Abstract
In recent years it has been demonstrated that current replacement therapy with glucocorticoids and mineralocorticoids fails to fully restore health-related quality of life in patients with adrenal insufficiency (AI). Accordingly, replacement of zona reticularis function by DHEA is of considerable interest. Available studies have demonstrated beneficial effects of DHEA on health perception, vitality, fatigue, and (in women) sexuality. DHEA restores low circulating androgens in women into the normal range and increases IGF-1 levels. Side effects are mostly mild and related to androgenic activity of DHEA in women and include increased sebum production, facial acne, and changes in hair status. Replacement consists of a single oral dose of 25–50 mg DHEA in the morning. However, not all investigators have found effects of DHEA on well-being, most likely because of small sample size and short duration of treatment. Thus, to fully explore the role of DHEA in the treatment of AI large trials for 12–24 months are still urgently needed. Until the results of such trials are available DHEA cannot be considered part of standard replacement in AI, but compassionate use of DHEA in individual patients with AI and impaired well-being may be justified.

Keywords: DHEA; Adrenal insufficiency; DHEA replacement

1. Introduction
There is mounting evidence that current replacement regimens for adrenal insufficiency (AI) fail to fully restore well-being in affected patients [32,44]. Lovas et al. (2002) have found reduced health perception and vitality in 79 patients with primary adrenal insufficiency receiving replacement therapy with cortisone acetate and fludrocortisone. In particular, fatigue was reported as a specific feature of adrenal failure despite standard replacement therapy. These data have been confirmed by a series of papers in both primary [22,24] and secondary AI [10,22,25,50]. Recently, an analysis of 989 patients with chronic AI from Denmark reported that patients with AI had a 2.68 times greater rate of affective disorders and a 2.12 times greater rate of depressive disorders compared to patients suffering from osteoarthritis [49]. Furthermore, a recent report from Sweden indicated that primary AI may be associated with increased mortality [7] particularly related to cardiovascular, malignant and infectious diseases. An increase in mortality had previously been reported also for patients with hypopituitarism and had long been attributed to growth hormone deficiency [45]. However, the above-mentioned reports on impaired well-being and increased mortality may indicate that secondary AI contributes to the premature mortality in hypopituitarism, despite the fact that these patients received standard glucocorticoid replacement. These observations suggest that improved replacement strategies for AI are needed.

Current standard replacement therapy for chronic AI consists of glucocorticoids and in primary AI also of mineralocorticoids [2] thereby replacing the secretory products of both the zona fasciculata and the zona glomerulosa of the adrenal. However, secretion of dehydroepiandrosterone (DHEA) and its sulphate ester DHEAS from the adrenal zona reticularis is also nearly abolished in adrenal failure. In fact, DHEA and DHEAS (DHEA(S)) are the most abundant steroids in the human circulation and, for that reason; it is tempting to speculate that lack of these steroids might contribute to the persistent impairment of well-being in patients with adrenal insufficiency receiving glucocorticoids and mineralocorticoids only.
2. Physiology of dehydroepiandrosterone (DHEA) and mechanism of action

The steroidogenic enzyme CYP17 catalyzes DHEA synthesis in the adrenal zona reticularis. It is thought that the vast majority of circulating DHEA(S) derives from this adrenal production, while the gonads contribute only about 5% to circulating DHEA(S) levels. Different from cortisol and aldosterone, DHEA(S) secretion follows a characteristic age-related pattern [38]: DHEA is a major secretory product of the fetal adrenal leading to high circulating concentrations at birth. DHEA(S) serum concentrations then decrease to very low levels until they gradually start to rise again between the 6th and 10th year of age, owing to the increasing DHEA production in the adrenal zona reticularis, a phenomenon termed adrenarche [43]. Peak DHEA(S) concentrations are observed in early adulthood and are then followed by a steady decline down to 20% of maximum levels around age 70 [39]. This age-associated decrease has been termed adrenopause despite the fact that the activity of the zona fasciculata and the zona glomerulosa does not change with age. The age-related decline in DHEA(S) levels shows high inter-individual variability and may be related to a reduction in size of the zona reticularis [41]. Secretion of DHEA is stimulated by ACTH and follows a diurnal rhythm similar to that of cortisol. In contrast, DHEAS with its much longer half-life shows no diurnal variation.

DHEA represents a crucial precursor of human sex steroids and is converted to androstenedione by 3β-hydroxysteroid-dehydrogenase (3β-HSD) and then to active sex steroids by isoenzymes of 17β-HSD, 5α-reductase, and CYP19 (P450 aromatase). Due to the almost ubiquitous expression of these enzymes, conversion of DHEA to sex steroids is widespread in peripheral tissues [35]. It has been estimated that 30–50% of androgen synthesis in men and 50–100% of estrogen synthesis in pre- and post-menopausal women occurs in peripheral target cells [27]. Administration of DHEA in humans leads to significant increases in circulating sex steroids and it has been suggested that the effects of DHEA administration show a sexual dimorphism with predominant generation of androgens in women and circulating estrogens in men [3,5]. In addition, beyond its role as a crucial sex steroid precursor, DHEA is also converted to intermediate steroids of yet unspecified but potentially distinct activity (e.g. androstenediol) [40].

Of specific importance is the observation that DHEA can also be synthesized within the human brain and act there as a neurotransmitter [16,17]. As the brain expresses a multitude of steroidogenic enzymes, DHEA may also be converted to other downstream steroids modulating neuronal activity [47,52]. DHEA has been reported to interact with a variety of neurotransmitter receptors including N-methyl-D-aspartate (NMDA) receptors [6], gamma-aminobutyric acid (GABA) receptors and sigma receptors [33]. An important role of DHEA(S) is derived from recent experimental studies describing a protective effect of DHEA on neuronal survival after oxidative, ischemic or traumatic stress [1,19,28,34].

In addition to its action via conversion to sex steroids or other steroids and its neurosteroidal activity, there is now growing evidence for a direct action of DHEA via specific membrane receptors. High affinity binding sites for DHEA were identified in bovine endothelial cells [30] and it has been shown that DHEA is able to activate endothelial nitric oxide synthase via a G-protein-coupled plasma membrane receptor [30,46]. Furthermore, DHEA affects extracellular signal-regulated kinase I (ERK-1) phosphorylation in human muscular smooth muscle cells [51].

It had been assumed for a long time that DHEA and DHEAS undergo continuous interconversion suggesting that most of the circulating DHEA is generated from peripheral DHEAS [9]. However, while a high percentage of circulating DHEAS is generated from DHEA via hepatic DHEA sulfotransferase (SULT2A1) activity, recent evidence indicates that only minimal amounts of circulating DHEA arise from DHEAS indicating that peripheral sulphatase activity does not contribute significantly to circulating DHEA [23]. This recent observation is of major significance, as for the assessment of the secretory status of the zona reticularis often only serum concentrations of DHEAS is measured. However, inhibitors of DHEA sulfotransferase (e.g. cytokines) may lead to a significant reduction in circulating DHEAS in the presence of normal or even increased DHEA secretion [4] and recent work has demonstrated a dissociation of circulating DHEA and DHEAS levels in acute sepsis [4].

3. DHEA replacement in adrenal insufficiency

Patients with AI suffer from severe impairment of DHEA(S) secretion, and normal circulating DHEAS concentrations virtually exclude the presence of significant adrenal failure. DHEA replacement in patients with AI represents, therefore, also a rational approach to clarify the physiological role of DHEA in a clinical setting.

Pharmacokinetic studies have demonstrated that oral administration of 25–50 mg DHEA in patients with AI restores serum DHEA(S) concentrations into the normal range of young adults [3]. Moreover, it has been shown that a single morning dose is sufficient to maintain normal DHEA(S) concentrations throughout the day [3]. In keeping with its role as a hormone, all studies in patients with AI have invariably shown that administration of DHEA not only increases circulating DHEA(S) concentrations but also leads to significant increases in circulating sex steroids. In particular, women with AI exhibit very low circulating androgen concentrations that are readily increased into the normal range by administration of oral DHEA (25–50 mg).

Beneficial and side effects of DHEA replacement in adrenal insufficiency are summarized in Tables 1 and 2.

3.1. Effects on quality of life

Based on the observation of impaired well-being in patients with AI and a study by Morales et al. [36] in middle-aged subjects suggesting that DHEA administration might positively influence well-being, analysis of quality of life was of major interest in studies investigating DHEA in AI.
Table 1
Beneficial effects of DHEA replacement in adrenal insufficiency

<table>
<thead>
<tr>
<th>Improved health-related quality of life (SF-36)</th>
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<tr>
<td>- general health perception ↑</td>
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<td>- vitality ↑</td>
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<td>- reduced fatigue</td>
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Reduced depression/anxiety (HADS)

Improved sexuality in women

Increase in IGF-1 (e.g. in hypopituitary women receiving GH replacement)

Regrowth of pubic/axillary hair

Table 2
Side effects of DHEA replacement (predominantly in women)

| Increased sebum production                     |
| Acne                                          |
| Hirsutism, alopecia (rare)                    |
| Reduced HDL cholesterol                       |

In the first randomized double-blind study on DHEA administration in adrenal insufficiency [3], 24 women with primary and secondary AI received 50 mg of DHEA or placebo for 4 months. DHEA replacement significantly improved overall well-being, largely due to highly significant improvements in depression and anxiety scores of validated self-assessment questionnaires. Treatment with DHEA also resulted in significant increases in aspects of sexual interest and satisfaction [3]. Improvements in mood and fatigue were also observed by Hunt et al. [24] in patients with primary AI (24 women, 15 men) receiving DHEA 50 mg per day for 12 weeks. This study was followed by another trial in 106 patients with primary adrenal insufficiency employing a parallel group study design. Again, administration of 50 mg of DHEA/day led to significant improvements in health-related quality of life [20]. Another randomized parallel trial employing lower doses of DHEA (20–30 mg) in women with secondary adrenal failure reported an increase in sexual interest and activity and significant improvements in alertness, stamina, and initiative after 6 months of treatment, as judged by the patients’ spouses [25]. In contrast, a study using a parallel group design failed to detect a benefit for well-being and sexuality in 39 patients with primary AI receiving DHEA (25 mg per day) for 9 months [31]. Similarly, in a placebo-controlled randomized study including 20 patients with Addison’s disease (13 men, 7 women), DHEA replacement (50 mg per day) for 4 months did not cause any relevant variation of subjective health scales and sexuality in both sexes [29].

More recent studies investigated the effects of DHEA on well-being in male and female patients with hypopituitarism on maintenance growth hormone replacement [10,50]. Brooke et al. [10] conducted a double-blind placebo-controlled trial over an initial 6 months followed by an open phase of 6 months of DHEA in 26 females and 18 males. Women showed a clear improvement in quality of life assessment in adult-onset GH-deficiency score and in the SF-36 subscales for social functioning and general health perception. Beneficial effects in men were less impressive. In contrast, in the study by van Thiel et al. [50] for 4 months in 15 hypopituitary males and 16 females using a double-blind placebo-controlled cross-over design, DHEA only marginally but still significantly improved the depression score (in women) and health perception (in women and men).

Improved life satisfaction on DHEA compared to placebo was also observed in five young women with hypopituitarism who were studied in a 12-month double-blind placebo-controlled cross-over trial of DHEA replacement in a dose of 50 mg [8].

Clinically most closely related to the loss of zona reticularis function in AI is the suppressive effect of pharmacological treatment with exogenous glucocorticoids on DHEA(S) secretion. Nordmark et al. [37] investigated the effects of DHEA substitution (20–30 mg per day) or placebo in 41 women with systemic lupus erythematosus receiving ≥5 mg prednisolone per day for 6 months. This was followed by 6 months open DHEA treatment to all patients. Health-related quality of life significantly improved in SF-36 scores and women improved also in McCoy’s sex scale during active treatment with DHEA (P < 0.05).

3.2. Effects on IGF-1

In the first published DHEA replacement study in AI patients [3], DHEA led to increased IGF-1 concentrations with DHEA treatment. This increase was observed only in women with primary AI, whereas women with secondary AI showed no clear increase in IGF-1. This suggested that DHEA might act via pituitary GH secretion to influence circulating IGF-1 levels. However, recent studies in patients with hypopituitarism on maintenance growth hormone replacement demonstrated that DHEA replacement increased serum IGF-1 concentrations in female patients by 18% (P < 0.001), but not in male patients. This indicated that the activity of DHEA is not related to changes in growth hormone secretion. In keeping with this observation, Brooke et al. [10] observed that DHEA replacement in patients with hypopituitarism reduced growth hormone dose requirements in female patients on GH replacement. Administration of DHEA led to a 14.6 ± 20% reduction in the dose of GH required for constant serum IGF-1. This effect was maintained for 12 months and was followed by a significant fall in serum IGF-1 2 months after withdrawal of DHEA. No such effect was observed in male patients. As administration in DHEA increases circulating androgen concentrations in women into the normal range while it does little change the androgen concentrations in hypopituitary males receiving androgen replacement, these findings suggest that the IGF-1 increase is related to androgenic effects of DHEA. However, increases in IGF-1 were not observed in other studies [24,31].

3.3. Effects on lipids and insulin sensitivity

Dhatariya et al. [18] studied 28 hypoadrenal women in a single center randomized double-blind placebo-controlled cross-over study, who received 50 mg per day or placebo for 12 weeks. Fasting insulin and glucagon were lower with DHEA and the average amount of glucose needed to maintain

similar blood glucose levels while infusing the same insulin dosages was higher during DHEA administration, whereas endogenous glucose production was unchanged. These findings suggest that DHEA increased insulin sensitivity in hypoadrenal women. However, no effects on DHEA on fasting glucose, insulin, or glucose-insulin-ratio were observed in other studies [11,13,29].

Effects on lipids are more consistent. Already the first study in patients with AI demonstrated a significant decrease of total cholesterol and HDL cholesterol. Similarly in the study by Dhataria et al. DHEA also reduced total cholesterol ($P < 0.005$), and HDL cholesterol ($P < 0.005$), but also LDL cholesterol ($P < 0.05$) and triglycerides ($P < 0.011$). The mechanisms for the reduction in HDL and total cholesterol are most likely mediated by the effects of androgens on increasing hepatic lipase activity, thus impairing hepatic cholesterol formation [48]. Thus, it is anticipated that the effects of DHEA in women are more pronounced than in men. Further studies are needed to analyze this question.

3.4. Muscle function, body composition, and bone

The available data provide no evidence that DHEA improves or changes muscular function in patients with AI [11]. Similarly, despite the fact that DHEA binding sites have been detected on endothelial cells, DHEA replacement in patients with adrenal failure had no impact on endothelial function or cardiovascular parameters despite clear changes in androgen status [12]. It has, however, to be noted that in this 6-month randomized double-blind cross-over study only eight patients were evaluated. Notably, all participants had evidence of concentric left ventricular remodeling by echocardiography prior treatment that remained unchanged throughout the study.

As most studies were of short duration ($<12$ months) changes in bone mineral density are difficult to assess. DHEA led to a small decrease in serum osteocalcin in women with AI [11], whereas bone resorption markers did not change. In one study, no differences were observed. In women with systemic lupus erythematosus, receiving chronic glucocorticoid therapy, DHEA (200 mg per day) prevented bone loss and significantly increased bone mineral density at both the lumbar spine and total hip in female patients in a randomized double-blind trial over 1 year. However, such a dose certainly leads to supraphysiological concentrations of DHEA (S) and circulating androgens ($P < 0.001$) and cannot be considered to represent a true replacement dose. Longer studies in a sufficient number of patients are needed to clarify these issues.

3.5. Immune effects of DHEA

The effects of DHEA on the immune system are of great interest. Studies in patients with systemic lupus erythematosus have demonstrated that DHEA can modify disease activity including the frequency of flares [42]. In patients with Addison’s disease baseline circulating regulatory T-cells are reduced compared to controls. Oral DHEA treatment had a bimodal effect on naturally occurring regulatory T-cells and lymphocyte FoxP3 expression. Natural killer cell numbers fell during DHEA treatment and lymphocyte proliferation was increased [15]. However, it has to be noted that the sample size of this study was small (ten patients) and that these results were generated in an open-label uncontrolled fashion.

3.6. Side effects

Serious adverse events have not been published so far in randomized controlled trials of DHEA replacement in AI. However, androgenic side effects have been reported in women receiving DHEA (mild facial acne, increased sebum production, and changes in hair status). Because the skin in women with AI often appears to be dry, some patients welcome higher sebum secretion and the observed regrowth of pubic and axillary hair is also generally considered positive. Growth of axillary and pubic hair from Tanner stage I to stage III was reported in a woman with primary AI receiving DHEA over 2 years [26] and also in women with hypopituitarism [25].

However, in a significant percentage of women with AI, a dose of 50 mg per day is too high and dose reduction may become necessary. Interruption of DHEA replacement usually results in a reversal of the reported side effects.

4. Conclusions

Despite a multitude of reports suggesting that DHEA may improve health-related quality of life and sexuality, DHEA is still not part of routine replacement therapy in AI, as large phase 3 trials would be required to securely establish the role of DHEA for replacement therapy in adrenal insufficiency.

Of major interest is the question why study results are often not fully consistent. Here, several observations are of major importance. The effects of DHEA differ clearly between men and women, as in males the testes (or the replacement of testicular function) provide large amounts of circulating androgens, whereas in women with AI a severe deficiency of circulating androgens is present, which is restored into the normal range by oral administration of DHEA, as has been shown with extraordinary consistency in all studies. Thus, while in women repletion of androgens may substantially contribute to the effects of DHEA replacement, it is expected that in men DHEA effects are largely restricted to non-androgenic actions. It is, therefore, of utmost importance to analyze men and women separately in future trials. Another important information is the fact that many changes are only detectable after sufficient duration of replacement. This has again been shown in the recent study by Brooke et al. in patients with hypopituitarism on growth hormone replacement. Clear benefits were seen only at 6 months but not at 3 months [10]. Thus, many studies suffer from too short study duration and may, therefore, have missed beneficial effects of DHEA. Furthermore, many studies lack adequate power to make detection of beneficial effects of DHEA likely [12,14,31]. Finally, a major aspect in all studies...
interested in health-related quality of life is the selection of the patients. It has now been established that patients with AI have a clear impairment of health-related quality of life with reduced general health perception, vitality, and increased fatigue. However, the impairment of subjective health status varies widely among patients, and some patients with AI may not differ significantly from the reference population. It is unlikely that patients with normal health-related quality of life at baseline will demonstrate a benefit of DHEA replacement in trials, as it is highly unlikely that DHEA has the potential to create supranormal well-being. If all these aspects are taken into account, most of the differences in the available randomized controlled double-blind trials are easily explained.

Future trials should, therefore, take great care to select a sufficient number of subjects, analyze women and men separately, use a sufficiently long duration of replacement therapy, and avoid the selection of a subgroup of patients with AI with unimpaired well-being, not representative for the majority of patients with AI.

5. DHEA – why, when, and how much

Based on the available evidence that DHEA has the potential to improve well-being in AI it seems to be justified to treat individual patients with DHEA on a compassionate basis. Pre-requisite is a clearly impaired well-being or sexuality with current standard replacement therapy that should be quantified by validated questionnaires (e.g. SF-36). Treatment is experimental and potential risks should be explained in detail to the patient. The starting dose is 25 (50) mg DHEA/day given as a single oral dose in the morning, and the intended treatment duration should be a minimum of 4–6 months. Compliance to treatment can easily be monitored by measuring DHEAS aiming at target DHEAS concentrations in the normal range of young adults.

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