1. 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 physical 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.

PART I: THEORETICAL BACKGROUND

2. 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.

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 for 1325 men in wave two [46]. The age-related changes in steroid concentrations in men are summarized in table 1.

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. (↓)).

3. 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.

4. Consequences of Age-Related Hormonal Changes

4.1 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.

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.

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. (↓)).