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Chapter 24

STEROID SECRETION AND PSYCHOLOGICAL WELL-BEING IN MEN 40+

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ABSTRACT

Current demographic statistics show that modern societies are rapidly aging. Aging in general is accompanied by an increased susceptibility to physical and mental disease as well as an increased risk of mortality. Health care costs are expected to rise enormously. Therefore, successful aging with less disease burden and dependency is emerging as one of the most crucial health care goals of the upcoming decades. Over the last 20 years, research on successful aging in men has increasingly focused on age-related hormonal changes. A gradual reduction in testosterone and dehydroepiandrosterone beginning around the age of 40 has been well documented. At the same age, other steroid hormones including estradiol and cortisol also show an age-dependent progressive change. These changing patterns of steroid hormone secretion play an essential role for general health and psychological well-being in males over 40.

In the following chapter, we will discuss the underlying biological mechanisms of age-related hormonal alterations and elucidate their influence in the context of psychological, sexual, cognitive and physical areas of life in aging men. Considering these widespread consequences due to age-related hormonal changes, we will also discuss the clinical implications for men facing these conditions. Apparent good health or specific lifestyle factors were shown to slow down age-related hormonal changes. Since clinical conditions cannot be prevented for every male by maintaining good health or establishing a healthier lifestyle, hormone replacement represents a reasonable opportunity to overcome certain psychological, sexual, cognitive and physical

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impairments caused by age-related steroid alterations. Besides individual psychological support for the successful management of severe symptoms of age-related hormonal changes, targeted psychoeducation at a population-based level would, in the long term, be one possibility to inform men about their options and to support them in countering these largely neglected disorders.

INTRODUCTION

Current demographic statistics show that modern societies are rapidly aging (Revision of the official United Nations population estimates and projections from 2012). Aging in general is accompanied by an increased susceptibility to physical and mental disease, as well as an increased risk of mortality [1-4]. As a result, health care costs are expected to rise enormously.

An age-related increase in mild to moderate depressive symptoms has been documented for males up to the age of 80 [4-7]. For example, from the 50-64 age group to the over-65 age group, there is an 11.1% rise in mild depressive symptoms [4]. In parallel to this trend, the epidemiology of suicide rates also shows a steady increase from young men to men up to the age of over 75 [8, 9]. Moreover, there is a strong correlation between aging and increased sexual dysfunction. Men aged 70-80 years are nearly seven times more likely to experience erection difficulties than men aged 50-59 years [10, 11]. In addition, the diminishment of cognitive abilities increases during the aging process [12]. Cognitive skills such as speed of processing, working memory, and long-term memory are associated with a continuous decline with age [12]. Furthermore, age-related bodily changes such as an increase in fat mass, a decrease in muscle mass and a loss of bone mineral density typically start to occur around the age of 40 [13-15]. These changes lead to a higher general frailty and increased risk of bone breakage after falls [16]. As a consequence of this combination of psychological, sexual, cognitive and physical changes, one of the greatest fears of aging people is the loss of the ability to live independently [17].

Therefore, successful aging with less disease burden and dependency is emerging as one of the most crucial health care goals of the upcoming decades [18]. Over the last 20 years, research on successful aging in men has increasingly focused on age-related hormonal changes and their consequences for physical and mental health. A gradual reduction in testosterone (T) starting around the age of 40 years, often referred to "andropause" or "late onset hypogonadism," has been well documented [19, 20]. *Andropause* defines a syndrome that requires the presence of both clinical symptoms and biochemical conditions. A decrease in sexual satisfaction or a decline in the general feeling of well-being, along with diminished serum levels of total (tT) and free T (fT), constitutes the andropause syndrome in older men [21]. *Late onset hypogonadism* is more strongly related to sexual functioning. It is defined similarly, in terms of tT serum levels below 11nmol/l, a fT level below 220pmol/l and the following three sexual symptoms: decreased frequency of morning erection, decreased frequency of sexual thoughts, and erectile dysfunction [22]. In the following, the term andropause will be used for the age-related continuous drop in T and the associated sexual symptomatology.

Although research has shown that andropause and late onset hypogonadism are strongly related to the decline in the marker T, it is important not to neglect other relevant steroid changes and their comparable impact on the aforementioned areas such as psychological well-being, sexual health, cognition and physical health. In the following, we will therefore provide an overview of how these different areas of life are affected by changes in steroid hormones over the course of the lifetime, and will derive the clinical implications for men facing such conditions. Furthermore, an overview of the efficiency and safety of hormone replacement protocols for specific psychological, sexual, cognitive and physical conditions will be given. Finally, we will discuss the need for systematic psychological support for the successful management of severe symptoms of andropause and the consequences of the accompanying changes in steroid secretion.

HORMONAL CHANGES IN MEN AGED OVER 40 YEARS

Testosterone (T) is the major male sex hormone and affects various biological systems and psychological dimensions. T is mainly produced in the Leydig cells of the testes and most of the circulating T is bound to sex hormone-binding globulin (SHBG) (44%), albumin (50%) or cortisol-binding globulin (4%) [23]. Only 2% of the circulating T remains free. Active or bioavailable T (bT) consists of free and albumin-bound T (52%) [24]. In 1991, Gray and colleagues conducted a meta-analysis indicating that healthy men have higher overall T levels than ill men [25]. Furthermore, for healthy men, a continuous T decline related to age has been reported, with an annual decline of 0.4% for tT and 1.2% for fT. Data from 250 healthy non-obese and 50 obese men confirmed the age-related T decline, even after controlling for body mass index (BMI), smoking or interactions with other hormones [26]. While these studies were based on cross-sectional data, the Baltimore Longitudinal Study of Aging and the Massachusetts Male Aging Study (MMAS) were the first studies to report an age-related T decline for longitudinal data [19, 20]. Besides baseline, follow-up was assessed in the MMAS seven to ten years later for 1156 healthy men aged 40 to 70. Feldman and colleagues [20] reported an annual decline of 1.6% for tT and of 2-3% for fT, resulting in a 30% loss of tT and 40-60% loss of fT for men over the age of 60 years. This more pronounced decline in fT is due to a parallel increase in sex hormone-binding globulin (SHBG) levels, lying at 1.6% per year [19, 20].

Dehydroepiandrosterone (DHEA) is synthesized by the adrenal glands, and works as a precursor hormone of different androgens and estrogens [24]. DHEA affects different body systems (e.g., immunity, musculoskeletal integrity, and cardiovascular health) and is assumed to be anti-ageing [27]. A gradual decline in DHEA with age has been well documented [20, 28-31]. Only 10-20% of the amount of DHEA found in young individuals remains in elderly people aged 70-80 [32-34]. This decline seems to be associated with an increased risk of osteoporosis, atherosclerosis and decreased immune function [32].

Estradiol (E2) is the main biologically active estrogen in the human hormone system. While in men, only about 20% of E2 is produced by the Leydig cells, most of the circulating E2 is metabolized via the aromatase enzyme in peripheral tissues from androgens and mainly from T [35]. There is an age-related increase in aromatase activity [36] and an age-related

increase in subcutaneous fat [37], which is a main site of aromatization of T to E2 [38]. Thus, when assessing age effects on E2 in men, fat mass or body mass index (BMI) should be controlled for. While in one study in 810 men aged 24-90 years, bioavailable E2 (bE2) was shown to decrease independently, total E2 (tE2) levels decreased with age only when controlling for confounders (weight and BMI) [39]. Additionally, an age-related decline in bE2 levels was reported in 419 men aged 24-79 years, but no such decline was found for tE2 levels (even after adjusting for fat mass) [35, 40]. In 403 healthy men aged between 73 and 94, Van den Beld and colleagues [41] reported that both tE2 and free E2 (fE2) levels decreased with increasing age. These findings were confirmed by Orwoll and colleagues [42]. Recent studies using modern hormone analysis methods have shown an age-related decline for tE2 [43, 44] and fE2 levels [45]. However, Kozloski and colleagues [46] found no age effect for salivary fE2, and an age-related increase in tE2 has even been reported [45]. To summarize, so far, the literature shows inconsistent findings for E2 level changes in aging men. Two of the major reasons for these inconsistencies are the low levels of circulating E2 in males and the differing sensitivity of the assays used to analyze different body fluids for the hormonal level.

Table 1. Age-related changes in steroid and SHBG concentrations in men

Hormone	Change across the lifespan	Change in %	References
Testosterone (T)	↓	Decline in tT: 1.6% per year Decline in fT: 2-3% per year	Feldman et al., 2002; Gray et al., 1991; Harman et al., 2001
Estradiol (E2)	(↓)	Moderate age-related decline	Ferrini & Barrett-Connor, 1998 Vermeulen et al., 2002
Dehydroepi-androsterone (DHEA)	↓	Decline of 80-90% in DHEA in 70-80-year old-men compared to young individuals	Genazzani et al., 2007; Parker, 1999
Cortisol (C)	↑	Increase in mean C levels by 20-50% between 20-80 years of age	Karlamangla et al., 2013; Kern et al., 1996; Van Cauter et al., 1996; Van Cauter et al., 2000
Progesterone (P)	≈	Remains unchanged	Kozloski et al., 2014; Oettel & Mukhopadhyay, 2004
Sex hormone-binding globulin (SHBG)	↑	Increase of 1.6% per year after the age of 40	Feldman et al., 2002; Harman et al., 2001

Declining concentrations are indicated by ↓; increasing concentrations are indicated by ↑; no change is indicated by ≈; moderate changes are represented in brackets (e.g., (↓)).

Cortisol (C) is a primary agent of the neuroendocrine response to stress as well as an important factor in regulatory processes of the immune system, metabolic activity or

cognition [47]. In the MMAS, no age-related change in C levels was observed [20], probably due to varying time points of blood sampling within four hours after awakening. Van Cauter and colleagues [48] reported an increase in mean plasma C levels of 20-50% between the ages of 20 and 80 years, and replicated these findings for 24-hour plasma cortisol profiles [49] and samples drawn during nocturnal sleep [50]. In a recent study with controlled sampling time points, an increase in the salivary C levels with age was reported for 1693 subjects, while older age and male gender were independently associated with higher cortisol peak, nadir, and area under the curve (AUC) [51]. Similar findings for hair cortisol measurements were reported in a study of 654 participants aged 47-82, where hair cortisol concentrations (HCC) increased with age and were higher for males than for females [52].

Progesterone (P), an important precursor of different steroid hormones, is mainly produced by men in the Leydig cells and to a smaller extent in the adrenals. P also exerts effects on several organ systems [53]. In the Luric-Jenapharm study, serum P levels of 1015 men aged 20-80 were measured cross-sectionally, and no age-related changes were found [53]. The National Social Life, Health, and Aging Project, a US-longitudinal study, reported no age-related P decline for 1220 men in wave one and for1325 men in wave two [46]. The age-related changes in steroid concentrations in men are summarized in table 1.

BIOLOGICAL MECHANISMS UNDERLYING AGE-RELATED HORMONAL ALTERATIONS

Recent literature favors two explanations for the biological causes of the reported T and E2 decline in aging males, which will be summarized in the following. First, an attrition of the T and E2-producing testicular Leydig cells and a diminished secretory capacity occurs as a function of age [54]. While a healthy man at the age of 20 is provided with more than 700 million Leydig cells, a reduction rate of 80 million per decade of life leads to an amount of 300 million Leydig cells at the age of 70 [55, 56]. Along with this degeneration and dissolution of Leydig cells, a decreased secretory capacity of T and E2 for elderly compared to young men has been reported from various stimulation tests [57-60].

Second, at the hypothalamic-pituitary level, age-related changes in the amplitude and frequency of gonadotropin-releasing hormone (GnRH) pulses [61] and subsequent luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion occur in men [62, 63]. Leydig cell function, including T secretion, is regulated through LH [64]. While an age-related decrease in LH pulse amplitudes is observed, the pulse frequency seems to increase [65-68]. One explanation seems to be the diminished GnRH release with age provoked by the hypothalamic GnRH pulse generator [62, 63]. This assumption is supported by the fact that stimulation with exogenous GnRH shows no difference in the subsequent LH secretion in young compared to old men, indicating equal pituitary responsiveness [64]. The paradoxical findings of an age-related decrease in LH pulse amplitudes and consistently elevated mean LH levels in the elderly [20] can be explained by the observation of increased plasma half-life of LH and increased LH pulse frequency in elderly men [63, 64, 68, 69]. Taken together, these age-related biological mechanisms lead to markedly lower T and slightly lower E2 levels in older compared to younger men.

Although T is the major source (about 80%) of plasma E2, due to its conversion via the aromatase enzyme, the age-related T decline is only slightly depicted in plasma E2 levels. The aromatase activity and the body fat mass, which is a main site of aromatization of T to E2, increase with age [36, 37], and both physiological conditions increase T conversion to E2 in older men. Therefore, a smaller decrease in E2 compared to T in elderly men is observed [35, 70].

The underlying biological mechanism which leads to a continuous DHEA decline is not fully understood [32]. Since steroids produced in the adrenals such as C do not decline [49, 51], the DHEA decline seems to be related to changes in the zona reticularis, which is the inner layer of the adrenals and the production site of DHEA and its sulfate (DHEAS) [32]. There are several potential causes which may explain this age-related reduction, such as a reduced number of LDL receptors, which are responsible for the import of plasma cholesterol, reduced hydroxymethylglutaryl coenzyme A reductase, which regulates cholesterol biosynthesis, reduced levels of ACTH receptors, or impaired signal transduction [32].

In line with these tissue-specific age-related alterations, a morphological reduction of the entire zona reticularis in relation to the other layers (zona fasciculata and glomerulosa) in aging men has been documented in some studies [71, 72], while others did not find such a decrease [73].

Van Cauter and colleagues [74] termed the elevation of basal C levels a hallmark of aging. An age-related C increase is due to different alterations of the hypothalamic-pituitary-adrenal (HPA) axis [75]. This has been demonstrated in several animal studies: In male rat brains, a reduction of corticosteroid receptors of type I (mineralocorticoid receptor) and of type II (glucocorticoid receptor) has been found as a function of age [76]. In the male rat, mRNA and protein levels of both receptors decrease with age. Furthermore, an increased secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, along with a functional decrement in corticosteroid negative feedback, has been reported [76]. In humans, both an age-related elevation of the number of CRH neurons and subsequently in the CRH secretion has been observed at the hypothalamic level [77]. Additionally, an age-related increase in adrenocorticotropin-releasing hormone (ACTH) and C secretion has been documented [52, 78-80], but has not been confirmed by all authors [e.g., 81]. Overall, the findings indicate an age-related hyperactive basal HPA axis regulation [80], while at the hypothalamic level, a decreased sensitivity for the negative feedback loop seems to maintain an elevated output of the initial releasing hormone CRH. In addition to the aforementioned central nervous system (CNS) modifications, another possible cause of higher C levels in the elderly might be age-related slower metabolic clearance rates of CRH, ACTH or C [79], or lower ACTH efficacy in older men [82].

To date, no age-related P decrease in males has been observed, although the main production site of P, the Leydig cells in the testes, experiences a continuous decline with age [55]. This indicates that P production in men can be maintained into old age, even though the number of Leydig cells strongly decreases. Whether this is due to compensatory processes of other body systems or a specific protection mechanism for P secretion remains unclear.

CONSEQUENCES OF AGE-RELATED HORMONAL CHANGES

Psychological Consequences: Well-being and Depression

Age-related changes in steroid hormones have a strong relationship with psychological well-being and depression.

As T levels decline in aging men, and mild to moderate depressive symptoms increase as a function of age, a variety of studies investigated the relationship between T and depression. In the Rancho Bernado study, which comprised 856 men aged between 50 and 89 years, higher depression scores with lower bT levels were found [83]. Seidman and colleagues [84] reported a relationship between low T levels and elderly dysthymic men. A cross-sectional study in 3987 men aged between 70 and 89 years showed that after adjusting for age and comorbidities, men in the lowest quintile of fT had a 2.7-fold increased risk of developing depression compared to men in the highest quintile [85]. In a longitudinal observation with a 2-year follow-up, the incidence of developing depression in men aged 45 or older with repeated low T levels was three times higher (21.7%) than in men with normal T levels (7.1%) [86]. A longitudinal study with a three-year follow-up replicated these findings in a sample of 608 men aged 65 years or older, since very low fT levels (<170 pmol/l) were associated with depressive symptoms, and low fT levels (<220 pmol/l) were predictive of the onset of depressive symptoms [87]. Furthermore, a simultaneous assessment of the CAG repeat length polymorphism in the androgen receptor encoding gene site, tT levels and self-reported depression showed that low T levels were associated with depression in men with the shorter allele only [88]. Although there is a large body of literature demonstrating an influence of T on well-being and depression in men, Amiaz and Seidman [89] conclude after reviewing the literature that there is no consistent relationship between T and mood. To summarize, recent findings indicate that in subgroups of men, an association between low T levels and depression is more pronounced. Treatment-resistant depressive men, men with major depression and HIV infection, hypogonadal men, dysthymic men, and elderly men (> 60 years) are at risk of lower T levels [7].

Due to the direct conversion of T to E2 via the enzymatic activity of aromatase, it is more difficult to study E2-induced effects exclusively. Suppression studies using aromatase-blockade for diagnostic purposes are extensive, and to a certain extent critical for human subjects. Although clinical evidence for the anti-depressant effect of estrogens in women is well documented [90, 91], comparable studies in men are rare. Almeida and colleagues [92] reported a significant decline in self-reported mood in men with prostate cancer following androgen blockade therapy (depletion of T and E2 levels). In 60 hypogonadal men (serum T levels $\leq$ 300 ng/dL) aged 60 or older, higher endogenous serum E2 levels were independently associated with a greater sense of well-being [93]. A study of 120 older community dwellers failed to report significant findings for the influence of E2 on mood or well-being, although there was a positive trend for self-reported quality of life [94]. Taken together, only a small number of results are available to interpret the effect of E2 on mood in men, but there is a tendency that higher E2 levels in elderly men seem to be associated with better well-being and quality of life. Nevertheless, there is substantial literature which stands in conflict with this finding [e.g., 83, 95].

Due to the widespread effects of DHEA, various studies have been conducted to elucidate the influence of DHEA on well-being and depression. A review by Davis and colleagues [96] suggested a positive relationship between DHEA and psychological well-being especially in elderly people. In depressed subjects, significantly lower levels of salivary DHEA levels have been found compared to non-depressed subjects [97]. A recent study in 170 healthy adults divided into the three age groups young (18–30), middle-aged (31–45) and old (>46) reported parallel findings of an age-related decline in DHEAS and an increase in depression, daily hassles and stress scores [98]. A study examining 41 healthy men who were enrolled in a military survival school showed a positive relationship between DHEA and DHEAS levels and stress tolerance and superior military performance, and a negative relationship with dissociative symptoms [99]. In addition, Izawa and colleagues [100] found that lower DHEA levels during a psychosocial stress test were correlated with increased negative mood during and after the stress test. The substantial DHEA decline with age seems to entail fundamental disadvantages, which the aging male needs to somehow compensate in order to preserve an overall state of psychological functionality and positive mood.

Table 2. The influence of steroid concentrations on psychological well-being and depression in men

Hormone	Psychological well-being	Depression	References
Testosterone (T)	↑	↓	Amiaz & Seidman, 2008; Joshi et al., 2010; Yeap, 2014
Estradiol (E2)	(↑)	(↓)	Almeida et al., 2004; Barrett-Connor, 1999; Borst et al., 2014
Dehydroepi-androsterone (DHEA)	↑	↓	Abraham et al., 2013; Bloch et al., 1999; Davis et al., 2011; Michael et al., 2000; Morales et al., 1994
Cortisol (C)	↓	↑	Hsiao et al., 2011; Lok et al., 2012; McKay & Zakzanis, 2010; Pariante, 2009; Stetler & Miller, 2011

Decreased well-being or depression is indicated by ↓; increased well-being or depression is indicated by ↑; moderate associations are represented in brackets (e.g., (↓)).

C, as the secretory end product of the HPA axis, is strongly related to depression. Elevated plasma or saliva cortisol levels are considered as main indicators of HPA axis hyperactivity and have been well documented in depressed patients [101], and seem to disappear after full remission of depressive symptoms [102-105]. Based on meta-analytic findings, Stetler and Miller [101] concluded that small-to-moderate elevations in C and ACTH and a reduction in CRH levels are associated with depression. Additionally, they found that elevated C levels are more likely to occur in specific subgroups of depressed subjects: older, hospitalized, melancholic depression, endogenous depression, depression with psychotic features and taking antidepressant medication. As a result of the age-related C

increase and the higher prevalence of mild-to-moderate depressive symptoms, it seems important to acknowledge the substantial impact of elevated C levels in elderly men on well-being and depression. The influence of steroid concentrations on psychological well-being and depression in aging men is summarized in table 2.

Sexual Consequences: Erectile Function and Sexual Desire

Age-related biological alterations seem to increase the risk of erectile dysfunction (ED). In men below the age of 40 years, the prevalence of ED ranges from 1-9%, increasing in the decade from 40 to 49 years to 2-30%, for older men (60 to 69 years) to 20-40%, and for men over 70 years to 50-75% [106]. As age is strongly associated with ED, and in parallel, hormonal changes in T, E2, DHEA and C also start at around 40 years, several studies have attempted to disentangle the specific relationship of these steroid hormones and ED or decreased sexual desire (SD).

Martin and colleagues [107] reported an association of low plasma T levels with moderate to severe ED and low SD in a sample of 1195 men aged 35-80. In a population-based study with 1744 men aged 75-95, low serum T levels were also reported to be associated with a lack of interest in sex, but not with other sexual problems [108]. Shi and colleagues [109] identified low tT and serum fT levels as independent risk factors for ED and low fT levels as predictor of ED in 476 men aged between 40 and 70. Similar findings were reported in a study of 136 men aged 20-49, where erectile function was associated with fT, but not with other studied hormones such as DHEAS, E2, LH or the binding protein SHBG [110]. Higher endogenous T levels might therefore be considered protective against ED and hypoactive SD.

A recent study demonstrated low T levels as the primary reason for decreased erectile function, but concomitantly elevated E2 levels seemed to show an additive impairment effect [111]. These results are supported by a study in rabbits, which reported that ED induced by a high-fat diet is rather more associated with high E2 levels than with low T levels. Furthermore, ED induced by a high-fat diet in rabbits could be restored with both T supplementation and estrogen receptor (ER) blockade reducing E2 action [112]. However, Finkelstein and colleagues [113] described contradictory evidence in terms of a suppression of endogenous E2 results in decreased erectile function and SD, raising the prospect of an optimal E2 level. A recent study examining T supplementation in 423 men reported that elevated levels of serum E2 were associated with increased SD [114]. To summarize, in males, the role of E2 in the development and maintenance of ED is not yet fully understood and requires further investigation, since E2 and ED as well as SD seem to be more strongly correlated than was previously assumed [115].

Basar and colleagues [95] reported an association between sexual dysfunction and low DHEAS levels for 348 men aged 21-76. Although in the MMAS [116], DHEAS showed a strong negative correlation with the prevalence of ED in men aged 40-70, the results on the impact of DHEA and DHEAS on male sexual function are still the subject of controversial debate [31].

There are only a small number of studies on the specific relationship between C and sexual function, although evidence of a negative impact of stress, resulting in an over-reactive

HPA axis and its suppressing influence on the hypothalamic-pituitary-gondal axis, is fairly consistent [117, 118]. This effect has been shown in patients with Cushing syndrome (chronic hypercortisolism), where patients show a decreased SD [119]. On the other hand, serum C levels were shown to decrease with increased sexual arousal, suggesting an inhibitory role for C in the mechanism of male sexual response [120]. Although in some studies no difference was observed between healthy men and patients with ED with respect to ACTH and C levels [121, 122], other studies did demonstrate such an association [123]. Kobori and colleagues [124] reported for 105 depressed men aged 30-72 that in patients without antidepressant intake, salivary C levels showed significant negative associations with different dimensions of self-reported sexual functioning such as erectile function, SD or intercourse satisfaction. Furthermore, a study with 31 men suffering from ED reported that higher levels of perceived stress were related to decreased orgasmic and erectile function, while elevated salivary C levels 45 min after awakening showed a negative association with SD [123]. In a review, Chrousos [125] discussed the effects of poor quality of life, chronic stress and depression in terms of causing chronic activation of the stress system, leading to aggravation of ED. Taken together, elevated C levels impair sexual function in men, and the fact of rising C levels with age, independently of stress, should be taken into account in the treatment of elderly men with ED.

The described results indicate the importance of assessing a broad spectrum of hormones in patients with ED and hypoactive SD. These data may help to identify suboptimal ranges of hormone concentrations and to differentiate between specific subgroups of men with ED (older, hypogonadal, obese, diabetic, with metabolic syndrome) for the implementation of specific treatment. The influence of steroid concentrations on erectile function and sexual desire in aging men is summarized in table 3.

Table 3. The influence of steroid concentrations on erectile function and sexual desire in men

Hormone	Erectile Function	Sexual Desire	References
Testosterone (T)	↑	↑	Hyde et al., 2012; Jastrzebska et al., 2014; Martin et al., 2012; Shi et al., 2014
Estradiol (E2)	mixed	mixed	El-Sakkar, 2013; Finkelstein et al., 2013; Ramasamy et al., 2014; Vignozzi et al., 2014
Dehydroepi-androsterone (DHEA)	(↑)	(↑)	Basar et al., 2005; Baulieu et al., 2000; Levy, 1994
Cortisol (C)	↓	↓	Derouet et al., 2002; Gray et al., 1998; Kalaitzidou et al., 2013; Kobori et al., 2009; Starkman et al., 1981; Ückert et al., 2003

Decreased erectile function or sexual desire is indicated by ↓; increased erectile function or sexual desire is indicated by ↑; moderate associations are represented in brackets (e.g., (↓)).

Cognitive Consequences: Cognition and Dementia

Cognition is at increased risk with advancing age. Recent research has referred to specific hormone concentrations in the aging male with respect to preserving a functional level of cognition and disease absence or with regard to possible therapeutic targets against dementia.

A positive association of bT with memory and concentration was shown in a sample of 547 men (55-89 years) [83]. In a sample of 371 men (> 50 years), better scores on cognitive functioning in three different cognitive tests were associated with higher bT levels [126]. In 400 men aged 40-80, associations were revealed for tT and bT with respect to cognitive processing capacity and speed. Interestingly, a curvilinear relationship with optimal T levels in the 3rd and 4th quintiles of values was shown [127]. In 1107 men aged 35-90, a positive association between higher fT levels and both memory and visuospatial ability was found [128]. In contrast, in 450 men aged 35-80, low fT levels were associated with better performance on spatial visualization tasks compared to high fT levels [129]. In a study with 2932 men (70-89 years), serum fT levels of 210 pmol/l or more were associated with better cognitive performance [130]. However, there is substantial literature which conflicts with these findings, showing no relationship between endogenous T concentrations and cognition for adjusted models (controlling for educational attainment and physical health measures) [131].

In terms of dementia, the predicted prevalence is sexually dimorphic, and 19-29% lower for men [132]. When focusing on men with Alzheimer's dementia (AD), lower ratios of tT:SHBG were found than in the healthy control group, while low fT levels were an independent predictor of AD [133, 134]. Rosario and colleagues [135] reported that in male brains analyzed post mortem, a significant decrease in brain levels of T was observed in cases with mild neuropathological changes as well as those with advanced AD neuropathology. By contrast, a study measuring fT and fE2 levels revealed no significant effects of these hormones on executive function or global cognitive function despite a large sample size and adequate hormone measurement [136]. Taken together, higher T levels seem to be protective against age-related cognitive decline in men and should be considered as a possible therapeutic treatment for males suffering from dementia.

There are few available studies on the association between E2 and cognition in males. In 547 men aged 59-89, higher levels of tE2 and bE2 were related to decreased global cognitive function after a 4-year follow-up [83]. In a cross-sectional study of 310 men aged 50 or older, Yaffe and colleagues [126] reported that higher tE2 but not bE2 levels were associated with decreased cognitive function. Another longitudinal study supported these findings by demonstrating in 242 elderly men (73-91 years) that higher levels of tE2 and bE2 are associated with increased risk of cognitive decline [137]. A longitudinal study conducted over 6 years examined 2974 men aged 71-93 and revealed that higher levels of bE2 were associated with increased risk of AD and with lower cognitive abilities, indicating a more rapid cognitive decline for higher than for lower E2 levels [138]. By contrast, Zimmermann and associates [139] reported a positive association between tE2 levels and a verbal memory test in 185 elderly men. Furthermore, a prospective cohort study observed no relationship between cognition and tE2 or fE2 levels [136]. In conclusion, these studies support the perspective that in middle-aged and older men, lower E2 levels are associated with better

cognitive performance [140]. Therefore, a moderate age-related decline in endogenous E2 levels in older men does not seem to be one of the main biological mechanisms supporting a more rapid decline in cognitive function.

Table 4. The influence of steroid concentrations on cognitive function and dementia in men

Hormone	Cognitive Function	Dementia	References
Testosterone (T)	↑	↓	Barrett-Connor et al., 1999; Fonda et al., 2005; Hogervorst et al., 2004; LeBlanc et al., 2010; Moffat et al., 2004; Muller et al., 2005; Thilers et al., 2006; Rosario et al., 2011; Yaffe et al., 2002; Yeap et al., 2008; Yonker et al., 2006
Estradiol (E2)	↓	↑	Barrett-Connor et al., Geerlings et al., 2006; LeBlanc et al., 2010; 1999; Muller et al., 2009; Yaffe et al., 2002; Yeap, 2014; Zimmermann et al., 2011
Dehydroepian drosterone (DHEA)	↑	↓	Fonda et al., 2005; Goldman & Glei, 2007; Haren et al., 2008; Hildreth et al., 2013; Moffat et al., 2000; Sanders et al., 2010; Sorwell & Urbanski, 2010; Valenti et al., 2009
Cortisol (C)	(↓)	(↑)	Csernansky et al., 2006; Elgh et al., 2006; Fonda et al., 2005; Franz et al., 2011; Hartman et al., 1997; Karlamangla et al., 2005; Lupien et al., 1994; Lupien et al., 1998; Moriarty et al., 2014; Pulopulos et al., 2014; Rasmouson et al., 2001; Schrijvers et al., 2011; Singh-Manoux et al., 2014;

Decreased cognitive function or dementia is indicated by ↓; increased cognitive function or dementia is indicated by ↑; moderate associations are represented in brackets (e.g., (↓)).

The strong age-related decline in DHEA and DHEAS in older people seems to be associated with a parallel decline in cognitive function [141]. In an analysis of 410 men (>65 years), low DHEAS levels at baseline were strongly associated with larger cognitive decline at a 3-year follow-up [142]. These findings were replicated by the documentation of a positive association between DHEAS and cognitive function in 124 men (50-65 years) [143]. A sex-specific relationship for men only was reported for low DHEAS levels and worse working memory and executive function in a sample of 49 men and 54 women aged 60- 88 [144]. Another study supported the beneficial sex-specific effects of DHEA on cognition in men, with longitudinal data showing an association between baseline DHEAS concentrations and the prediction of the subsequent 3-year cognitive decline in men only (n = 472, mean age 66) [145]. However, data from the large sample of 981 older men of the MMAS were unable to replicate any association between DHEA or DHEAS and cognitive function [131]. Moffat and colleagues [146] also reported no significant effect of DHEAS levels on several dimensions of cognition in 883 men aged 22-91. Furthermore, a 10-year longitudinal study

found no relationship between DHEAS levels and cognitive decline in men aged 65 years or older [147].

As the underlying mechanisms in cognitive aging remain poorly understood, HPA axis dysregulation is one possible explanatory pathway, with C as peripheral marker. Derived from animal models, Sapolsky and colleagues [148, 149] hypothesized that HPA dysregulation impairs cognitive functions such as memory and learning processes. Increasing cortisol levels with age and elevated basal cortisol levels in 19 healthy adults (11 men and 8 women) aged 60-80 years were related to inferior performance in memory and attention tests [150]. These authors also reported prolonged cortisol elevations associated with memory impairment and decreased hippocampal volume in 11 subjects (mean age 76.5) [151]. Several groups found that dementia patients showed elevated serum cortisol levels compared to healthy controls [152-154]. In 33 patients (19 men, mean age 75 years) with very mild and mild AD, higher plasma C levels were associated with more rapid disease progression [155]. In a sample of 538 men and women (70-79 years), a significant negative effect of urinary cortisol on cognitive function was detected independently of gender over a 7-year follow-up [156]. Supporting these results, data from the MMAS showed that fully adjusted models relate higher serum C levels to lower cognitive functioning [131]. By contrast, in 3341 subjects (1420 men; >50 years), Schrijvers and colleagues [157] reported no association between serum morning cortisol levels and cognitive function at baseline or annual follow-up. There was no association between serum morning cortisol and dementia at an average of 7.1-year follow-up. Several studies investigated the relationship between the circadian rhythm of C secretion and cognitive function or dementia. The findings show an association between a flatter slope and worse verbal fluency and a greater decline in memory and executive function [158-160]. In 778 middle-aged twin men, Franz and colleagues [161] reported that an overall higher C output per day was associated with poorer performance on several cognitive domains (executive functioning, processing speed and visual-spatial memory). In addition, a 35-year longitudinal examination of this study revealed that general cognitive ability at age 20 was a significant predictor of midlife cortisol levels. Furthermore, a specific genetic polymorphism in the apolipoprotein E gene (APOE-ε4 allele) has been related to modulating the relationship between C and cognition [162]. While some studies reported an unhealthy diurnal C secretion profile (low morning C, high evening C and flatter slope) to be associated with faster decline in memory or verbal fluency in the risk-allele carriers [163, 164], others failed to replicate these findings for the association with dementia [157]. Taken together, C does not seem to be a strong contributor to cognitive decline in older men [164], or there appears to be a U-shaped relationship between C levels and cognitive function [165]. Low long-term cortisol levels (measured in scalp hair) were associated with worse performance in working memory, learning, and short- and long-term verbal memory in 14 healthy men (56-77 years). However, higher daily salivary cortisol output was related to worse cognitive performance [166]. Taken together, although there is considerable conflicting evidence, the findings indicate an essential role of C in the age-related cognitive decline, suggesting higher serum, salivary and urinary cortisol levels to be related with overall worse cognitive performance and increased risk of dementia as well as disease progression in older men. The influence of steroid concentrations on cognition and dementia in aging men is summarized in table 4.

PHYSICAL CONSEQUENCES: BODY COMPOSITION AND FRAILTY

Lifetime risk of a fracture after the age of 50 years has been reported to lie at 20% in men [167], while other studies report a lifetime fracture risk of 24% for men at the age of 45 [168]. Age-related sarcopenia, a clinical condition defined as muscle mass two standard deviations below the sex-specific level of young-normal mean, is prevalent in up to 15% of over-65-year-olds [169]. The age-related decrease in muscle mass and bone mineral density (BMD) as well as the age-related increase in fat mass plays a key role in frailty, suggesting hormonal changes as a therapeutic target to prevent general frailty in older men.

A cross-sectional study examined 121 males and 180 females aged 65-97 years and revealed that muscle mass and strength decreased significantly with increasing age in both sexes, whereas only in men was muscle mass significantly positively associated with serum fT levels [170]. Roy and colleagues [171] reported similar findings for 262 men aged 24-90 years from the Baltimore Longitudinal Study of Aging. A prospective cohort study demonstrated in 3616 community-dwelling men (70-88 years) that lower fT was independently associated with frailty at baseline and at 6-year follow-up [108]. In 3690 men (>70 years), low baseline serum T levels were related to higher all-cause mortality assessed 10 years later [172].

Along with the strong evidence that T is related to body composition and frailty, an essential influence of E2 on these parameters has been described [173]. Finkelstein and colleagues [113] reported an independent effect of low E2 levels on increased fat mass. An examination of serum sex steroid levels in young and older men in relation to longitudinal changes in BMD revealed that bE2 levels play a key role in both the acquisition of peak bone mass by promoting bone anabolism in young men and in bone loss by inhibiting bone resorption in elderly men [174, 175]. The authors also conclude that an age-related decrease in bE2 levels under a certain concentration (40 pmol/l) may be a major cause of bone loss in elderly men. This perspective is further supported by other studies, which consistently replicated the influence of E2 levels on BMD [176-178]. Another large cross-sectional study of 2908 men with a mean age of 75.4 years reported serum E2 to be an independent predictor of BMD in all bone sites studied [179]. Overall, cross-sectional observational as well as prospective studies in men have documented that serum E2 is positively associated with BMD, and higher endogenous E2 levels in older men are associated with a decreased risk of fractures [173, 180]. Taken together, low levels of E2 in older men seem to be associated with increased fat mass and decreased BMD, and therefore low E2 levels are a considerable risk factor for bone fractures after falls.

Since DHEA is considered as an anabolic hormone, the relationship between DHEA and muscle mass and general frailty has been addressed. Voznesensky and colleagues [181] reported a significant negative association between serum DHEA levels and frailty (assessed as weight loss, grip strength, sense of exhaustion, walking speed and physical activity) in 898 adults (591 men; mean age 74.6 years). Low DHEAS levels were significantly related to an increase in fat mass in 170 subjects aged 18-60 or over [98]. In a longitudinal study, lower serum DHEAS levels were associated with increased odds of frailty at a 10-year follow-up in 254 subjects aged 65-70 [182].

Table 5. The influence of steroid concentrations on body composition and frailty in men

Hormone	Body Composition	Frailty	References
Testosterone (T)	↑	↓	Baumgartner et al., 1999; Hyde et al., 2012; Roy et al., 2002; Yeap et al., 2014
Estradiol (E2)	↑	↓	Amin et al., 2000; Finkelstein et al., 2013; Hoppe et al., 2011; Khosla et al., 2001; Mellström et al., 2006; Mellström et al., 2008; Nguyen et al., 2014; Szulc et al., 2001; van Pottelbergh et al., 2003
Dehydroepiandrosterone (DHEA)	↑	↓	Abraham et al., 2013; Baylis et al., 2012; Voznesensky et al., 2009
Cortisol (C)	↓	↑	Baylis et al., 2012; Feller et al., 2014; Holanda et al., 2012; Warriner & Saag, 2013

Worse body composition or decreased frailty is indicated by ↓; better body composition or increased frailty is indicated by ↑.

Due to the fact that C is a catabolic hormone, and owing to the negative impact of glucocorticoids through its direct action on bone cells and indirect effects on calcium absorption, several studies investigated the relationship between C and frailty [183]. Holanda and colleagues [184] reported for 69 residents of long-stay institutions (37.7% men; mean age 77.5 years) a positive association between salivary C levels and frailty assessed as weight loss, fatigue, slowness, weakness and low physical activity. In a longitudinal study, a higher C:DHEAS ratio was associated with increased odds of frailty at a 10-year follow-up in 254 subjects aged 65-70 years [182]. As chronically elevated C levels are associated with reduced bone formation, persistent bone destruction and increased osteocyte and osteoblast apoptosis, glucocorticoid-induced osteoporosis seems to be particularly responsible for fractures in elderly people [183]. Elevated C levels are also associated to worse body composition [52]. Taking the age-related increase in C levels into account C plays a key role in frailty, risk of fractures and worse body composition in elderly men. The influence of steroid concentrations on body composition and frailty in aging men is summarized in table 5.

CLINICAL IMPLICATIONS

Hormone Replacement

In men aged over 40 years, age-related hormonal changes are common and derive from altered secretion from the testes, adrenals and pituitary gland [185]. One of the cornerstones of the treatment of age-related disorders is hormone replacement. In the attempt to counter the widespread effects of hormone decline, supplementation of T and DHEA in men has become quite common. Therefore, it is surprising that studies on specific indications, long-term effects, and risks of such replacement therapies are broadly lacking [24].

T replacement therapy (TRT) is the most frequently used hormone replacement therapy in men and especially in older men with symptoms of andropause. The primary aim of TRT is to restore serum T levels to the normal range, relieving men from hypogonadal symptoms, recovering quality of life, reducing disability, compressing major illnesses into a narrow age range, and prolonging longevity [186].

With regard to affective disorders, several intervention studies in eugonadal and hypogonadal men provide evidence that T substitution in men with low or low-normal T levels improves mood and reduces depressive symptoms [140]. A recent meta-analysis of T supplementation in depressed men concluded that T supplementation has a positive effect on mood, especially in dysthymic men and men with minor depression [187]. As recent findings showed that in specific subgroups of men, associations between low T levels and depression are quite consistent, TRT as a therapeutic treatment seems to be indicated and beneficial. Especially elderly men (aged over 60 years), treatment-resistant depressive men, men with major depression and HIV infection, hypogonadal men and dysthymic men are assumed to benefit from TRT.

Significant improvements in erectile function and SD were shown in an intervention study with 712 hypogonadal men (aged 18-99 years) following exogenous testosterone administration [188], replicating findings from previously conducted studies of beneficial effects with respect to several aspects of sexual functioning [e.g., 189]. As 20-30% of adult men have at least one manifest sexual dysfunction [106], the restoration of T levels, especially in hypogonadal men, promises substantial symptom relief. Therefore, men with ED and hypoactive SD should be screened for low T levels and receive treatment accordingly [190].

Intervention studies examining the effect of T supplementation on cognition have yielded mixed results, while existing RCT data in men with dementia indicate beneficial effects of T administration on cognition [140, 93].

Several intervention studies evaluating the effect of exogenously administered T on body composition and frailty have been conducted. A randomized double-blind placebo-controlled trial in 44 healthy men aged 60-75 reported that following TRT, significant dose-dependent increases in skeletal muscle mass and leg strength were observed [191]. In 122 men (mean age 70.8 years), TRT led to improvements in lean mass and muscle strength and reductions in body fat [192]. 209 men aged 65 or over with mobility limitations were randomly assigned to either a placebo or a TRT group [193]. The follow-up examination showed significant improvements in muscle strength and stair-climbing power. TRT in 131 men (mean age 77.1 years) with low endogenous T levels improved body composition and axial BMD [194]. Finkelstein and colleagues [113] reported that in men with chemically induced depletion of endogenous androgen levels and subsequent administration of different exogenous T doses in different groups, a dose-dependent improvement in muscle mass and strength was observed. Taken together, T shows a consistent association with body composition and frailty, and overall TRT in older men significantly improves body composition and reduces frailty.

Bassil [186] summarized the potential benefits of TRT as improvements in mood, energy, and quality of life, erectile function and SD, cognitive function, muscle mass and strength, and BMD.

Several risks of TRT have been reported. Although most studies show that atherosclerosis is mostly related to low T levels [195, 108], an increased risk of

cardiovascular disorders with T administration has also been described [196]. Therefore, T supplementation in andropause patients with higher cardiovascular risk should only be undertaken with great caution, and TRT should not be initiated in patients with recent ischemic heart disease or heart failure [24]. Another concern of TRT in patients is polycythemia. As an increase in hematocrit in relation to TRT has been described, subsequent observation of hematocrit levels after a TRT is recommended [24, 197]. TRT has often been related to prostate cancer growth [198], but so far, there is not sufficient empirical evidence to support this assumption [199]. However, follow-up prostate-specific antigen levels should be continuously observed in TRT patients. Furthermore, TRT has been linked to benign and malignant hepatic tumors, intrahepatic cholestasis, hepatotoxicity, and liver failure, but only for oral forms of TRT [186]. Therefore, other delivery systems like transdermal gels or intramuscular injections are recommended. In addition, sleep apnea has been discussed to correlate with TRT in hypogonadal men, but empirical evidence in this regard is lacking [186]. Other TRT side effects such as edema, dyslipidemia, hypercalcemia, decreased testicular size, acne, azoospermia, gynecomastia and alopecia have been reported [186, 197]. Taken together, TRT is one possible strategy to counter symptoms of andropause, and the safety profile is considered to be rather good.

E2 is administered to men under special clinical conditions only. For example, the experience of hot flushes after prostate cancer treatment can be treated with E2 [200]. Falahti-Nini and colleagues [201] reported beneficial effects of E2 administration in hypogonadal elderly men in terms of the maintenance of bone formation. E2 administration in men is accompanied by several negative side effects. Reis and colleagues [202] reported findings of nipple/breast tenderness and gynecomastia, while other studies have reported ED, changes in blood coagulation and genotoxic changes in the liver [203]. E2 administration is not indicated as a therapeutic treatment against symptoms of age-related hormonal changes in men.

DHEA is seen as a youth-preserving hormone and its replacement is common in anti-aging medicine. When DHEA was administered in healthy adults aged between 40 and 70 years, restoring their DHEA levels to levels found in young adults, a significant improvement in perceived psychological well-being was found [204]. Schmidt and colleagues [205] reported a significant improvement in depressive symptoms of patients suffering from midlife-onset major and minor depression. Similar findings of beneficial DHEA supplementation were reported for midlife-onset dysthymia [206]. Therefore, DHEA could also be seen as a protective biological factor with the potential to improve mood and to buffer stress or promote resilience during stress.

In an intervention study, half of a group of 40 impotent patients aged 41-69 underwent a DHEA supplementation of 50mg/day over six months, while the other half received placebo. Significant improvements in erectile function, intercourse satisfaction, SD, overall satisfaction, and orgasmic function were reported [207]. In a six-week DHEA supplementation in depressed men and women aged 45-65 years, significant improvements in sexual functioning were documented [205]. However, in men with sexual dysfunction, Morales and colleagues [208] found that 50mg DHEA supplementation twice per day over 16 weeks had no influence on sexual function. A recent review concluded that controlled trials conducted to date have not definitively proven that DHEA administration is useful for improving male sexual function [209].

Several intervention studies in older men failed to find any significant improvements following DHEA(S) supplementation for different dimensions of cognition [210-213]. However, few studies reported beneficial effects of DHEA administration in cognitive dimensions such as episodic memory recollection in healthy young men [214]. Maggio and colleagues [34] concluded, after reviewing the literature on DHEA(S) and replacement therapy, that DHEA supplementation is not useful in improving or maintaining memory and other cognitive domains in older individuals. Therefore, DHEA seems to exert little effect as a therapeutic treatment against dementia or other forms of cognitive decline in elderly men, while higher endogenous DHEA(S) levels seem to be associated with better cognitive functioning in older men.

Most intervention studies on DHEA supplementation in older persons failed to report any significant improvements in muscle mass or strength [215, 216], but others found, with a daily dose of 100mg DHEA, a significant decrease in fat mass and an increase in knee muscle strength and lumbar back strength in 9 men aged 50-65 years [217]. Morley and Malmström [218] concluded that at present, DHEA does not play a main role in sarcopenia or frailty.

Reviewing the literature, Samaras and colleagues [24] concluded that potential benefits of DHEA replacement are the improvement of well-being, erectile function and SD, muscle mass and muscle strength, BMD and overall frailty, and a decrease in depression, risk of atherosclerosis and overall mortality.

Table 6. The effect of hormone replacement on different areas of life in men

Hormone Replacement	Testosterone (T)	Dehydroepiandrosterone (DHEA)	Estradiol (E2)
Psychological Consequences	Mood ↑ Depression ↓	Psychological well-being ↑ Depression ↓	
Sexual Consequences	Erectile function ↑ Sexual desire ↑	Erectile function ↑ Sexual desire ↑	Erectile function ↓
Cognitive Consequences	Cognitive function (↑) Dementia ↓	Cognitive function (↑)	
Physical Consequences	Muscle mass ↑ Fat mass ↓ Frailty ↓ BMD ↑	Muscle mass (↑) Fat mass (↓) Frailty (↓) BMD (↑)	Bone formation ↑
References	Amanatkar et al., 2014; Bassil, 2011; Borst et al., 2014; Buvat et al., 2010; Finkelstein et al., 2013; Kenny et al., 2010; Pexman-Fieth et al., 2013; Sattler et al., 2009; Storer et al., 2008; Wang et al., 2004; Yeap, 2014	Bloch et al., 1999; Kim & Morley, 2005; Kritz-Silverstein et al., 2008; Maggio et al., 2014; Morales et al., 1994; Morales et al., 1998; Percheron et al., 2003; Reiter et al., 1999; Samaras et al., 2014; Schmidt et al., 2005; Van Niekerk et al., 2001; Wolf et al., 1997; Wolf et al., 1998	Falahti-Nini et al., 2000; Kuebler et al., 2002; Reis et al., 2014

The reduction of a specific condition caused by hormone replacement is indicated by ↓; the increase of a specific condition caused by hormone replacement is indicated by ↑; no change is indicated by ≈; moderate effects are represented in brackets (e.g., (↓)).

Negative side effects of DHEA supplementation such as acne, seborrhea, facial hair growth, and ankle swelling have been reported, but these were rather mild and no relation to prostate cancer has been described [24]. However, so far, studies on long-term DHEA administration (more than 2 years) and its impact on health-related domains are lacking. Taken together, the general positive associations of higher DHEA levels in the aging male and the mild side effects of its supplementation indicate DHEA treatment as another possible strategy, besides TRT, to address symptoms of age-related hormonal changes. The effect of hormone replacement on different areas of life in men is summarized in table 6.

GENERAL HEALTH AND SUCCESSFUL AGING

For men, a continuous decline in circulating androgen levels (e.g., T and DHEA) with age has consistently been reported throughout the literature [20, 46]. Higher endogenous androgen levels were shown to be associated with various positive outcomes in older men, such as increased well-being [96], decreased symptoms of depression [140], increased erectile function and SD [109, 209], better overall cognition [140, 144], increased muscle mass [113, 98], and lower risk of frailty [108, 182].

Therefore, in older men, maintenance of androgen levels in a normal range (serum T levels 300-400 ng/dL) is a crucial aim in healthy aging. In the MMAS, apparent good health defined as absence of chronic illness, prescription medication, obesity, or excessive drinking, added 10-15% to the level of several androgens in the cross-sectional analysis. The authors conclude that incident poor health accelerates age-related decline in androgen levels and suggest a parallel track model, where not apparently healthy males are on a lower track, losing androgen levels at a greater rate compared to men with maintained good health [20]. Similar findings were replicated for obese versus non-obese men [219]. In 400 men aged 40-80, general health status modified the association of tT with age [220]. These results were extended by findings by Sartorius and colleagues [221], who examined 325 men with self-reported very good or excellent health. Repeated measures of serum T, Dihydrotestosterone and E2 levels showed no age-related decline [221]. Thus, age-related T decline and accompanying nonspecific symptoms in older men seem to be strongly associated with accumulating age-related comorbidities [221]. Although decreased health contributes to lower T levels, age remains a major independent factor for T decrease in older men [140].

The concept of successful aging has been proposed to reach beyond avoidance of disease and disability [222]. While Rowe and Khan [223] characterized successful aging as involving freedom from disability, and high cognitive, physical, and social functioning, Depp and colleagues [224] pointed out that successful aging is a multidimensional construct, with the biological age as an important dimension. Since the endocrine systems are strongly linked to the biological age, several lifestyle factors related to successful aging are considered to beneficially modify hormone concentrations in the aging male. Therefore, instead of implementing “routine” medical intervention programs offering long-term hormonal replacement therapy to restore or reduce hormone concentrations in older men, modification of specific lifestyle factors emerges as a crucial goal for healthy endocrine aging in men.

A recent review focusing on the maintenance of physical and cognitive function as well as the quality of life and independence in aging men identified crucial lifestyle factors [225]. Longevity with preserved good health and postponed disability were significantly associated with physical activity, sedentary behaviors, smoking, diet and alcohol consumption [225]. For example, a longitudinal study in 12,201 older men showed a positive effect of weekly physical activity on survival and successful aging [226]. Along with a direct relationship of different lifestyle factors on successful aging, studies demonstrate an association of several lifestyle factors and endocrine health (T, E2, DHEA and C), therefore also contributing on an indirect pathway to successful aging (Figure 1) [e.g., 227, 219, 110, 52].

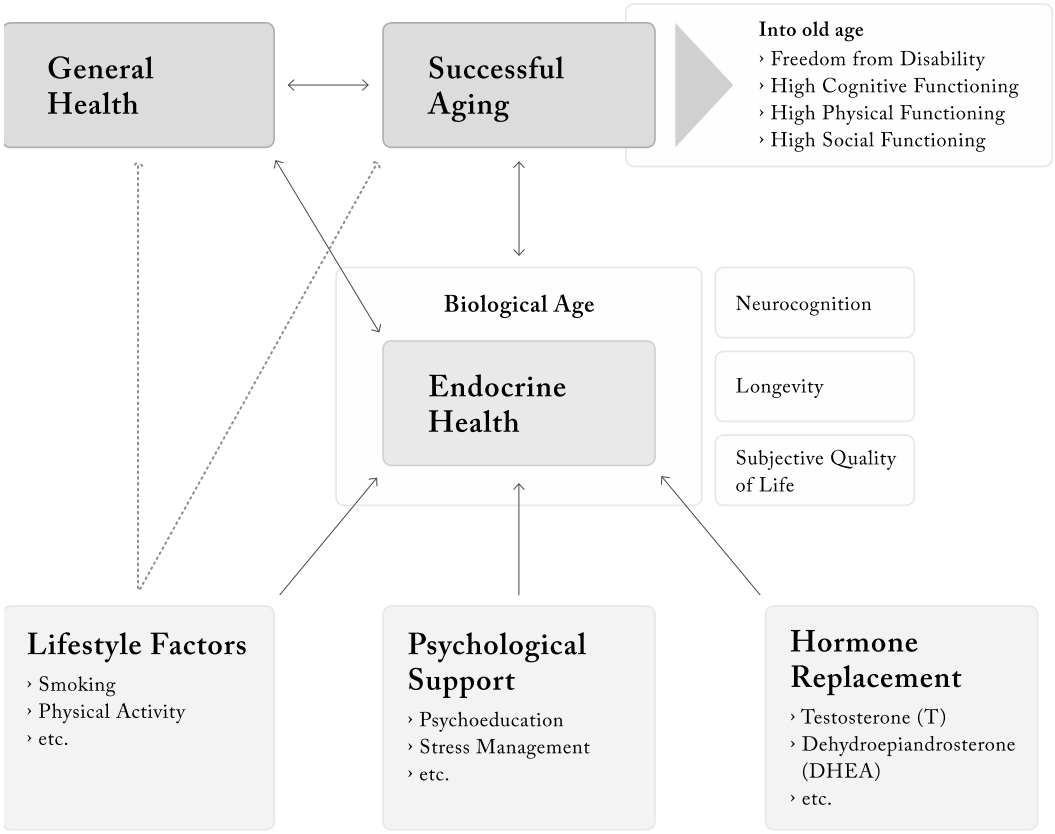

Figure 1. Lifestyle factors, psychological support and hormone replacement as possible targets to improve endocrine health and successful aging in men.

Prevention of disability, mental disorders, sexual dysfunction, and cognitive decline are of paramount interest for successful aging and can only be achieved within a multidimensional framework of intervention. Endocrine health plays a key role in preserving not only a functional state in various areas of life but also a high quality of life into old age, as shown in Figure 1.

CONCLUSION

Demographic changes are leading to a far larger proportion of elderly people in modern societies. Preserving good health and postponing disability into late life has been shown to be a vital goal for the future. Age-related hormonal changes in men are partially responsible for several clinical conditions in different areas of life. Psychological, sexual, cognitive and physical disorders may originate in declining T, DHEA, E2, or increasing C levels. Therefore, a greater understanding of the specific contribution of each hormone and its age-related change to the onset and progression of different clinical conditions such as depression, ED, dementia, or frailty is necessary.

Successful aging with less disease burden is strongly related to a healthy steroid profile. Since age-related hormonal changes occur as part of aging, strategies to restore or maintain healthy steroid levels are being established. TRT or the replacement of DHEA and E2 have been shown to significantly improve some clinical conditions related to the aging process, while they have not been found to improve others. A key role concerning age-related hormonal changes is played by lifestyle factors which contribute to a preserved healthy steroid profile, general health and successful aging (shown in Figure 1). Endogenous hormone concentrations in the optimal range seem to provide better protection against disease than supplemented hormone systems. Therefore, much more emphasis should be given to the prevention of age-related hormonal changes, by implementing psychoeducation about age-related hormonal changes in males at a population-based level. This would be one strategy to inform men about suitable healthy lifestyle habits, further options and to support them to counter these disorders. In individual cases, different psychological interventions, such as stress management training to maintain or restore optimal HPA axis functioning, could be applied to further improve endocrine health in aging men. However, as clinical conditions cannot be prevented for every male by maintaining good health and providing psychoeducation, hormone replacement represents a reasonable opportunity to overcome specific impairments caused by age-related steroid alterations. Men with severe symptoms caused by age-related hormonal changes should consider, besides consulting an endocrinologist, seeking psychological support for the successful management of the widespread effects.

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