Andrenal Androgens and Ageing

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Introduction

Dehydroepiandrosterone (DHEA) and its active metabolite DHEA sulfate (DHEAS), are steroid hormones synthesized and excreted primarily by the *zona reticularis* of the adrenal cortex in response to adrenocorticotropic hormone (ACTH). They exert weak androgenic effects and are therefore considered precursor hormones that need to be transformed to potent androgens or estrogens to exert their effects. The potential clinical roles of DHEA/DHEAS have been studied extensively, as previous epidemiologic and prospective studies associated the age-related decrease of DHEA/DHEAS levels with higher prevalence of degenerative disorders and increased frailty and mortality from all causes in the elderly, attributing to adrenal androgens anti-ageing properties. But do they really suggest that they are hormones related to longevity or just another pointless alchemy against ageing? This chapter summarizes the physiology and pathophysiology of adrenal androgen synthesis, secretion and action and provides current evidence regarding their efficacy in the management of aging-related disorders.

1. The Adrenal androgens

1a. The adrenal cortex; embryology and normal structure

The adrenal cortex is derived from the mesoderm lining the posterior abdominal wall. The fetal cortex begins its development in the 5-week-old fetus. At 2 months of gestation it is already identifiable as a separate organ and is composed of the inner fetal zone (85% of the cortex) and the outer permanent definitive zone. The anatomic relation of the fetal and definitive zones is maintained during gestation; at birth the adrenal glands are 10–20 times larger than the adult gland, relative to kilograms of body weight. After birth, the fetal zone undergoes rapid involution resulting in rapid decrease of the adrenocortical weight in the 3 months following birth. During the next 3 years, the adult adrenal cortex develops from cells of the outer layer of the cortex and differentiates into the three adult zones, the subcapsular *zona glomerulosa*, the *zona fasciculate,* which is the thickest zone (70% of the cortex), and the inner *zona reticularis*.

1b. Biosynthesis of Adrenal Androgens

The adrenal cortex produces many steroid hormones among which the major ones are cortisol, aldosterone and the adrenal androgens. The subcapsular *zona glomerulosa* produces aldosterone while the inner two zones *fasciculata* and *reticularis* appear to function as a unit and produce cortisol, androgens and small amounts of estrogens under the regulatory effect of ACTH and maybe of some other factors produced within the adrenal gland, including neurotransmitters, neuropeptides and nitric oxide. The biosynthetic pathway of the adrenal androgens is shown below (Fig. 1).

Quantitatively, the most abundantly produced adrenal androgens are dehydroepiandrosterone (DHEA) and its sulphated form dehydroepiandrosterone sulphate (DHEAS); the later is the most abundantly produced adrenal steroid. It also has a long half-life and provides a stable pool of circulating DHEA. The ovaries also synthesize DHEA; however, they lack the enzyme DHEA-sulphotransferase so that DHEAS is almost exclusively synthesized and secreted by the adrenals. DHEA is further metabolized to androstenedione [1,2], which may in turn be aromatized to estrone. Whether the adrenals may also produce small amounts of testosterone by further metabolism of androstenedione is controversial [3]. Although DHEA and DHEAS are secreted in greater quantities, androstenedione is qualitatively more important since it is more readily converted to testosterone in peripheral tissues. Roughly, the relative androgenic potency of DHEA, androstenedione, testosterone and dihydrotestosterone (DHT) is 5:10:100:300, respectively [4]. As ACTH is the main regulator of adrenal androgen production in adults, both DHEA and androstenedione exhibit circadian periodicity in concert with ACTH and cortisol and their plasma concentrations increase rapidly following ACTH administration; also they are suppressed by glucocorticoid administration. Because of its slow metabolic clearance, DHEAS does not exhibit diurnal rhythm variation.

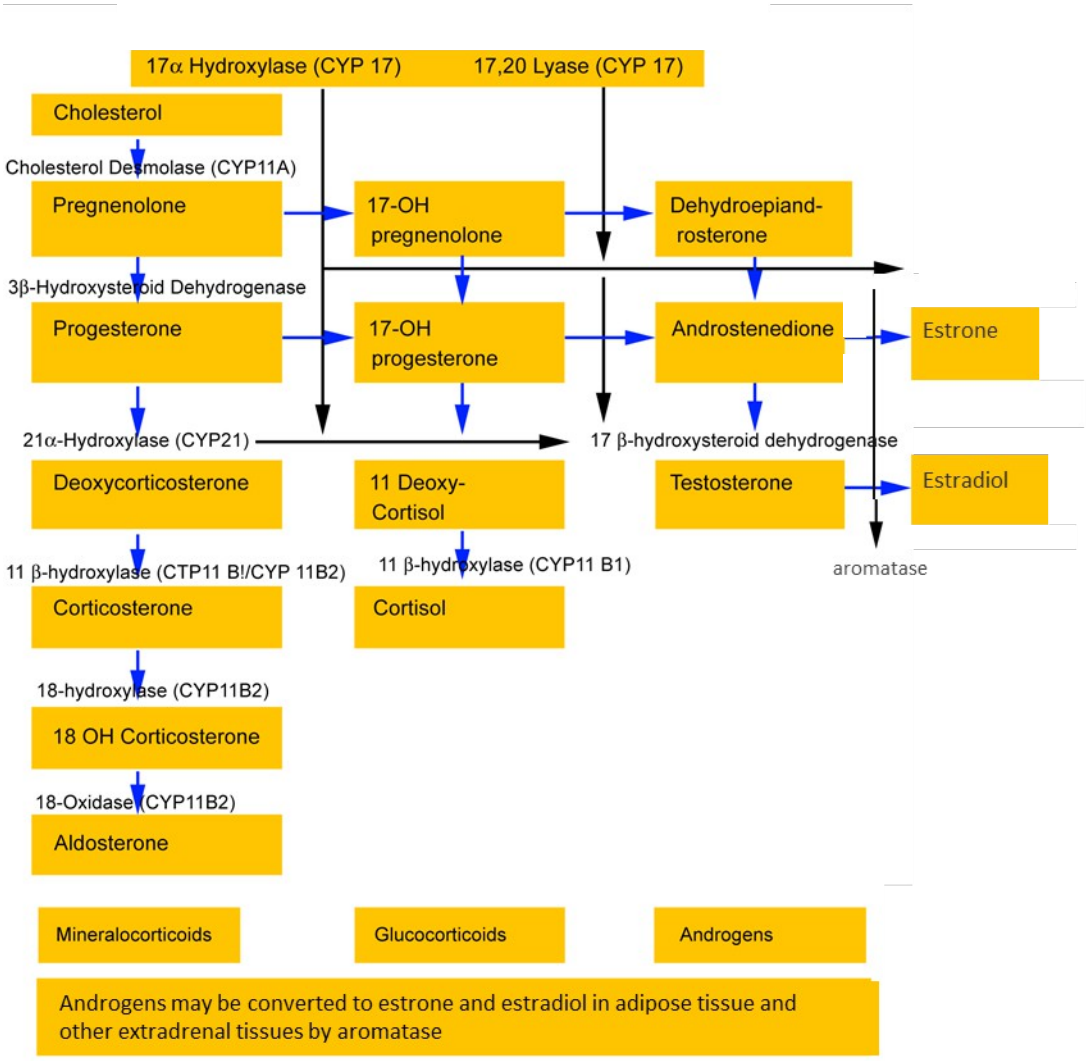

Figure 1. Steroid biosynthesis in the adrenal cortex.

1c. Circulation of Adrenal Androgens

The adrenal androgens are secreted in an unbound state. Soon after their release in the circulation they bind to plasma proteins, chiefly to albumin (90%). Androstenedione, DHEA and DHEAS circulate weakly bound to albumin, while testosterone is bound extensively to the sex hormone binding globulin (SHBG). Bound steroids are biologically inactive; the unbound steroids are free to interact with target cells either to exert their effects or to be transformed into inactive or active metabolites.

1d. Metabolism of Adrenal Androgens; Gender-dependent Synthesis of DHEA/DHEAS

Due to lack or only minor inherent steroidogenic activity, adrenal androgens are precursor hormones (pro-hormones) that need to be transformed to potent androgens or estrogens to exert their effects [5,6]. Their transformation into active sex steroids depends upon the level of expression of the various steroidogenic and metabolizing enzymes in each cell type which allows all androgen-sensitive and estrogen-sensitive tissues to have some control over the local levels of sex steroids according to their needs [7]. Active androgens and estrogens thus

synthesized exert their activity in the target cells with little diffusion, resulting in low levels in the general circulation. This intracrine mechanism serves to eliminate the exposure of other tissues to androgens or estrogens, minimizing unwanted side effects [8-11].

In *males* with normal gonadal function, the conversion of adrenal androgens to testosterone accounts for less than 5% of the total amount of this hormone, and thus the physiologic effect is negligible. In *females* of reproductive age, the adrenal contribution to total androgen production is more important; during the follicular phase, the adrenal precursors account for 2/3 of total testosterone production and 1/2 of DHT production. During midcycle, the ovarian contribution increases, and the adrenal precursors account for only 40% of testosterone production.

Apart from their peripheral conversion to more potent androgens, the adrenal androgens may be also aromatized to estrogens [5,6] or undergo degradation and inactivation (Fig 2). In more detail, DHEA is readily converted within the adrenal gland to DHEAS. DHEA secreted by the adrenal glands and the ovaries is also converted to DHEAS by the liver and the kidneys or it may be converted to Δ4-androstenedione. The adrenally produced DHEAS may be excreted without further metabolism or it may further undergo limited conversion to DHEA. Both DHEAS and DHEA may be metabolized to 7alpha- and 16alpha-hydroxylated derivatives and by 17β reduction to Δ5-Androstenediol and its sulfate. Androstenedione is converted either to testosterone or by reduction of its 4,5 double bond to etiocholanolone or androsterone, which may be further converted by 17 alpha reduction to etiocholanediol and androstanediol, respectively. Testosterone is converted to DHT in androgen-sensitive tissues by 5 alpha reduction and it in turn is mainly metabolized by 3 alpha reduction to androstanediol. The metabolites of these androgens are conjugated either as glucuronides or sulfates and excreted in the urine. Regarding aromatization to estrogens, it was shown that not only androstenedione and testosterone, but also DHEA, may be converted to estrogens in peripheral tissues such as brain, bone, breast and ovaries [7,12]; this might be of importance, especially in women during the menopausal transition (see below) [13,14].

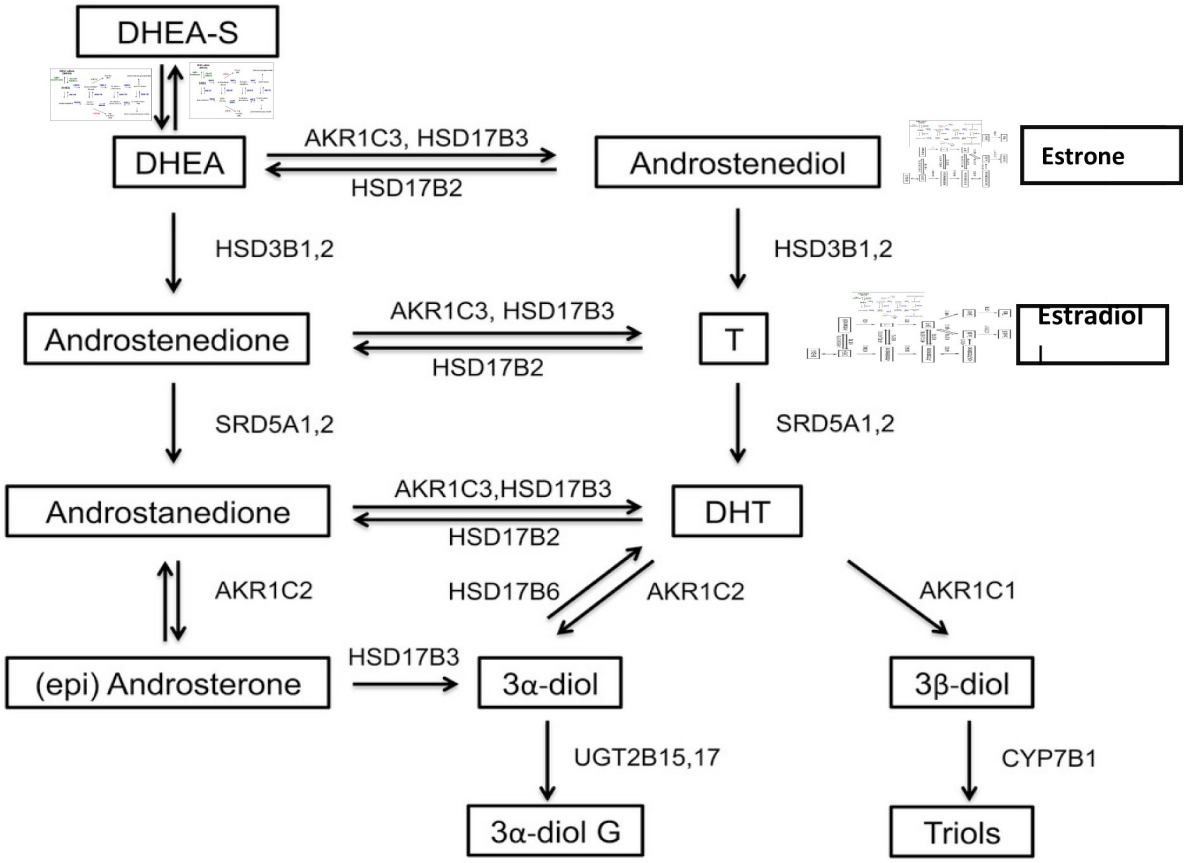

Figure 2. Metabolism of adrenal androgens ; HSD3B, 3 β-hydroxysteroid dehydrogenase isozymes; HSD17B, 17 β -hydroxysteroid dehydrogenase isozymes; SRD5A, 5α -reductase isozymes; AKR1C, aldo-keto reductases 1C; CYP19, P450 aromatase.

1e. Age-dependent synthesis of DHEA/DHEAS

Fetal DHEA and DHEAS fall rapidly after birth and remain low until adrenarche; they then start rising again and peak during the third decade of life after which the serum levels of DHEA and DHEAS progressively decline with advancing age by around 2–5% per year [12,15], so that by menopause the DHEA level has decreased by 60% [16], and by 80-90% of the peak production by the eighth or ninth decade of life [17, 18]. This decline has been termed “adrenopause” in spite of the fact that cortisol secretion does not decline with age or may even increase [19,20]. Adrenopause is independent of menopause and occurs in both sexes as a gradual process at similar ages. A decrease in 17,20-lyase activity may be responsible for the progressive diminution of DHEA and DHEA-S with advancing age [21], although other mechanisms, such as a reduction in the mass of the *zona reticularis* [22] or a decrease in IGF-I and IGF-II [23] have also been proposed. Recent study by Heaney et al. [19] in accordance with previous research [24] found that older subjects exhibited lower

plasma and saliva DHEA levels overall, while with increasing age, the DHEA area under the curve was attenuated and the slope of decline became less steep.

Although DHEAS concentration does not vary throughout the day, DHEA secretion exhibits a diurnal rhythm similar to that of cortisol. Studies have indicated that DHEA secretion is reduced in the morning period resulting in a flatter diurnal rhythm among the oldest old, in contrast to cortisol which remains stable or even increases in the morning [19,25]. The above diurnal rhythms of cortisol and DHEA, lead to an elevated cortisol:DHEA ratio, which is most pronounced in the morning period.

The age-related decline in DHEA/DHEAS levels shows high inter-individual variability [22]. There is a clear sex difference in DHEA/DHEAS concentrations with lower DHEAS concentrations in adult women compared to men [26], while there is also a clear genetic component predetermining circulating DHEA/DHEAS. Notably, data from the largest population-based twin study to estimate the genetic and environmental contributions of diurnal DHEAS concentrations demonstrated that salivary DHEAS is a heritable measure, with genetic effects accounting for 37%–46% of the total variance for the late morning and afternoon age-adjusted measures [27].

Since DHEA is the main source of androgens in women, its age-related decline leads to a corresponding decrease in the total androgen pool. Although there is actually no defined level of androgen below which women can be said to be deficient, the decline of DHEA in postmenopausal women would suggest they are “deficient” in both estrogens and androgens [16]. The declining circulating levels of adrenal androgens with advancing age have been related to clinical symptoms and disorders (see below).

In the last few years, the concept that adrenal androgen production gradually declines with advancing age has changed following the analysis of the longitudinal data collected in the Study of Women’s Health Across the Nation (SWAN) [28]. When the annual serum levels of DHEAS were aligned according to ovarian status [29], it was recognized that despite the overall age-related decline in DHEAS, in the majority of women (85% of those studied) the adrenal androgen production actually rose during the menopausal transition, starting in the early peri-menopause and continuing into the early post-menopause. The DHEAS rise was attributed to the adrenals and not the ovaries, as a similar rise was also observed in intact and ovariectomized women [30]; the gender-related rise of adrenal DHEAS and the time course of that rise that returns to a progressive decline following menopause, implies ovarian influences over adrenal steroidogenesis [31]. Considering previous failure to adequately attribute phenotype, symptoms, and health trajectories to the observed longitudinal changes in circulating estradiol and progesterone [32], the perimenopausal rise in adrenal androgens could potentially suggest a more important role of these hormones in the occurrence of symptoms during the menopausal transition [33]. The observational, epidemiologic, and interventional studies addressing this hypothesis are analyzed below.

1f. Biologic effects of Adrenal Androgens; Cellular and molecular actions

Role as pro-hormones

DHEA possesses pleiotropic effects. Epidemiologic and prospective studies have associated the decline of circulating levels of androgens with the development and progression of degenerative disorders. The exact mechanism of action and clinical role of DHEA and

DHEAS, if any, remain unclear. Due to lack or only minor inherent steroidogenic activity, the adrenal androgens need to be transformed to potent androgens or estrogens to exert their effects on peripheral tissues. Recent data suggest additional direct actions of the adrenal androgens further to those exerted through the androgen and estrogen receptors (see below).

The principal biologic effects of the adrenal androgens typically seen during adrenarche consist mainly of pubic and axillary hair growth and the change of sweat composition that produces adult body odor [34]. During the reproductive years, in *males* with normal gonadal function, the adrenal androgens account for less than 5% of the daily production rate of testosterone and thus the physiologic effect is negligible. When produced in excess however, the adrenal androgens may have no clinical consequences in adult males or result in LH /FSH suppression and oligospermia/infertility. In boys, the adrenal androgen excess is associated with clinical manifestations including premature penile enlargement, early development of secondary sexual characteristics, premature closure of the epiphyseal growth plates and short final height. In *females* the excessive production of adrenal steroids as seen in Cushing syndrome, adrenal carcinoma, and congenital adrenal hyperplasia via peripheral conversion to testosterone and eventually to DHT result in acne, hirsutism and menstrual/fertility defects or even virilization in more severe cases.

Membrane-associated DHEA Receptors

Further to their effect via the estrogen and androgen receptors, recent data support direct actions of DHEA through specific Gi protein-coupled membrane receptors in bovine aortic and primary human umbilical vein endothelial cells (HUVECs) [35-37] through which DHEA activates the endothelial NO synthetase (eNOS) (eNOS/cGMP pathway) [38] and increases the production of nitric oxide (NO), a key modulator of vascular function, by endothelial cells. Such receptors are also seen in the kidney, heart, and liver but at lower level than that in bovine aortic endothelial cells [38] as well as in pulmonary artery smooth muscle cells (PASMCs), where DHEA inhibits voltage-dependent T type Ca-channels [39]. In systemic circulation, a plasma membrane receptor has been suggested in the anti-remodeling action of DHEA involving inhibition of the Akt/GSK-3β signaling pathway [40]. Other studies have shown inhibitory effect of DHEA on proliferation and apoptosis of endothelial and vascular smooth muscle cells independently of both estrogen and androgen receptors [41,42]. The above suggest the presence of a membrane-associated DHEA specific receptor; the molecular structure of this receptor remains to be elucidated.

Cytosolic/nuclear receptors

Steroid action involves cytosolic/nuclear hormone receptors [43]; thus, most of the studies looking at the mechanism(s) responsible for DHEA action focused on such receptors [44]. However, since DHEA can be metabolized into androgens/estrogens, it is not always easy to determine whether DHEA exerts its effects directly through the estrogen/androgen receptors or after conversion to these hormones. There is some new evidence showing that DHEA and some of its metabolites either bind to or activate nuclear receptors such as pregnane X receptor, constitutive androstanol receptor, estrogen receptor-β and peroxisome proliferators activated receptors [45-48]. Through the activation of peroxisome proliferator-activated receptor *alpha* for example, DHEA inhibits the activation of nuclear factor-κB and the secretion of interleukin-6 and interleukin-12, through which DHEA exerts anti-inflammatory

effects [49,50]. 7α-and 7β-hydroxylated derivatives of DHEA also seem to have direct effects on nuclear receptors, but their physiological function is not clear [38]. Finally, DHEA inhibits apoptosis and promotes proliferation of osteoblasts in rats through MAPK signaling pathways, independently from androgens and estrogens [51]; this action could be beneficial for preservation of bone mass and reduction of fracture risk.

Endoplasmic reticulum receptor: sigma-1 receptor

More recently, it has been suggested that DHEA is an agonist of sigma-1 receptor (Sigma-1R) expressed in the endoplasmic reticulum of the heart, kidney, liver and brain [52,53]. Under physiological conditions, the sigma-1 receptor chaperones the functional inositol 1,4,5 trisphosphate receptor at the endoplasmic reticulum participating in the calcium signaling pathway [52, 54]. Animal studies have shown that via sigma-1R, but also by Akt– eNOs signaling pathway stimulation, DHEA may improve cardiac function [55] and exert vasculo-protective effects [56,57]. There is a great volume of data suggesting antioxidant properties of DHEA; overproduction of oxygen-free radicals (oxidative stress) upregulates inflammation and cellular proliferation and is believed to play a critical role in the development of cancer, atherosclerosis, and Alzheimer's disease, as well as the basic aging process [58-61]. DHEA inhibits glucose-6-phosphate dehydrogenase (G-6-PDH) [62,63] and NADPH production. The decrease in NADPH levels results in reduced oxygen-free radical production via NADPH oxidase [63].

In summary, DHEA mediates its action via transformation into androgen and estrogen derivatives acting through their specific receptors, but also via multiple signaling pathways involving specific membrane, cytosolic/nuclear and endoplasmic reticulum receptors.

2. Potential treatment benefits. Treatment modalities

Data from epidemiologic and prospective studies indicate an inverse relation between low circulating levels of DHEA and DHEA-S and a host of ageing-associated pathologies such as sexual dysfunction, mood defects and poor sense of well-being [30,31], as well as higher risk of hospital admission [64], poor muscle strength [65,66] and mobility [67], and higher prevalence of frailty [68,69], insulin resistance, obesity, cardiovascular disease [70] and mortality from cardiovascular disease [71]. At the same time, a positive relation between higher levels of DHEA-S and better health and well-being was documented [72]. Furthermore, animal (primarily rodent) studies have suggested many beneficial effects of DHEA treatment, including improved immune function and prevention of atherosclerosis, cancer, diabetes, and obesity. Therefore, the therapeutic role of DHEA replacement as an anti-ageing factor for the prevention and/or treatment of the above conditions was studied; recent systematic reviews of the reports do not seem promising, however[73-79].

Treatment modalities

DHEA is considered as a hormone in Europe and thus becomes available only by prescription, while in the United States it is considered as a nutritional supplement and is sold over the counter without a prescription. This difference has no scientific foundation and is mostly a matter of declaration. Most DHEA supplements are made in laboratories from a substance called diosgenin, a plant sterol found in soy and wild yams. DHEA supplements were taken off the U.S. market in 1985 because of their unproven safety and effectiveness, but were reintroduced as a dietary supplement after the Dietary Supplement Health and

Education Act was passed in 1994. At present, questionable over-the-counter DHEA preparations lacking pharmacokinetic and pharmacodynamic data are widely used in the United States. There is no standard dosage of DHEA replacement; some studies have used between 25 and 200 milligrams a day, or sometimes even higher amounts. DHEA in current preparations has a long half-life [44], which allows a single intake a day. Target levels of DHEA are around the middle of normal range for healthy young subjects, controlled by a blood sample 24 hr after the last intake [80].

The adrenal androgens are mainly thought to act as prohormones and exert at least part of their action via conversion to androgens and/or estrogens. Previous studies have shown that the end- products of DHEA supplementation depend on the patient's gender, with a non-symmetrical transformation of DHEA favoring androgens in women and estrogens in men [73,81,82]. The above refer to oral administration of DHEA supplements; percutaneous administration of DHEA seems to provoke similar increases in both estrogens and androgens in the two genders [83].

3. Low DHEA/DHEAS levels and associated comorbidities

3a. DHEA and Musculoskeletal disorders

The increasing incidence of fractures with advancing age has been related, among other factors, with the ageing-related reduced muscle mass and strength, that increase the propensity for falling [84,85]. A body of evidence exists on the effect of circulating DHEA/DHEAS on various markers of strength and physical function in older individuals. Studies in elderly individuals support a positive relation between DHEA blood levels and muscle mass [65], muscle strength [65,66] and mobility [67], as well as better self-reported [86] and objectively assessed physical function [87], and measured peak volume of oxygen consumed per minute [88] in elderly with higher DHEA/DHEAS concentrations. In this direction, higher DHEAS levels were associated with increased bone mass density (BMD) in both men [89] and post-menopausal women [90] and inversely related to risk for falls [91]. Finally, low DHEAS levels have been associated with a higher prevalence of frailty, a geriatric syndrome of loss of reserve characterized by weight loss, fatigue, weakness and vulnerability to adverse events [68, 69], and low back pain in both genders and slow rehabilitation of low-back pain in women [72,92,93].

Reports from interventional studies support a therapeutic role of DHEA replacement in ageing-associated musculoskeletal defects. For example, DHEA exerted positive effects on muscle strength, body composition [94-97] and physical performance [98], as well as on bone mass density (BMD) in both lumbar spine and the hip [70,73,95,99-103] when administered to post-menopausal women and elderly people over a period of 52 weeks. The above positive effects on musculoskeletal system were attributed to the DHEA-related increase of insulin-like growth factor-1 (IGF-1) levels [104,105] and bioavailability (decrease of insulin growth factor binding protein-1 [IGFBP-1]) [105] in both men and women and/or to the increase of androgen levels mostly in women [104-106]. Some other data also suggest aromatase activity of primary human osteoblasts converting DHEA to estrone [90], while it was shown *in vitro* that DHEA inhibits apoptosis and promotes proliferation of rat osteoblasts through MAPK signaling pathways, independently from androgen and estrogen effects [51]. The above support a positive effect of DHEA on bone through conversion to estrogens, but also independently from its hormonal end-products. Other studies, however, failed to show a

beneficial effect of DHEA supplementation on muscle function [107-111] or on BMD [94,98,112]; of note all of these studies were conducted over a shorter period (26 weeks only). Whether these conflicting data result from DHEA's mild/moderate effect or from great differences between study designs, such as short duration of treatment and small number of participants, is difficult to say. Overall, the effect of DHEA supplementation on BMD is small in relation to other treatments for bone loss, and no fracture data are available. Therefore, its therapeutic utility in rehabilitation and/or fracture/frailty prevention and treatment protocols for older patients remains unclear.

A recent systematic review [74] of the literature [73, 94,111,113-117] concluded that overall, the benefit of DHEA on muscle strength and physical function in older adults remains inconclusive. Some measures of muscle strength may improve, although DHEA does not appear to routinely benefit measures of physical function or performance. Therefore, consensus has not been reached. Further large clinical trials are necessary to better identify the clinical role of DHEA supplementation in this population.

3b. DHEA, Well-being and Sexual Function

If DHEA's effects on musculoskeletal disorders are inconclusive, its utility for the management of ageing-related poor sense of well-being and sexual dysfunction is a question for top puzzle solvers. What we know so far from epidemiologic studies is that sexual function problems are common among women [118,119] and increase with increasing age [119,120]. The sex steroid hormones estrogens and androgens seem to play an important role in sexual life in women; androgens affect the arousability, pleasure, and intensity of orgasm in women and are particularly implicated in the neurovascular smooth muscle response of swelling and lubrication, whereas estrogens contribute to vulval and vaginal congestive response and affect mood and sexual responses [121]. Conditions such as menopausal symptoms, loss of libido, vulvovaginal atrophy-related sexual dysfunction and poor sense of well-being seen in menopausal and peri-menopausal women were related to the age-associated decline in sex steroids [122]. Furthermore, interventional studies in postmenopausal women with estrogens have shown much improvement on vaginal atrophy and vasomotor symptoms [122-125]; there is also much clinical evidence for the efficacy of testosterone treatment for low sexual function in women [126-131].

Given that a) the adrenal steroids are the most abundant sex steroids in post-menopausal women and provide a large reservoir of precursors for the intracellular production of androgens and estrogens in non-reproductive tissues, b) DHEA levels decline with age, c) pre- and post-menopausal women with lower sexual responsiveness have lower levels of serum DHEAS [132] and d) treatment of postmenopausal women with estrogen and testosterone have shown some improvement in sexual function, it was proposed that restoring the circulating levels of DHEA to those found in young women may improve sexual function and well-being in postmenopausal women [81]. Some early randomized trials that suffered from methodological issues, such as small number of participants, short treatment duration and supraphysiological doses, demonstrated positive effects of DHEA replacement on sexual function and well-being [70,133-136], as well as on relief of menopausal symptoms [136,138]. Similarly, women with adrenal insufficiency treated with oral DHEA replacement demonstrated significant improvement in overall well-being, as well as in frequency of sexual thoughts, sexual interest, and satisfaction [139, 140]. Other studies, however, failed to show any benefit of DHEA replacement on sexual function, well-being and

menopausal symptoms in peri- and post-menopausal women [75,76,105,141,142] and women with adrenal insufficiency [143-145]. A recent review of the available data concluded that current evidence does not support the routine use of DHEA in women with adrenal insufficiency [77]. Furthermore, the more recent placebo-controlled randomized trials that are of superior design compared to the early trials, as they use validated measures of sexual function, have larger sample sizes and are of longer duration, failed to document any significant benefit of oral DHEA therapy on well-being or sexual function in women [73,75,76,78]. It has been hypothesized that the efficacy of DHEA to improve sexual function might be dependent on the route of its administration. In women, androgens and estrogens are produced from DHEA in the vagina tissue. As vaginal atrophy and dryness are common symptoms of estrogen deficiency during menopause, causing dyspareunia and sexual dysfunction [146], a possible benefit that emerged is that vaginally administered DHEA may improve the postmenopausal vaginal atrophy-related sexual dysfunction [147] without increasing the circulating levels of estrogen above the postmenopausal range [81,147-149]. Despite initial promising, beneficial effects on sexual function, again, even with intravaginally administered DHEA, a study failed to show significant benefits [78].

Apart from women, lower circulating levels of DHEA were also related to erectile dysfunction in men. A double-blind, placebo-controlled study that enrolled men with erectile dysfunction treated with *per os* with DHEA 50 mg daily has shown some promise for improving sexual performance in men who had low DHEA blood levels [150]. However, high-quality studies have demonstrated inconsistent results regarding DHEA supplementation for improving sexual function, libido, and erectile dysfunction. Although research in this area is promising, additional well-designed studies are required.

3c. DHEA and mood disorders

The prevalence of depression increases in cohorts of the elderly and has been independently related to high morbidity and mortality [151]. In the central nervous system, DHEA is considered a neurosteroid with a wide range of functions. Animal studies demonstrated several DHEA-modulated neurotransmitters, including dopamine, glutamate, and c-amino butyric acid [38], as well as DHEA-induced increased activity of 5-hydroxytryptamine (5-HT) neurons [152], providing the cellular basis for a potential antidepressant effect of DHEA. Furthermore, typical neuroleptic-like effects of DHEA were displayed in animal models of schizophrenia suggesting potential role of DHEA replacement in the treatment of schizophrenia [153].

Previous studies suggested a strong relation between low levels of DHEA/DHEA-S and major depression in children and adolescents [154], as well as adults and the elderly [155, 156]. On the contrary, higher DHEA-S levels were positively associated with depressive symptoms during the menopausal transition [157] and depression in patients with major depression [158, 159]; whether the elevated DHEA-S levels in the above studies represent increased adrenal activity that could explain the depressive symptoms is not clear, as cortisol was not measured. Moreover, successful treatment of depression was followed by reductions in both DHEA-S [158, 160] and DHEA levels [160], making the relation between DHEA/DHEAS and depression even more confusing.

Several interventional studies have shown that DHEA replacement may improve negative and depressive symptoms [134,135,161-163]. In women with adrenal insufficiency, in

particular, oral DHEA replacement significantly improved the overall well-being, as well as scores for depression and anxiety [108]; similar results were found in the management of the negative symptoms of schizophrenia [163]. Most recent placebo-controlled randomized trials, however, failed to demonstrate a beneficial effect of DHEA therapy on mood, quality of life, perceptions of physical and emotional health, and life satisfaction in postmenopausal women [73,75,76]. Thus the therapeutic role of DHEA on mood disorders remains unclear.

3d. DHEA & psychosocial stress

It has long been suggested that long-term psychosocial stress may cause or contribute to different diseases and symptoms, including atherosclerosis [164], coronary heart disease [165] and acute coronary events [166], as well as accelerated aging [167,168]. Whether DHEA/DHEAS levels are related to psychological stress or not is still debatable. Exposure to prolonged psychosocial stress has been related to reduced [169-171] or elevated levels of DHEA/DHEA-S [172], while some other studies failed to show any clear association in any direction [173,174]. A recent study by Lennartsson et al. demonstrated that DHEA and DHEA-S levels are markedly lower in individuals that report perceived stress at work than in individuals who report no perceived stress at work [175]. Whether this is of clinical importance is not clear.

3e. DHEA & age-related cognitive decline

The incidence of dementia increases exponentially with increasing age in both men and women [176]. The number of elderly people nowadays is the fastest growing segment of the population, which means the related personal, social, and economic burdens are extremely high and could increase dramatically over the next few decades. Therefore, effective prevention/treatment of neurodegenerative disorders is imperative. It has been proposed that DHEA and DHEAS may exert neuroprotective effects in the brain mainly through DHEA-dependent neural stem cell stimulation, genomic activity modulation, and upregulation of androgen receptor levels [177,178], as well as via the DHEA-induced inhibition of pro-inflammatory factor production, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [38] that are involved in the pathogenesis of the amyloid plaques of Alzheimer disease [179]. Higher serum levels of DHEAS have been related to more favorable cognitive function in older people, such as better concentration and working memory [180,181] and higher scores on the Mini Mental State Examination [182]. In this direction, low DHEA/DHEAS levels in particular brain regions were thought to play a role in the development of Parkinson disease, which is the second most common neurodegenerative disorder, just behind Alzheimer [183], while DHEA administration showed some beneficial effect in a primate model of Parkinson disease [184]. Inverse relations between DHEAS levels in saliva [185] and circulation [180] and some domains of memory impairment were also documented, supporting the hypothesis that DHEA supplementation may improve cognition in the elderly; yet solid evidence of associations between the endogenous levels of these steroids and measures of cognitive function is lacking.

No studies with DHEA replacement, either acute administration or chronic (up to 12 months) supplementation, have shown a benefit in cognitive function in healthy elderly populations [75,141, 185-189]. Furthermore, DHEA supplementation failed to show any benefit in patients with Alzheimer disease [190] and had only minimal beneficial effect on specific cognitive domains such as the verbal fluency in older women with mild to moderate cognitive

impairment [191]. Remarkably, some other studies have actually shown a negative effect of DHEAS replacement on cognitive performance [186,192,193]. It should be noted however, that most studies included only small groups of patients and were up to a yearl ong, which is probably not enough time to address the potential role of DHEA / DHEAS in neurodegenerative disorders.

3f. DHEA and Metabolism

Lipids

In women, the effects of sex steroids on lipid profile differ according to the steroid treatment (estrogen or androgen) and to the route of administration. Thus oral methyltestosterone lowers high-density lipoprotein (HDL)-cholesterol [194], and oral estrogen increases HDL-cholesterol and triglycerides and lowers low-density lipoprotein (LDL)-cholesterol and total cholesterol [195,196], while transdermal estradiol and transdermal testosterone have little or no effect on lipids [194,197]. Combined oral estrogen and methyltestosterone is associated with lowering of HDL-cholesterol [198,199]. Considering that DHEA can be converted intracellularly to estrogens and androgens, the effect on the lipid profile could be mixed and may vary between individuals. Most of the recent well designed studies, addressing this issue report no association or even an adverse association (at least in women) [200,201] between plasma levels of DHEA [202,203] or DHEA administration [104,107,196,204,205] and lipid profile.

Body mass index (BMI)

Animal studies support a beneficial effect of DHEA administration on obesity [206-208]. In humans, two sets of longitudinal analyses of studies with women in menopausal transition showed that elevated DHEAS level is negatively related to BMI [30,31]. On the other hand, baseline analyses by Santoro et al [209] did not find much association between DHEAS and BMI, waist-hip ratio, or waist. Similarly, a 2-year, placebo-controlled, randomized, double-blind study involving elderly men and women with low levels of DHEAS, showed no significant effect of DHEA replacement (75 mg per day, *per os*) on body composition measurements [73]. Interestingly, a, recent meta-analysis of intervention studies showed that DHEA supplementation in elderly men can induce only a small positive effect on body composition which is strictly dependent on DHEA conversion into its bioactive metabolites such as androgens or estrogens [210]. Putting together these results, current data regarding DHEA effect on BMI contradict each other, and its usage in clinical practice for body weight management is not suggested or recommended at the present.

Insulin Resistance

DHEA may at least theoretically improve endothelial function [41], and ameliorate local/systemic inflammation [49,50] and oxidative stress [58-61]. These effects in association with DHEAS's inverse relation with body mass index (BMI) [30,31,210] would most probably suggest beneficial effect of DHEA/DHEAS supplement on insulin sensitivity [211]. This hypothesis was confirmed by reports from animal studies in which DHEA replacement had a beneficial effect on insulin sensitivity [207, 208]. In humans studies, however, the results are rather inconsistent. In some studies, the lower levels of DHEA seen with aging have been associated with impaired glucose tolerance, insulin resistance and diabetes [212-215], while in another [216] exactly the opposite relation was shown as higher levels of DHEA were

associated with impaired glucose tolerance and diabetes mellitus in post-menopausal women. The truth regarding DHEA/DHEAS and insulin resistance and its associated conditions gets even more complicated considering conflicting results from interventional studies with DHEA replacement. Thus, an ameliorating effect of long-term treatment with DHEA on insulin resistance was described in a group of middle-aged hypo-adrenal women treated with DHEA [217], but also in groups of elderly men [97] and postmenopausal women [97,217-220] replaced with DHEA. The DHEA dose used ranged between 25 and 100 mg/day *per os* and the duration of treatment varied between 3 and 12 months; in one study transdermal DHEA was used [220]. Most other interventional studies addressing this issue, failed to demonstrate any significant effect of DHEA on insulin resistance/sensitivity [73,94,105,108,111,112,143,205,221-224] and so did a recent review of the available data regarding use of DHEA in women with adrenal insufficiency [77]. Remarkably, Mortola and Yen [140] reported worsening insulin resistance with DHEA replacement in postmenopausal women; in this study however, the number of participants was small (n=6), the duration of treatment short (28 days), and the DHEA dosage supraphysiological (1600 mg/day *per os*). Puting together the above, the relation between DHEA and carbohydrate metabolism is still uncertain.

3g. DHEA & cardiovascular disease (CVD)

CVD represents a serious public health problem; its prevalence increases with advancing age [225]. Low androgen levels have been related to atherogenic profile in men [226,227], while data from acute coronary units have shown transient fall of the testosterone levels in the first 24 hours after myocardial infarction (MI) [228,229], which probably deprives these patients of testosterone's pro-fibrinolytic activity [230-232] and may actually result in increased 30-day mortality rate following acute MI [233]; the above findings suggest a strong relation between sex steroid hormones and CVD morbidity and mortality. Many studies have previously documented significant inverse relations between low DHEA/DHEAS levels and key elements involved in the development of atherosclerosis and CVD, including carotid artery intima-media thickness (IMT) [234,235], oxidative stress [58-61] and endothelial dysfunction [236], independent of other coronary risk factors. Low DHEAS levels were also predictive of severe coronary atherosclerosis on coronary angiography [237], but also of earlier cardiac allograft vasculopathy development in heart transplant patients [238].

These findings are suggestive of anti-atherogenic and cardioprotective effect of DHEA/DHEAS. Numerous epidemiological studies have, therefore, looked at the specific relation between plasma levels of adrenal androgens and CVD. Most have shown that low plasma levels of DHEA/DHEA-S were clearly associated with increased incidence of atherosclerotic vascular diseases [239-243] and cardiovascular morbidity [241,244-250], independently from classic cardiovascular risk factors, as well as with increased CVD-related mortality in elderly men [18,71,251-253] but not in postmenopausal women [18,246,251-253], unless they had pre-existing coronary disease [203].

The plasma levels of DHEA were also inversely associated with the progression [254] and prognosis of heart failure [255], at least in men. The exact pathophysiologic background is still more or less unclear. Some preliminary data in patients with type 2 diabetes mellitus suggest that the adrenal androgens may increase the generation of activated protein C, an important anticoagulant protein that protects from acute coronary events [235]. Furthermore, DHEA may directly stimulate eNOS phosphorylation/activation in endothelial cells and NO

production [38,256,257], which in turn induces vasodilation, and preserves myocardial perfusion [258]. DHEA may also exert anti-inflammatory actions [38,259], through which it may alleviate endothelial dysfunction, atherogenesis [260], and the acute thrombotic complications of atheroma [38,259,261-264] enhanced by systemic inflammation. The protective effects of DHEA on endothelium were also shown in several *in vitro* studies in which DHEA increased endothelial proliferation [41] and protected endothelial cells against apoptosis [59, 265]. Finally, DHEA can alleviate oxidative stress and inflammation in vascular smooth muscle cells (VSMCs) via ERK1/2 and NF-κB signaling pathways, although ig has no effect on their phenotype transition [266].

Other studies, however, have failed to show a significant relation between DHEA/DHEA-S and CVD. In men for example, myocardial infarction occurrence was not altered by DHEA-S levels [267,268], and acute myocardial infarctions were seen in patients with either low [269] or high [270] DHEA-S levels. Similarly in women, lower DHEA-S levels in ischemic heart disease patients versus control were observed in some studies [242,271] but not in others [272]. The reasons that account for the discrepancies among the above studies are not clear. It can be argued that smoking could be a possible confounding variable for both DHEA-S levels and CVD, as smoking increases DHEA-S levels but also increases the incidence of adverse cardiovascular events [273,274]. The discrepancies among the above studies may also be attributed to population variability; for example, in the study by Mazat et al. the relative risk of a 8-year mortality associated with low DHEA-S was 3.4 times higher in males under 70 years compared to older men (odds ratio of 6.5 versus 1.9) [18]. Finally, DHEA-S was checked just once in some retrospective studies, often several years before the adverse cardiovascular events [275].

Whether exogenously administered DHEA could ameliorate key elements involved in the generation and progression of the atherosclerotic process was addressed in humans with atherosclerosis and experimental animal models. The human studies have shown a beneficial effect of DHEA on angiographic evidence of atherosclerosis [241] and improvement of vascular endothelial function [41,276]. Several animal studies have also clearly demonstrated the inhibitory effect of orally administered DHEA on atherosclerosis and plaque progression [277,278] as well as beneficial effects on ischemia–reperfusion injury in the microcirculation [279,280] and cardiac dysfunction [55,56]. Arterial stiffness, which is also considered a risk factor for CVD [281], significantly improved after DHEA replacement in both elderly men and women [282]. Whether the above findings could be translated into DHEA administration in clinical practice for the reduction of CVD morbidity and/or mortality is definitely not well documented and supported by current reports. However, since DHEA is a well-tolerated molecule and an inexpensive drug, additional large multi-centric clinical studies could address its role in the prevention and/or management of CVD.

3h. DHEA & Cerebrovascular disease

Stroke is the third-leading cause for disability worldwide [283]; therefore, early risk stratification for an optimized allocation of health care resources is imperative. The ischemic strokes that account for the great majotiry of all stroke cases (87 percent) occur as a result of acute obstruction of atherosclerotic blood vessels supplying blood to the brain [284]. Considering DHEAS has neuroprotective and antiatherosclerotic properties [248,285,289] and its synthesis has been documented in the brain [179,290,291], the role of DHEA/DHEAS

in acute stroke incidence and outcome was investigated. Interestingly, in women from Nurses' Health Study, lower DHEAS levels were associated with a greater risk of ischemic stroke [292]. In addition, it was suggested that DHEAS circulation levels may actually predict the severity and functional outcome of acute strokes [293,294]. Whether the above findings suggest baseline DHEAS levels could alter stroke management in clinical practice or whether DHEA replacement has a therapeutic potential role in stroke management need to be addressed.

3i. DHEA and pulmonary hypertension

The previously described vasorelaxant properties of DHEA in systemic circulation were also investigated in pulmonary hypertension in animal models and also in humans. Several studies have shown that DHEA replacement could effectively prevent and also reverse hypoxic pulmonary hypertension, pulmonary arterial remodeling, and right ventricular hypertrophy in rats [295-297] in a dose-dependent manner [298] and also prevent the age-related frailty induced by hypoxic pulmonary hypertension in older mice [299]. The effect of DHEA is selective to the pulmonary circulation since the systemic blood pressure was not altered. It was shown that the beneficial effects of DHEA on pulmonary hypertension were at least partly independent of its conversion to estrogen/testosterone and eNOS activation. Some of the potential molecular mechanism by which DHEA promotes pulmonary artery relaxation appear to involve K^+ channel activation, upregulation of soluble guanylate cyclase [296,300,301], downregulation of hypoxia inducible factor 1a (HIF-1a) [302] and by NADPH oxidation-elicited subunit dimerization of protein kinase G 1α [303].

As previously discussed, DHEA may inhibit and reverse chronic hypoxia-induced pulmonary hypertension in rats. Little is known, however, about the effects of DHEA on the pulmonary circulation in humans. The levels of DHEA/DHEA-S in patients with pulmonary hypertension over time have not been determined, but the recent Multi-Ethnic Study of Atherosclerosis (MESA) - Right Ventricle (RV) Study found that higher DHEA levels were associated with increased RV mass and stroke volume in women [304]. Another prospective study suggested a strong inverse correlation between natural DHEA/DHEA-S blood levels and the ten-year mortality in old male smokers and ex-smokers [305]. Prompted by the experimental findings in the pulmonary circulation, a recent study investigated whether DHEA can improve the clinical and hemodynamic status of patients with pulmonary hypertension associated to chronic obstructive pulmonary disease; eight patients with the disease were treated with DHEA (200mg daily orally) for 3 months. The results were very promising as DHEA treatment significantly improved the pulmonary hemodynamics and the physical performance of the patients, without worsening gas exchange, as do other pharmacological treatments of pulmonary hypertension [306].

Putting together the above evidence, there are to date experimental data to support the beneficial role of DHEA treatment in models with pulmonary hypertension, but only only few studies supporting its beneficial effect in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease. Further clinical studies would probably clarify its therapeutic role in the management of pulmonary hypertension in clinical practice.

3j. DHEA and autoimmune disorders

Inflammatory bowel disease (IBD)

DHEA has anti-inflammatory properties [49,50]. Its levels appear to be low in people with ulcerative colitis and Crohn disease, irrespective of patient's age [307,308]. A phase II small pilot trial in patients with active inflammatory bowel disease refractory to other drugs, treated with 200 mg dehydroepiandrosterone per day orally for 56 days [309] showed that DHEA

may decrease the clinical activity of the disease and may even cause a remission. More studies are needed before saying for sure whether DHEA helps IBD or not.

Systemic Lupus Erythematosus (SLE)

SLE is another autoimmune disorder. A number of randomized controlled clinical studies have reported that regardless of patient's age, taking DHEA (50-200mg/day) along with other medications improves quality of life for people with mild to moderate SLE, decreases corticosteroid requirements and reduces the frequency of flare-ups [310], though it probably does not change the overall course of their disease [311-316]. A study had actually shown DHEA replacement may increase bone mass in women with lupus [314]. A 2007 report in the Cochrane Database of Systematic Reviews [79] suggests a "modest but clinically significant impact" of DHEA replacement on health-related quality of life in the short-term for people with SLE; the impact on disease activity was inconsistent. Long- term outcomes and safety remain unstudied.

Rheumatoid arthritis (RA)

DHEA levels have been found to be low in people with rheumatoid arthritis [317,318] and get even lower with glucocorticoid therapy that is often employed in RA [319]. Considering the well-demonstrated immune-suppressive activities exerted by the adrenal androgens and their derivatives [320-322], the utility of DHEA as potential therapy for management of male and female RA patients was studied. Preliminary data from animal studies showed benefits of DHEA treatment in collagen-induced arthritis [323-325]. However, in previous carefully controlled human clinical trials, DHEA treatment produced only modest benefits [326], probably with the exception of female-treated RA patients who benefit the most by DHEA replacement [327]. The noted discrepancy in benefits from DHEA treatment between animals and humans may be related to the little endogenous DHEA in rodents relative to humans because of low levels of cytochrome P450 17α-hydroxylase [179], but also because of different DHEA metabolism between species; remarkably, in rodents DHEA has many highly oxygenated metabolites and a surprisingly complex metabolism that results in production of a multitude highly oxygenated species that may exert the beneficial effects on arthritis [328].

4. DHEA and Adverse Health Outcomes

DHEA supplements are generally well tolerated in studies using oral or percutaneous administration, with daily doses ranging from 25 mg to 1,600 mg. DHEA is an important precursor for estrogen and androgen production. In women DHEA when administered *per os* is mainly converted to androgen metabolites. As a result, some minimal androgenic adverse effects have been reported, including mild acne, seborrhea, facial hair growth, and ankle swelling [38,44,76].

A hormonal etiology has long been suspected for breast and endometrial cancer as several risk factors for each cancer, such as obesity, nulliparity, and early menarche are hormonally related [79,329-331]. The plasma concentrations of the adrenal androgens in premenopausal women were previously associated with higher risk for development of breast cancer [332-334]. Furthermore, DHEA-S levels above a cut off limit predicted disease progression in hypoestrogenised women treated for breast cancer [335]. On the other hand, in vitro studies support an inhibitory effect of DHEA on the growth of human

mammary cancer cells and the growth of chemically-induced mammary cancer in rats [63,336,337]. It was shown that the effect of DHEA in mammary tissue depends on the level of plasma estrogens. Thus, growth inhibition occurs only in the presence of high estrogen concentrations, and growth stimulation occurs in the presence of a low-level estrogen milieu [338,339]. The exact role of DHEA supplementation on breast cancer in humans has not been fully studied. A previous review of clinical, epidemiological and experimental studies suggests late promotion of breast cancer in postmenopausal women by prolonged intake of DHEA, especially if central obesity coexists, and suggests extra caution when DHEA supplements are used by obese postmenopausal women [340]. A more recent review of the medical literature for key papers investigating DHEA physiology and randomized controlled trials of the use of DHEA in postmenopausal women, however, did not find any adverse effect of DHEA supplementation [133].

Unopposed oestrogen is also known to be associated with an increased risk of endometrial carcinoma [329]. DHEA supplementation did not increase the endometrial thickness in postmenopausal women treated with 25 mg/day oral DHEA for 6 months [341] or 50 mg daily for 12 months [342]. In addition, DHEA administered percutaneously for 12 months to postmenopausal women was shown to have an estrogenic effect on the vagina without affecting the endometrium that remained atrophic [343].

In men, DHEA supplements are mainly transformed to estrogen metabolites but also to more potent androgens. As a result, concerns regarding effect of DHEA supplementation on prostate were raised, especially after the finding that about 15% of DHT present in the prostate comes from DHEA metabolism [344]. A 2-year, placebo-controlled, randomized, double blind study involving elderly men receiving DHEA did not show any adverse effects in prostate [73].

As long as long-term safety data for DHEA supplementation are lacking, the American Cancer Society advices caution in its use in people who have cancer, especially types of cancer that respond to hormones, such as certain types of breast cancer, prostate cancer, and endometrial cancer [310].

5. Conclusion

Theoretically, supplementing a pre-hormone is extremely interesting as it would provide peripheral tissues with levels of sex steroids according to local needs and would eliminate the exposure of other tissues to androgens or estrogens, minimizing unwanted side effects. Therefore, DHEA administration is closer to ‘‘hormonal optimization’’ than hormonal supplementation. In older people, lower than normal levels of DHEA/DHEAS were previously related to ageing-associated degenerative disorders, including metabolic and cardiovascular diseases, poor physical performance, mood and memory defects, sexual dysfunction and poor sense of wellbeing. Whether this is just a statistical finding with no practical clinical meaning has been investigated by many interventional studies most of which, however, were of short duration and had small number of participants. Without exception, all recent reviews of the available data regarding DHEA replacement utility for the management of ageing-related disorders do not support its usage in clinical practice [73-79]; no significant adverse or negative side effects of DHEA were reported in clinical studies, but also no significant evidence that low levels of DHEA cause the ageing-related degenerative disorders or that taking DHEA can help prevent/treat them. Thus, current clinical modalities with DHEA

supplements do not comply with evidence-based medicine. Since there are several known biochemical actions by which DHEA could ameliorate disorders affecting the elderly population and is a well-tolerated molecule and an inexpensive drug, additional large multi-centric clinical studies would probably give us a better understanding of its clinical utility in the management of ageing-related disorders. Till then, we should probably reconsider suggesting patients to start on a pro-hormone that would help them only as much as a placebo would help.

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