
[39] C.M. Jankowski, W.S. Gozansky, R.S. Schwartz, D.J. Dahl, J.M. Kittelson, S.M. Scott, R.E. Van Pelt, W.M. Kohrt, Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial, J Clin Endocrinol Metab 91(8) (2006) 2986-2993.
[40] D. von Muhlen, G.A. Laughlin, D. Kritz-Silverstein, J. Bergstrom, R. Bettencourt, Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial, Osteoporos Int 19(5) (2008) 699-707.
[41] V. Sherk, C. Jankowski, S. Khosla, D. Kritz-Silverstein, G. Laughlin, S. Nair, K. Shah, D. Villareal, D. Von Muhlen, D. Weiss, P. Wolfe, W. Kohrt, Sex-specific Effects of DHEA Supplementation on Bone Mineral Density and Body Composition: A Pooled Analysis of Four Randomized Controlled Trials. Abstract ASBMR Annual Meeting, J Bone Miner Res 27 (Suppl 1) (2012).
[42] D. Liu, J.S. Dillon, Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to Galpha(i2,3), J Biol Chem 277(24) (2002) 21379-21388.
[43] D. Liu, M. Iruthayanathan, L.L. Homan, Y. Wang, L. Yang, J.S. Dillon, Dehydroepiandrosterone stimulates endothelial proliferation and angiogenesis through extracellular signal-regulated kinase 1/2-mediated mechanisms, Endocrinology 149(3) (2008) 889-898.
[44] M.R. Williams, T. Dawood, S. Ling, A. Dai, R. Lew, K. Myles, J.W. Funder, K. Sudhir, P.A. Komesaroff, Dehydroepiandrosterone increases endothelial cell proliferation in vitro and improves endothelial function in vivo by mechanisms independent of androgen and estrogen receptors, J Clin Endocrinol Metab 89(9) (2004) 4708-4715.
[45] M.R. Williams, S. Ling, T. Dawood, K. Hashimura, A. Dai, H. Li, J.P. Liu, J.W. Funder, K. Sudhir, P.A. Komesaroff, Dehydroepiandrosterone inhibits human vascular smooth muscle cell proliferation independent of ARs and ERs, J Clin Endocrinol Metab 87(1) (2002) 176-181.
[46] M. Ii, M. Hoshiga, N. Negoro, R. Fukui, T. Nakakoji, E. Kohbayashi, N. Shibata, D. Furutama, T. Ishihara, T. Hanafusa, D.W. Losordo, N. Ohsawa, Adrenal androgen dehydroepiandrosterone sulfate inhibits vascular remodeling following arterial injury, Atherosclerosis 206(1) (2009) 77-85.
[47] R. Altman, D.D. Motton, R.S. Kota, J.C. Rutledge, Inhibition of vascular inflammation by dehydroepiandrosterone sulfate in human aortic endothelial cells: roles of PPARalpha and NF-kappaB, Vascul Pharmacol 48(2-3) (2008) 76-84.
[48] J.S. Dillon, Dehydroepiandrosterone, dehydroepiandrosterone sulfate and related steroids: their role in inflammatory, allergic and immunological disorders, Curr Drug Targets Inflamm Allergy 4(3) (2005) 377-385.
[49] C.C. Chen, C.R. Parker, Jr., Adrenal androgens and the immune system, Semin Reprod Med 22(4) (2004) 369-377.
[50] P. Alexandersen, J. Haarbo, I. Byrjalsen, H. Lawaetz, C. Christiansen, Natural androgens inhibit male atherosclerosis: a study in castrated, cholesterol-fed rabbits, Circ Res 84(7) (1999) 813-819.

[51] H. Kawano, H. Yasue, A. Kitagawa, N. Hirai, T. Yoshida, H. Soejima, S. Miyamoto, M. Nakano, H. Ogawa, Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitivity in men, J Clin Endocrinol Metab 88(7) (2003) 3190-3195.
[52] J.J. Christiansen, N.H. Andersen, K.E. Sorensen, E.M. Pedersen, P. Bennett, M. Andersen, J.S. Christiansen, J.O. Jorgensen, C.H. Gravholt, Dehydroepiandrosterone substitution in female adrenal failure: no impact on endothelial function and cardiovascular parameters despite normalization of androgen status, Clin Endocrinol (Oxf) 66(3) (2007) 426-433.
[53] S.P. Rice, N. Agarwal, H. Bolusani, R. Newcombe, M.F. Scanlon, M. Ludgate, D.A. Rees, Effects of dehydroepiandrosterone replacement on vascular function in primary and secondary adrenal insufficiency: a randomized crossover trial, J Clin Endocrinol Metab 94(6) (2009) 1966-1972.
[54] W. Arlt, M. Hewison, Hormones and immune function: implications of aging, Aging Cell 3(4) (2004) 209-216.
[55] J. Hazeldine, W. Arlt, J.M. Lord, Dehydroepiandrosterone as a regulator of immune cell function, J Steroid Biochem Mol Biol 120(2-3) (2010) 127-136.
[56] G. Zhai, A. Teumer, L. Stolk, J.R. Perry, L. Vandenput, A.D. Coviello, A. Koster, J.T. Bell, S. Bhasin, J. Eriksson, A. Eriksson, F. Ernst, L. Ferrucci, T.M. Frayling, D. Glass, E. Grundberg, R. Haring, A.K. Hedman, A. Hofman, D.P. Kiel, H.K. Kroemer, Y. Liu, K.L. Lunetta, M. Maggio, M. Lorentzon, M. Mangino, D. Melzer, I. Miljkovic, A. Nica, B.W. Penninx, R.S. Vasan, F. Rivadeneira, K.S. Small, N. Soranzo, A.G. Uitterlinden, H. Volzke, S.G. Wilson, L. Xi, W.V. Zhuang, T.B. Harris, J.M. Murabito, C. Ohlsson, A. Murray, F.H. de Jong, T.D. Spector, H. Wallaschofski, Eight common genetic variants associated with serum DHEAS levels suggest a key role in ageing mechanisms, PLoS Genet 7(4) (2011) e1002025.
[57] M.E. Poynter, R.A. Daynes, Peroxisome proliferator-activated receptor alpha activation modulates cellular redox status, represses nuclear factor-kappaB signaling, and reduces inflammatory cytokine production in aging, J Biol Chem 273(49) (1998) 32833-32841.
[58] E. Barrett-Connor, D. Goodman-Gruen, The epidemiology of DHEAS and cardiovascular disease, Ann N Y Acad Sci 774 (1995) 259-270.
[59] E. Barrett-Connor, D. Goodman-Gruen, Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women. The Rancho Bernardo Study, Circulation 91(6) (1995) 1757-1760.

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

Reference	Cohort Age at baseline	Follow-up time*	Association with mortality	Comments
Barrett-Connor et al. N Engl J Med, 1986 [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. N Engl J Med, 1987 [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. Proc Natl Acad Sci, 1996 [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. Aging, 1999 [8]	Helsinki Aging Study 75-85 yrs n=150 ♂, 421 ♀	5 yrs	↔ (DHEA-S vs all-cause and CV mortality)	
Trivedi et al. J Clin Endo Metab, 2001 [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. Ann Epidemiol, 2006 [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. Arch Int Med, 2007 [11]	InCHIANTI 65-92 yrs n=410 ♂	6 yrs	↑ all-cause mortality with lower DHEA-S (♂)	
Cappola et al. J Gerontol A Biol Sci Med Sci, 2009 [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. J Clin Endo Metab, 2010 [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. Rejuvenation Res, 2012 [14]	Conselice Study of Brain Aging >65 yrs n=416 ♂, 504 ♀	8 yrs	↔ (DHEA-S vs all-cause mortality; ♂ = ♀)	
Haring et al. Clin Endocrinol, 2012 [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

*As defined by the authors. CV = cardiovascular