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Review

Late-onset hypogonadism: Clinical evidence, biological aspects and evolutionary considerations

Nikolai Jaschke [a,*], Andrew Wang [b,c], Lorenz C. Hofbauer [a], Martina Rauner [a], Tilman D. Rachner [a]

[a] Department of Medicine III & Center for Healthy Aging, Technische Universität Dresden, Dresden, Germany
[b] Department of Medicine (Rheumatology, Allergy & Immunology), Yale University School of Medicine, New Haven, CT, USA
[c] Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA

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ABSTRACT

The growing life expectancy in modern societies has raised scientific interest in identifying medical interventions to alleviate age-associated pathologies such as vascular calcification, cognitive decline, sarcopenia, osteoporosis and sexual dysfunction. Although no such single treatment has thus far been established in humans, some clinicians and patients have set their hopes on testosterone replacement therapy (TRT) as a potential "fountain of youth" for aging men. While TRT has proven effective in ameliorating distinct symptoms of late-onset hypogonadism (LOH), its safety remains to be demonstrated. Besides humans, multiple other species exhibit age-related reductions in circulating testosterone levels, raising the question whether such changes are an inherent, pathological feature of growing organismal age or rather reflect an adaptive response. In this manuscript, we apply key principles of evolutionary medicine to testosterone biology and LOH to provide a novel perspective on these two fields. Additionally, we discuss insightful data derived from the animal kingdom to illustrate the plasticity of individual testosterone trajectories across the lifespan, outline cost-benefit-considerations of TRT in LOH and highlight potential caveats of such therapies.

1. Introduction

Evolution refers to changes in biological characteristics over consecutive generations, which are driven by evolutionary processes such as natural selection. The latter operates when four key requirements are met: 1.) there must be variation in a trait, 2.) there must be variation in reproductive success, 3.) the correlation between the trait and reproductive success must be non-zero and 4.) the state of the trait must be heritable. In other words, genetic variation conferring enhanced reproductive fitness of an organism will be favored and ultimately selected for. At the same time, almost any given trait is involved in trade-offs, which describes the notion, that improvement in one aspect of physiology (e.g. reproduction) may negatively impact another (Stearns and Medzhitov, 2016). Compared to other non-human primates, the human species has developed a distinct reproductive phenotype characterized by relatively late sexual maturity, low offspring number, and, in most cases, a long post-reproductive lifespan (Stearns, 2012; Stearns et al., 2008). Whereas in women the beginning of the latter is sharply marked by the onset of menopause, male individuals do not exhibit such obvious changes. Rather, men experience a modest age-related decline in circulating testosterone levels (roughly 1–2% per year starting at the age of ~40 years), which is paralleled by deterioration of sperm quality and may eventually result in the development of symptomatic hypogonadism (Feldman et al., 2002; Johnson et al., 2015). This clinical picture was coined "late-onset hypogonadism" (LOH) almost two decades ago and has extensively been studied ever since then (Nieschlag, 2019). LOH is characterized by low testosterone levels in the presence of typical symptoms such as diminished libido and erectile dysfunction (Wu et al., 2010). Of note, the diagnosis of LOH is complicated by the lack of a consensus threshold to define testosterone deficiency in the elderly, although levels below 10 nmol/l have been widely considered pathological (Wu et al., 2010; Nieschlag et al., 2004). In contrast to other forms of hypogonadism, LOH cannot be readily classified as either of primary (testicular defect) or secondary (hypothalamic and/or pituitary defect) origin since these patients exhibit features of both perturbations (Khera et al., 2016). While much has been learned about the

* Corresponding author at: Division of Endocrinology and Metabolic Bone Diseases, Department of Medicine III & Center for Healthy Aging, Technische Universität Dresden, Fetscherstraße 74, D-01037, Dresden, Germany.
E-mail address: nikolaipirmin.jaschke@uniklinikum-dresden.de (N. Jaschke).

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epidemiology and clinical presentation of LOH, very little is known concerning its evolutionary background and medical significance. Most importantly, it remains unclear whether declining testosterone levels (and specifically, LOH) in older men reflect an adaptive or maladaptive trait.

2. LOH: a disease after all?

The biological effects of the testes had been recognized since antiquity, long before the concept of hormones arose. Yet, it took researchers up until the 20th century to identify testosterone as the active agent facilitating the androgenic effects of testicular tissue. Subsequent scientific efforts culminated in the synthetic production of testosterone as well as the development of radioimmunoassays to adequately measure circulating levels of the hormone. Both discoveries were prerequisites to gain mechanistic insights into testosterone (patho)biology and thus of great medical significance (Nieschlag and Nieschlag, 2019).

Postnatally, testosterone regulates a plethora of physiological functions in males including development and maintenanceof secondary sexual characteristics, sexual desire, body composition, bone mass, mood, hematopoiesis, hemodynamics and metabolism (Gagliano-Jucá and Basaria, 2019; Finkelstein et al., 2013; Kelly and Jones, 2013). Reciprocally, hypogonadism impairs these functions to various extents, thereby causing significant morbidity (Fig. 1) (Corona et al., 2011; Saad et al., 2020). Since aging is associated with perturbations in most testosterone-regulated functions and growing age is paralleled by declining testosterone levels in men, the assumption that testosterone replacement therapy (TRT) could be used to positively modulate various aspects of male health was an obvious conclusion. This hypothesis was supported by cross-sectional studies revealing inverse associations between testosterone and markers of glycemic control, BMI, waist circumference, muscle mass, bone mineral density, serum triglycerides and risk for cardiovascular disease (Corona et al., 2011; Tang et al., 2007; Lopes et al., 2009; Zitzmann et al., 2006). In this respect, the tight interconnection between the metabolic syndrome and hypogonadism has drawn special attention, since both pathologies reciprocally deteriorate each other (Zitzmann, 2009).

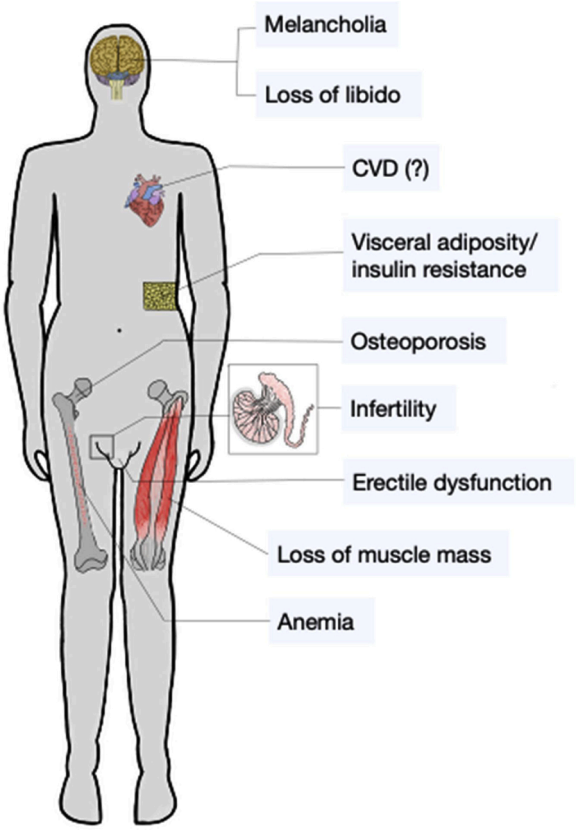

Fig. 1. *Symptoms of hypogonadism.* Low circulating testosterone levels are associated with several detrimental health effects including diminished libido, erectile dysfunction, loss of muscle and bone mass, increased visceral adiposity (potentially yielding impaired glucose tolerance), melancholia (eventually culminating in depression) and anemia. Whether hypogonadism actually confers an enhanced risk for cardiovascular disease is still a matter of controversy.

Subsequent prospective clinical trials demonstrated that testosterone replacement therapy could indeed positively impact distinct symptoms of hypogonadism in older men. The so-called Testosterone Trials (TTrials) were the first studies to prospectively evaluate the effects of TRT over a 12-month period on clinically meaningful endpoints in men with LOH (reviewed in (Snyder et al., 2018)). A total of 790 participants were randomly assigned to either receive transdermal testosterone supplementation or a placebo. Inclusion criteria included age >65 years and circulating testosterone levels <275 ng/dl, whereas a high risk for (and history of) prostate cancer as well cardiovascular disease (among others) served as exclusion criteria. The TTrials revealed improvements in several aspects of LOH including sexual desire, erectile dysfunction, lean body mass, walking distance or bone mineral density (Storer et al., 2017; Snyder et al., 2016). However, safety concerns were raised by the observation that TRT yielded a significant increase in non-calcified coronary artery plaque volume22], which was affirmed by a meta-analysis demonstrating an elevated risk for cardiovascular events (OR = 1.54, 95% CI 1.09–2.58) in patients undergoing TRT (Xu et al., 2013). Conversely, other studies did not find evidence for such an association (REF 24 and see below). Similarly, the effects of testosterone on prostate cancer development are still a topic of debate. While most investigations have not found a consistent increase in prostate cancer risk in patients undergoing TRT, sample sizes of these studies were generally small and follow-ups were too short to draw valid conclusions (Snyder et al., 2018; Calof et al., 2005). Of note, a large meta-analysis including 20 prospective studies found that low endogenous free testosterone levels (i.e. the lowest study-specific decile) were associated with a reduced risk for developing prostate cancer, whereas higher levels did not confer an elevated hazard (Watts et al., 2018). These observations are in accordance with the saturation model of androgen receptor signaling (Morgentaler and Traish, 2009). In contrast to previously published literature (Thompson et al., 2003), the cited study did not find evidence for a higher frequency of more aggressive (i.e. higher Gleason grade) tumors in men with low testosterone.

In summary, TRT in (adequately diagnosed) LOH elicits several beneficial effects. However, these benefits may also come at a certain cost, i.e. potentially detrimental adverse events. From an endocrine perspective, the supplementation of a true hormonal deficit should not be associated with major adverse events if the exogenous delivery system resembles the physiological secretory pattern of the respective hormone. Indeed, parenterally administered testosterone preparations as commonly used several years ago exhibited a rather unfavorable pharmacokinetic profile, resulting in both sub- as well as supraphysiological testosterone serum levels, thus yielding adverse effects. In contrast, presently used topical formulations and subcutaneously administered short-acting esters resemble endogenous testosterone secretion more closely (Nieschlag, 2015; Srinivas-Shankar and Wu, 2006; Kaminetsky et al., 2019, 2015). However, clinical data suggest that these therapies are still not entirely safe in older men (Snyder et al., 2016; Vigen et al., 2013). Conversely, the benefits of TRT in younger men with classical primary or secondary hypogonadism are well documented and (for the most part) associated with very few adverse events (Bhasin et al., 2018). Of note, similar observations were also made in females, where hormone replacement therapy (HRT) in younger postmenopausal individuals elicited mainly beneficial effects, whereas an increased risk for cardiovascular events was described in older women (Chester et al., 2018; Marjoribanks et al., 2017)

Therefore, the most relevant conceptional aspect concerning TRT in the elderly is the question whether declining testosterone levels in these individuals should be considered a pathological deficit (i.e. perturbation of homeostasis) or rather reflect a physiological, adaptive response. While the former point has already been extensively discussed in the scientific literature, little attention has been paid to the latter. In the following sections, we use common concepts of evolutionary biology to provide an alternative view on LOH.

3. Evolutionary considerations of testosterone biology

Life history theory reflects a theoretical framework to understand how finite organismal resources are allocated to competing and often opposing biological programs through trade-offs (Stearns, 1992). These programs include growth, reproduction and maintenance, the latter being further divided into dormancy and defense (Wang et al., 2019). Depending on the environmental conditions an organism is facing at a given time, resource investment may differ significantly. While favorable environments (sufficient nutrient supply, few predators) promote resource allocation into growth and reproduction, hostile environments (characterized by nutrient scarcity, insults and other challenging conditions) favor investments into maintenance programs (Wang et al., 2019). This may be exemplified by defense strategies such as the inflammatory response: The high energetic burden imposed by fighting invading pathogens necessitates a temporal suppression of competing biological responses, which themselves are metabolically costly (Okin and Medzhitov, 2012).

This holds especially true for reproductive functions. Indeed, testosterone levels are uniformly low in patients inflicted with inflammatory conditions such inflammatory bowel disease, arthritis or sepsis (Christeff et al., 1988; Grosen et al., 2019; Kanik et al., 2000). In fact, almost any evolutionary relevant environmental challenge such as cold, starvation or stress (requiring prioritization of energy distribution) provokes reduction in circulating testosterone levels (Fanjul and Ruiz de Galarreta, 1981; Parua et al., 1998; Muehlenbein and Bribiescas, 2005). Pertinent to this, strenuous endurance exercise yielding an imbalance between energy consumption and expense (male exercising syndrome) associates with hypogonadism and subfertility (Hackney and Aggon, 2018). Thus, low testosterone levels under these conditions can be considered an adaptive response to reduce the energetic burden of sex hormone-driven biological functions, thereby allowing allocation of resources into other costly programs.

It is worth noting, that not only nutrient scarcity but also excess as found in obesity is associated with hypogonadism and infertility (Lotti et al., 2014, 2013). Several lines of evidence have demonstrated that the persistent induction of pro-inflammatory cytokines in obese individuals ("low-grade inflammation") causally contributes to low testosterone levels by impairing hypothalamic GnRH secretion (Morelli et al., 2014). Additionally, hypothalamic inflammation in obesity is fueled by nutrient excess per se (Cakir and Nillni, 2019). Conversely, treatment of obese male individuals with the Interleukin-1 beta antagonist Anakinra increases systemic testosterone abundance (Ebrahimi et al., 2018). Since the pro-inflammatory state in obesity is considered as an example for overwhelmed organismal homeostatic capacities (Okin and Medzhitov, 2012), low testosterone secretion in these individuals likely reflects a pathological, rather than an adaptive response.

Physiologically, most (if not all) of testosterone can be considered anabolic and require high metabolic activity. Of note, these processes are not only energy-consuming, but also yield side-products, i.e. "waste". For example, cellular protein synthesis (which is stimulated by testosterone (Griggs et al., 1989)) is inevitably paralleled by a certain accumulation of defective and/or misfolded proteins requiring clearance. This is accomplished by maintenance programs (e.g. proteasomal degradation) (Stearns and Medzhitov, 2016; Balchin et al., 2016). With increasing age, the capacity of maintenance programs progressively declines, which is considered as one of the main drivers of highly prevalent pathologies of old age such as neurodegenerative diseases (Hipp et al., 2019). These disorders are thus examples for causes of intrinsic mortality. In contrast, extrinsic mortality (i.e. predators, starvation, dehydration etc.) has largely been eliminated in industrialized ("westernized") countries. From an evolutionary perspective, the age-related impairment of maintenance programs reflects antagonistic pleiotropy (by genetic means) and a trade-off (by phenotypic means): the selection of traits ensuring sufficient reproductive success early in life opposes those favoring maintenance and survival later in life because high investment into one program (anabolism) will unavoidably reduce available resources for the other (catabolism). Thus, human aging may be considered a trade-off, where reproduction is prioritized over longevity (Fig. 2) (Kirkwood and Cremer, 1982). If one further expands this notion, then age-related reductions in anabolic hormones would represent an adaptive mechanism to alter the cost-benefit ratio of this trade-off. In other words, declining testosterone levels in aging men impair several functions regulated by the hormone (cost), while eventually allowing the fostering of others (benefit). This principle may also be exemplified by observations made among the animal kingdom.

4. Testosterone biology: lessons from the animal kingdom

The baleen (i.e. the keratin-containing feeding-filter system inside the whale's mouth) of baleen whales contains a multi-year record of the animal's endocrine history because hormones are embedded into the baleen matrix in a continuous manner (Hunt et al., 2018). Thus, studying these materials reflects a unique opportunity to longitudinally follow testosterone trajectories of an individual. Indeed, such studies have revealed that testosterone levels in baleen whales exhibit annual cycles with peaks during the winter months (breeding season) and astonishingly low values in summer (Cates et al., 2019). Moreover, the magnitude of testosterone peaks gradually declines with increasing age of the animal and exposure to stressors (entanglement, sickness) results in blunted androgen levels in the subsequent cycle (Fig. 3) (Hunt et al.,

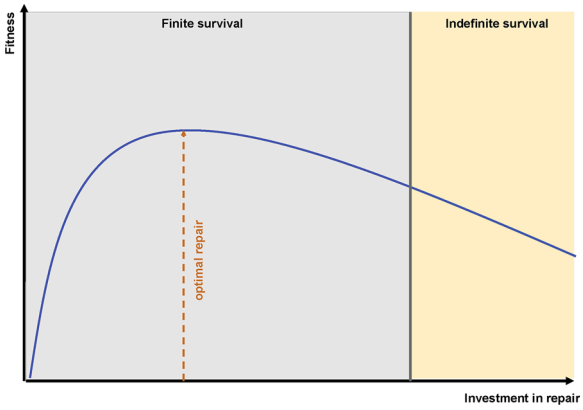

Fig. 2. *Aging as a trade-off between reproduction and repair.* According to Darwin's theory of evolution, natural selection favors traits conferring enhanced fitness. The term "fitness" is often loosely defined but essentially refers to reproductive success, i.e. higher fitness (better adaptation to a given environment) equals enhanced reproductive success. However, selection of traits conferring higher reproductive fitness will inevitably result in lower resource allocation into repair programs (maintenance) because organismal resources are finite. Consequently, prioritization of reproductive success limits lifespan (trade-off). Neither too much, nor too little investment into repair is favorable because both will result in reduced fitness: the former because of "over-investment" of resources into repair programs, the latter due to premature death. Yet, indefinite survival would only be achieved if resources were placed sub-optimally. Since this strategy would culminate in impaired (reproductive) fitness, such traits will not be selected for. Hence, organisms do not exhibit these extensive repair programs, which may explain their finite lifespan (after Kirkwood & Cremer, 1982).

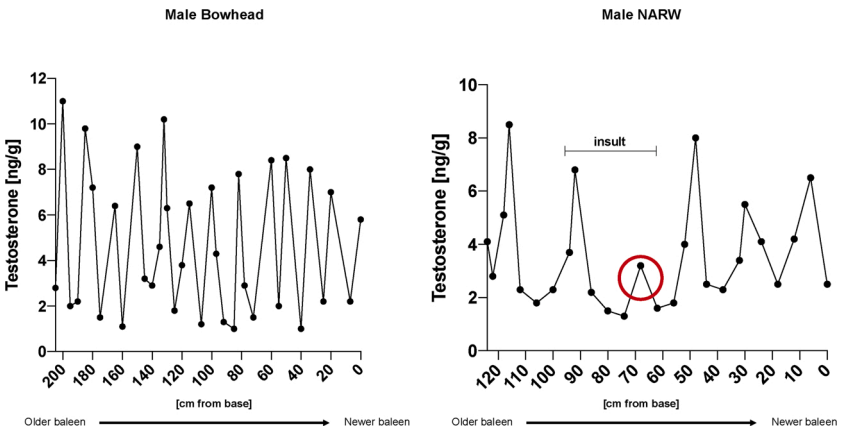

Fig. 3. *Testosterone trajectories in baleen whales.* In baleen whales, hormones are embedded into the baleen matrix in a continuous fashion, thus providing a unique opportunity to study individual testosterone trajectories over the lifespan. The left panel shows annual testosterone cycles in a baleen bowhead whale. Material close to the base reflects new baleen corresponding to a more recent endocrine status. Note that the magnitude of the annual testosterone peak progressively declines with growing age of the animal, reminiscent of decreasing circulating testosterone levels in aging humans. The right panel illustrates similar dynamics in a male North Atlantic Right Whale (NARW). After being challenged by an insult in one year (entanglement, sickness), the animal exhibited a strongly decreased testosterone peak in the consecutive year perhaps reflecting a prioritization of resource allocation into maintenance and repair programs rather than growth/reproduction. Comparable adaptations occur in humans, where almost any persistent evolutionary relevant stressor (e.g. infection, starvation, cold) evokes suppression of testosterone levels (after Hunt et al., 2018).

2018).These observations have several important implications: 1.) for baleen whales, the cost of maintaining high testosterone levels throughout the year is apparently higher than its benefit, suggesting that androgen biology does not confer major advantages for the most part in these animals 2.) as in humans (and most other species), hostile environments suppress androgen secretion to allow resource allocation into other biological programs, 3.) age-associated reductions in testosterone levels are not restricted to humans but also found in other mammals and 4.) the cyclicity of testosterone levels and fertility in baleen whales (i.e. peaking in winter) mirrors human whale hunting season (summer). Whether the latter phenotype is actually shaped by human behavior (i.e. extrinsic mortality) in the sense of an adaptive response or has already been existent much longer remains elusive. Remarkably, age-associated reductions in testosterone secretion have also been described in many other species including primates, mice, or guinea pigs (Machida et al., 1981; Rigaudière et al., 1976; Beehner et al., 2009).

The plasticity of testosterone secretion depending on the current environmental conditions may also be illustrated by data derived from lions. In these animals, the darkness and length of the animal's mane correlate with testosterone levels, nutritional status, reproductive success and offspring survival but negatively impact the animal's surface temperature and food intake in areas with hot climate. Consequently, both mane characteristics can vary along the lifespan of an animal because the cost of maintaining the trait may become higher than its benefit if environmental conditions change sufficiently enough (phenotypic plasticity) (West and Packer, 2002).

In general, an adaptive trait is characterized by a cost that is lower than its benefit. Vice versa, a trait with a stable, unfavorable cost-benefit ratio in a given environment will undergo natural selection to either shift this ratio (mostly through lowering its cost) or eliminate it after all (Okin and Medzhitov, 2012). Applying this principle to the lion kingdom, persistently altered climatic conditions (i.e. high temperatures) and poor nutrient availability (secondary to climate changes) would presumably favor lions with shorter and lighter colored manes (as well as lower testosterone levels) because under these environmental circumstances, the benefits generated from such characteristics (enhanced reproductive fitness) would fall below their costs (energy consuming growth of hair despite nutrient scarcity and eventually death due to insufficient temperature regulation). Of note, it would require a considerable amount of time and millions of selective events until the most optimal mane phenotype in the new environment has been established.

Similarly, LOH could reflect one of those diseases, where genetics are still running behind rapidly changing environmental conditions because distinctly increased life expectancies are a rather recent phenomenon in human evolution (i.e. reflecting an evolutionary mismatch). On the other hand, LOH may confer adaptive benefits tailored to meet altered demands with growing age. If this holds true, TRT in the elderly would impose unfavorable consequences by disrupting energetic adaptations required for maintenance programs. There are several examples for such maintenance functions: removal of defective (pre-cancerous) cells, misfolded proteins, old organelles or membrane lipids, all of which accumulate with growing organismal age and impose metabolic costs in order to be fixed (Wang et al., 2019; Eskelinen, 2019; Almanza et al., 2019).If these demands cannot be met because other pathways (e.g. testosterone-driven anabolism) are overriding, maintenance capacities are overwhelmed, thus resulting in cellular and/or organ dysfunction and ultimately, culminating in disease.

5. Kennedy Syndrome as a paradigm for androgen-mediated toxicity

As outlined in the previous sections, testosterone secretion is highly dynamic and always tailored to meet the current environmental and/or organismal requirements. The consequences of perturbing these adaptations may be exemplified by a rare genetic disorder known as spinal and bulbar muscular atrophy (SBMA), also referred to as Kennedy Syndrome. SBMA is an X-chromosomal, recessively inherited disease caused by an abnormally extended polyglutamine stretch (encoded by a CAG repeat) within the n-terminal region of the androgen receptor (AR) that exclusively manifests in males. The length of the CAG-repeat inversely correlates with age at onset of the disease, i.e. longer repeats yield earlier manifestations (Atsuta et al., 2006).

Typical symptoms include progressive muscle weakness, bulbar dysfunction and fasciculations. Moreover, SBMA patients exhibit endocrine abnormalities such as erectile dysfunction, testicular atrophy or gynecomastia reflecting impaired androgenic actions of poly-glutamine AR (Rosenbohm et al., 2018). The molecular mechanisms evoking other alterations of the disease are incompletely understood but nuclear accumulation of toxic receptor aggregates, mitochondrial dysfunction, impaired autophagy, defective proteasome activity and altered transcriptional regulation have been proposed (Beitel et al., 2013). Most intriguingly, chemical or surgical castration reduces motor symptoms, neuronal degeneration and disease progression in animal models of SBMA (Arnold and Merry, 2019; Katsuno et al., 2002). Of note, these improvements could not be explained by decreased testosterone-mediated AR expression, but presumably included altered AR stability and reduced nuclear abundance of toxic AR aggregates68]. In view of elevated circulating estradiol levels secondary to disrupted negative feedback inhibition in SBMA (Ni et al., 2015), one could speculate that estrogens contribute to the pathogenesis of the disease. However, neither preclinical, nor clinical evidence has thus far

established a beneficial role for interfering with estrogen biology (e.g. via aromatase inhibitors) to ameliorate SBMA symptoms or diseases trajectories.

Taken together these observations suggested that SBMA is primarily caused by abnormal proteostasis, i.e. gain-of-function mutation of AR yielding pathological accumulation of the protein.

However, additional studies revealed that activation of the AR by its cognate ligands (i.e. dihydrotestosterone and testosterone, respectively) is required to evoke toxicity of poly-glutamine AR (Finsterer, 2010). Initially, this was interpreted as the necessity of ligand-dependent nuclear translocation of AR to promote local protein accumulation within this cellular compartment. Based on these assumptions, clinical trials employing the GnRH analogue leuprorelin (i.e. androgen deprivation therapy) for the treatment of SBMA were initiated, which revealed promising, although ambiguous results (Hashizume et al., 2017; Katsuno et al., 2010; Banno et al., 2009), suggesting that effective therapeutic approaches may require a more sophisticated approach.

Subsequent investigations demonstrated that nuclear translocation of polyglutamine AR is necessary but not sufficient to evoke toxicity. Rather, DNA binding and amplification of native AR interactions were found to exert toxic effects (Nedelsky et al., 2010). As such, specific functions of the AR (excluding those promoting androgenicity) are not only preserved in SBMA but actually enhanced and function as drivers of the disease, indicating that unrestrained AR signaling (i.e. opposing catabolism) is not compatible with maintaining cellular homeostasis. Pertinent to these observations, a preclinical study in mice (Badders et al., 2018) revealed improvements in several SBMA symptoms including reduced grip strength, weight loss, gait disturbances as well as testicular atrophy elicited by the selective androgen receptor modulator MEBP (1-[2-(4-methylphenoxy)ethyl]-2-[(2-phenoxyethyl)sulfanyl] 1-*H*-benzimidazole). Mechanistically, MEBP attenuated distinct aspects of pathologically amplified AR functions through increasing corepressor recruitment to the AF2 (activation function 2) domain of the protein. Importantly, the burden of toxic AR aggregates remained unchanged by the treatment. On the other hand, testicular atrophy (i.e. a prototypical androgenic function of the AR) was attenuated upon MEBP exposure. Together, these results support the concept that a.) SBMA is not primarily driven by accumulation of toxic receptor aggregates but rather dysregulated transcriptional AR activity and b.) fine-tuning of the latter to promote abolished androgenic receptor functions, while counteracting the amplification of others is sufficient to positively modulate disease trajectories in SBMA:

Notably, the question if androgen antagonism also elicits favorable effects in other neurodegenerative diseases with less obvious links to testosterone biology (e.g. Parkinson's disease) remains obscure. Vice versa, no convincing clinical data are available on the effects of TRT on the course of such diseases. One small study (n = 15 per group) investigated the effects of TRT in patients with Parkinson's disease. These authors did not find evidence for beneficial effects of testosterone replacement but rather reported adverse events such as worsening of dyskinesia (Okun et al., 2006). While the very small sample size of this study limits its significance, preclinical data has already pointed towards unfavorable effects of androgens in promoting early (but not more advanced) Parkinson's disease (Gillies et al., 2014; Dluzen et al., 1994; Yu and Wagner, 1994).

In summary, the biological programs promoted by testosterone mainly foster anabolism, which oppose those pathways favoring catabolism. As exemplified by the impressive case of SBMA, amplification of certain AR functions is highly pathological and evokes devastating disease. With respect to ageing, the importance of maintenance programs increases and under specific circumstances, disrupting such responses is detrimental. Thus, it may be tempting to speculate that promoting anabolism through testosterone supplementation with growing age may exert negative effects on health and longevity.

6. Testosterone and cardiovascular disease

Cardiovascular diseases (CVD) have emerged as the leading causes of mortality in westernized countries (Finegold et al., 2013; Mathers et al., 2009). In other words, these pathologies are currently the main drivers of limited lifespan in modern societies. Although an extensive body of literature has suggested that testosterone is linked to cardiovascular health and disease (elegantly reviewed in REF 11), the precise nature of this association has still not been fully resolved. In fact, some cross-sectional studies have reported inverse associations between circulating testosterone and the risk for cardiovascular disease (Yeap et al., 2009), whereas several others have not (Shores et al., 2014; Haring et al., 2013a). Furthermore, clinical trials investigating the effects of TRT in older men have thus far not been adequately powered to assess clinically relevant cardiovascular endpoints, but retrospective studies have reported neutral, protective as well as detrimental effects (Vigen et al., 2013; Sharma et al., 2016, 2015). On the other hand, supraphysiological testosterone levels (i.e. anabolic steroid abuse) are well-known to exert detrimental effects on cardiovascular health (Nieschlag and Vorona, 2015). Along these lines, women with biochemical hyperandrogenemia (i.e. Polycystic Ovary Syndrome) display an increased risk for CVD (de Groot et al., 2011), although this observation might be partly driven by associated metabolic perturbations such as insulin resistance (Osibogun et al., 2020).

Thus, the several clinical benefits associated with TRT in older men could be outweighed by unfavorable cardiovascular consequences, as already documented for HRT in women. From an evolutionary perspective, this raises two important questions: 1.) Why does testosterone modulate cardiovascular biology in the first place and 2.) why are testosterone and cardiovascular health involved in a trade-off?

The first question can be explored by the phenomenon of co-evolution in the Bornean Rock Frog (*Staurois Parvus*). These animals have developed a distinct hind limb movement pattern (known as the "foot flag") to attract females for mating. This process is testosterone-driven and facilitated by high androgen receptor expression in the corresponding muscles, which is not found in other frog species devoid of the foot flag. Together, these observations suggest that the enhanced fitness conferred by specific testosterone effects required the co-evolution of other traits (i.e. high muscular AR expression) to implement such functions sufficiently (Mangiamele et al., 2016). Similarly, the fitness advantage conferred by testosterone-mediated muscle protein synthesis (that is, dominance/reproduction/survival) might have required an evolutionary linkage to the cardiovascular system in order to ensure sufficient oxygen and nutrient supply to these organs. This may explain why testosterone regulates cardiomyocyte physiology, vascular tone or hematopoiesis.

The second question, on the other hand, is more puzzling. In industrialized countries, the hemodynamic costs of maintaining physiological sex hormone concentrations with growing age may be exceptionally high (due to the risk of erythrocytosis, clotting, hypertension) because of the high prevalence of comorbidities associated with CVD (Yusuf et al., 2020). Vice versa, men in environments without such factors would be expected to be spared from age-related reductions in circulating testosterone. Indeed, aging men from the US display a more prominent testosterone decline than those from Paraguay or Nepal (Ellison et al., 2002; Ellison and Panter-Brick, 1996). Importantly, these results should be interpreted with caution since testosterone levels in the cited study (Ellison et al., 2002) were measured from saliva samples, which provide an acceptable, although not fully accurate estimation of systemic testosterone abundance (Fiers et al., 2014; Andersson et al., 2017).

Nevertheless, if one expands the notions highlighted above, low sex hormone levels in the elderly in industrialized countries might confer protection from CVD (adaptation), whereas TRT would perturb this phenotype. The latter hypothesis is supported by mendelian randomization studies demonstrating an increased hazard for thromboembolism in men with genetically determined higher endogenous testosterone

levels (Luo et al., 2019).

Generally speaking, organismal death can be considered a trade-off between different ways to die. Thus, a "low testosterone" trait in older men might protect from cardiovascular death (currently being the most prevalent limitation to lifespan), while enhancing the risk to succumb to other diseases (e.g. fragility fracture due to osteoporosis), potentially reflecting a favorable trade-off in our current environment. Of note, both exogenous and endogenous testosterone is aromatized to estradiol by CYP19A1 and the latter fulfills several important physiological functions in males that have traditionally been ascribed solely to androgens (e.g. regulation of visceral fat mass, libido or erectile function) (Finkelstein et al., 2013; Hammes and Levin, 2019). Reciprocally, some of the adverse effects arising from TRT could, in fact, be estradiol mediated. On the other hand, the clinical use of non-aromatizable androgens is obsolete because such treatments would render patients devoid of a variety of beneficial effects associated with TRT (e.g. increase in bone mass).

Taken together, potential cardiovascular side-effects remain the most prominent safety concern for TRT in older men, reminiscent of the debate on HRT in postmenopausal women. In 2018, the first large, prospective, randomized controlled trial (TRAVERSE) with a long-term follow-up (i.e. 5 years) investigating cardiovascular safety as the primary endpoint was initiated (NCT03518034) and this study will hopefully aid in resolving the longstanding controversy about cardiovascular consequences (and ultimately, mortality) of TRT in aging men.

7. Does testosterone affect lifespan?

Considering the points outlined above, it would be reasonable to assume that low testosterone levels are correlated with an increased lifespan. The most obvious example for this notion is the difference in longevity between males and females as such that on average, women live longer than men (Austad and Fischer, 2016). Moreover, a population of Korean eunuchs was found to exhibit a significantly increased lifespan compared to socio-economically matched controls (Min et al., 2012). Similar observations were made in other mammals such as primates, sheep, cats or mice (Brooks and Garratt, 2017). It is worth emphasizing, that these findings are heavily influenced by multiple confounders such as hormone-driven behavioral changes (e.g. risk-taking, aggression etc.). For example, alpha male Baboons exhibit the highest testosterone but also the highest corticosterone levels, suggesting that defeating an alpha status (and high testosterone levels) comes at the cost of stress, although influences on lifespan were not explored in the cited study (Gesquiere et al., 2011).

Nevertheless, a shared mechanism of various lifespan-increasing interventions lies in a reduced activation of anabolic pathways. Genetically, this may be exemplified by Laron-Syndrome characterized by defective growth hormone-signaling yielding a short stature in the presence of longevity (Aguiar-Oliveira and Bartke, 2019). The latter effect can also be achieved by both caloric restriction as well as pharmacological mTOR blockade (via rapamycin) (Weir et al., 2017; Harrison et al., 2009). Given that long-term caloric restriction lowers systemic testosterone abundance (Cangemi et al., 2010) and mTOR is a direct molecular target of the hormone (Basualto-Alarcón et al., 2013), decreased circulating testosterone should result in reduced anabolism and thus increased lifespan. Pertinent to this, a study comparing various genetic as well as pharmacological longevity interventions found that "feminization" of gene expression was a shared characteristic of these manipulations (Tyshkovskiy et al., 2019). Unfortunately, testosterone levels were not reported by the authors. On the other hand, castrated rats exhibited a moderately increased lifespan compared to matched controls, supporting a protective role of low testosterone in aging (Drori and Folman, 1976). Moreover, male C57BL/6 mice were found to exhibit the longest lifespan among a variety of different mouse strains and these animals also display exceptionally low circulating testosterone levels (Yuan et al., 2009; Brouillette et al., 2005).

In contrast to these notions, several studies in humans have reported an inverse correlation between circulating testosterone and mortality (Adelborg et al., 2019; Araujo et al., 2007). Notably, most of these findings were likely blurred by reverse causality, i.e. men with poor health develop low testosterone and have higher chances succumbing to a disease rather than the other way round (Snyder et al., 2018). However, the European Aging Male Study (EMAS) found an increased mortality in patients with LOH even after adjusting for potential confounders such as poor general health status and BMI (Pye et al., 2014). On the other hand, mendelian randomization studies did not find evidence for such an association (Haring et al., 2013b). Another layer of complexity is added to the association between testosterone and mortality by sex-hormone binding globulin (SHBG). Reduced levels of the latter have been linked to an increased risk for developing type II diabetes in longitudinal studies (Wallace et al., 2013). Given that insulin resistance lowers hepatic SHBG production (Plymate et al., 1988a, b), this association could arise from reverse causality. However, mendelian randomization studies have indeed supported a causal role of SHBG in glycemic dysregulation (Perry et al., 2010). On the other hand, high SHBG levels have been associated with increased mortality in diabetic men, although this effect was very modest (HR = 1.03, 95% CI 1.01–1.04)(Ramachandran et al., 2018). Conversely, lower SHBG levels conferred a reduced risk for ischemic heart disease mortality in the general population112].

Taken together, definite conclusions concerning the relationship between testosterone, mortality and longevity are currently difficult to draw since the interpretation of most available studies is complicated by a plethora of confounders. However, as outlined above, testosterone biology likely involves trade-offs between different ways to die.

Another unresolved aspect of testosterone physiology potentially affecting mortality are its proposed immunomodulatory functions. Given the opposing effects of testosterone and inflammatory signals on resource allocation, several authors have suggested an immunosuppressive role of the hormone (Muehlenbein and Bribiescas, 2005). Yet, experimental evidence supporting this hypothesis is scarce (O'Brien et al., 2018). Interestingly, however, one study found impaired antibody responses upon influenza vaccination in men compared to women. Subsequent machine-learning approaches revealed that this inefficacy in male individuals was indeed explained by circulating testosterone abundance (Furman et al., 2014). Whether similar effects also account for the higher cancer and lower autoinflammatory disease incidence in men compared to women remains elusive.

8. Concluding remarks

The question whether age-related changes in circulating testosterone reflect a pathological deficit or an adaptive response remains difficult to answer. The former notion is corroborated by several retrospective and some prospective clinical trials demonstrating distinct benefits of TRT in older men, whereas the latter is supported by adverse events associated with such therapies as well as data derived from animals. The observation that other species besides humans experience exhibit age-related reductions in testosterone levels suggests that the evolutionary cost of maintaining high androgen levels throughout lifespan are simply too high and/or the generated benefit is too low. While longevity might be compromised by TRT, most patients do not strive for an indefinite survival, but rather a high quality of life. Thus, the reasonable amount of data supporting beneficial effects of TRT in LOH currently justifies its clinical use under specific circumstances. On the other hand, the expectations of a pharmacological "fountain of youth" will most likely never be fulfilled, neither by TRT, nor by another therapy because the basic evolutionary principle of trade-offs simply cannot be overcome.

Declaration of Competing Interest

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