Late-onset hypogonadism: a concept comes of age

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ABSTRACT
The term Late-onset hypogonadism (LOH) was coined in 2002 and defined as a disease entity in the ISA, ISSAM, EAU, EAA and ASA endorsed Recommendations for Investigation, Treatment and Monitoring of LOH (2005 and 2008) as ‘a clinical and biochemical syndrome associated with advancing age, characterized by symptoms and a deficiency in serum testosterone (T)’. LOH was classified as a combined primary and secondary hypogonadism since the endocrine capacity of the testes and the pituitary are impaired. Symptoms of LOH include loss of libido, erectile dysfunction, loss of muscle mass, increased body fat, anemia, osteoporosis, depressed mood, decreased vitality, sweating, and hot flushes. Since these symptoms may also have origins other than LOH, exclusion of other disease entities and subnormal serum T levels are considered prerequisites for the diagnosis and possible treatment of LOH. However, during following years these guidelines were often neglected and, especially in the USA, indiscriminate prescribing of T was widely practised so that the US FDA warned against such irresponsible behavior. In Europe, T prescribing remained largely restricted to LOH as defined above. Nevertheless, a discussion started whether LOH really exists or is only a consequence of age-related comorbidities. Numerous studies have helped to clarify the situation, in particular, the European Male Aging Study (EMAS) and the US-initiated 7 T trials. Consequently, the newest US Endocrine Society Practice Guideline on T treatment (2018) includes advanced age as a cause of organic hypogonadism and recommends that ‘in men >65 years who have symptoms or conditions suggestive of T deficiency … and consistently and unequivocally low morning T concentrations we suggest that clinicians offer T therapy on an individualised basis after explicit discussion of the potential risks and benefits’. Thus, the concept of LOH as conceived two decades ago has weathered criticism and survived the times.

HISTORICAL PERSPECTIVE
The functions of the testes have been known since antiquity. However, the active agent responsible for virility—that is testosterone—has only been identified quite recently. Nevertheless, on the assumption that the testes contain the ingredients required for manhood, organotherapy with animal testes and testis transplantation have been used over centuries in different medical cultures for treatment of symptoms of hypogonadism, for example in Greco-Roman, Arabic, Chinese, Voodoo, and modern medicine (for historic details see Nieschlag & Nieschlag 2019). Moreover, ever since antiquity rejuvenation and eternal youth continue to be a much-desired wish. While in the past some sought an imaginary ‘fountain of youth’ (e. g., Fig. 1), more recently others turned to testicular organotherapy and transplantation, thereby blurring the borders between defined medical disorders and socio-cultural desires, a problem persisting until today in the form of ‘life-style medicine’.

By transplanting testes from roosters to capons and documenting regained androgenicity in the transplanted animals, in 1849 Adolf A. Berthold (1803–1861) first postulated the existence of a substance transmitted by blood to the target organs and responsible for the observed effects (Berthold, 1849). Although the term ‘hormone’ was only coined some 5 decades later, Berthold was the first to propose a hormonal action caused by the transplanted testes and the testes in general. It is not known whether Charles-Edouard Brown-Séquard (1817–1894) was stimulated by Berthold’s transplantation experiments when he injected himself subcutaneously with a cocktail from dog and guinea pig testes extracts, testicular vein blood, and semen (Brown-Séquard, 1889). He reported miraculous effects of
revigoration. Although these results can only be interpreted as placebo effects, the ‘Brown-Séquard-elixir’ manufactured subsequently became a booming business worldwide for treatment of hypogonadism in aging men and for rejuvenation in general in the decades following its initial publication.

Moreover, both in the USA and Europe at the beginning of the 20th century, and as a direct translation of Berthold’s and his followers’ animal experiments, surgeons began transplanting human as well as animal testes to patients for treatment of hypogonadism and for rejuvenation (for details see Nieschlag & Nieschlag 2019).

TESTOSTERONE IS BORN
Recognition of testicular organotherapy and transplantations as ‘poppy cock’ (as an international committee sent by the Royal Society of Medicine to Tunis in 1927 called Serge Voronoff’s (1866–1951) testicular transplantations from monkeys to humans) or at best placebos (Cussons et al., 2002) stimulated academic research and pharmaceutical companies active in the young field of endocrinology to intensify the search for the active substance secreted by the testes. Using different approaches, in 1935 these efforts culminated in the isolation of testosterone by Ernst Laqueur’s team (1880–1947) (David et al., 1935), as well as the chemical synthesis of testosterone simultaneously by Adolf Butenandt’s team (1903–1995) (Butenandt & Hanisch, 1935) and Leopold Ruzicka’s (1887–1976) (Ruzicka & Wettstein, 1935). Shortly thereafter testosterone became available for clinical use. Since then various oral, intramuscular and transdermal preparations have been developed and applied in health care.

FROM ‘MALE CLIMACTERIC’ TO LATE-ONSET HYPOGONADISM
Following growing knowledge about female reproductive endocrinology and the climacteric, the hypothesis of a ‘male climacteric’ emerged. However, in the absence of accurate methods for measuring androgens and gonadotropins, this misunderstanding was based only on symptoms and was lacking a sound pathophysiological basis (Walker, 1938; Landau, 1951). Despite the lack of biochemical evidence for a testosterone deficiency, testosterone was prescribed for ‘the male climacteric’ more or less indiscriminately. At that time, predominantly short-acting intramuscular testosterone propionate was used (Werner, 1946).

With the establishment of radioimmunoassays and the possibility of measuring testosterone in blood (Nieschlag & Loriaux, 1972), knowledge about testicular function in general and also in advanced age slowly accumulated. Although the endocrine capacity of the testes and the pituitary decline in aging males (Nieschlag et al., 1982; Veldhuis et al., 1992), serum testosterone levels (as well as sperm counts) are maintained in many healthy men. Epidemiological studies confirmed that only a small group of seniors develop testosterone levels below the threshold for younger men (Harman et al., 2001; Araujo et al., 2004; Wu et al., 2008). When these testosterone-deficient patients also
Table 1 Late-onset hypogonadism (LOH) as defined, diagnosed, and treated in the guidelines endorsed by ISA, ISSAM, EAU, EAA, and ASA (Nieschlag et al., 2005d; Wang et al., 2008b)

| Definition: | A clinical and biochemical syndrome associated with advancing age, characterized by specific symptoms, and a deficiency in serum testosterone (T) |
| Diagnosis: | Clinical symptoms and low total serum T (7.00–11.00 a.m.) and/or free T calculated from total T and SHBG. |
| Treatment: | Prostate and mammary carcinoma must be excluded. Natural T (i.e., no synthetic androgens) preparations to be used. At start, short-acting preparations (transdermal, oral, buccal) should be preferred over long-acting preparations (intramuscular, subdermal). |
| Monitoring: | Red blood, DRE and PSA after 6 and 12 months. Thereafter: yearly. Failure to benefit should result in discontinuation. |

SHBG, Sex hormone binding globulin; DRE, Digital rectal exploration; PSA, Prostate specific antigen.

demonstrate symptoms of testosterone deficiency, a diagnosis of hypogonadism appears justified. Ensuing studies showed that among the various symptoms, sexual complaints such as loss of libido, decreased morning erections and erectile dysfunction were well correlated with decreasing testosterone levels and most indicative of this type of hypogonadism in aging men (Wu et al., 2010).

In analogy to ‘late-onset diabetes’, we called this disorder ‘late-onset hypogonadism’ as a combined form of primary and secondary hypogonadism. The author first used this term officially in a lecture at the XVII Congress of the Polish Endocrine Society in Warsaw on May 26, 2002, and in an ensuing publication (Zitzmann & Nieschlag, 2003). We also suggested this term at the 10th World Congress on the Menopause on June 2, 2002. As a result of the discussions at this congress, the recommendations drafted by the International Society for the Study of the Aging Male (ISSAM) were changed from ‘Androgen deficiency of aging men (PADAM)’ (Morales & Lunenfeld, 2001) to ‘Investigation, treatment and monitoring of late-onset hypogonadism in males’ (Morales & Lunenfeld, 2002).

GUIDELINES FOR LATE-ONSET HYPOGONADISM

In due course, these recommendations were extended and became the official guidelines not only of ISSAM but also of the International Society of Andrology (ISA) and the European Association of Urology (EAU) (Nieschlag et al., 2005a, 2005b, 2005c, 2005d, 2006a, 2006b). Three years later the guidelines were re-edited and extended and also became the official guidelines of the European Academy of Andrology (EAA) and the American Society of Andrology (ASA) (Wang et al., 2008a, 2008b, 2009a, 2009b, 2009c, 2009d). According to the Web of Science (as of July 15, 2019), the 2005 and 2008 editions of the guidelines have been quoted 586 and 840 times, respectively, and the term ‘late-onset hypogonadism’ has slowly replaced misnomers such as male climacteric, male menopause, andropause, and partial androgen deficiency of aging men (PADAM). The essence of these guidelines (Table 1) remains valid until today and has been adopted by later guidelines of other organizations such as EAU (Dohle et al., 2012–2017), International Society of Sexual Medicine (ISSEM) (Dean et al., 2015), Canadian Society of Urology (Morales et al., 2015), the European Menopause and Andropause Society (Dimopoulou et al., 2016), and the US Endocrine Society (Bhasin et al., 2018).

However, while all guidelines agree that a combination of symptoms of testosterone deficiency and low serum testosterone levels are prerequisites for testosterone substitution, no agreement on the threshold levels signifying low testosterone has been found. When first recognized, the different thresholds ranging from 7.5 to 12.0 nmol/L appeared to be simply national differences between countries—in this case Germany, France, Spain, and UK (Nieschlag et al., 2004). However, further research revealed that there are in fact different threshold levels for the various symptoms (Kelleher et al., 2004). In a large cohort of patients suffering from LOH, it has been shown that loss of libido and vigor may occur at testosterone levels below 15 nmol/L, abdominal obesity below 12 nmol/L, depressed mood, sleep disturbance, lack of concentration and diabetes mellitus type 2 below 10 nmol/L and hot flushes and erectile dysfunction below 8 nmol/L (Zitzmann et al., 2006). Hence, it depends on the perception of physicians— or committee—which symptoms they give priority for treatment. This may explain why even today the discrepancies concerning threshold levels for testosterone substitution between the above listed guidelines still range from 8 to 12 nmol/L.

TRANSATLANTIC DISCREPANCIES

In Europe, the guidelines were generally followed so that the number of patients receiving testosterone prescriptions increased moderately over the following years (e.g., Layton et al., 2014). However, in the USA a fivefold increase in total and new testosterone users among men over 30 years was noted from 2002 to 2013 (Baillargeon et al., 2018). Only 12% of these men underwent proper pre-treatment evaluation, while 33% had none and 55% had only one testosterone measurement before prescription (Table 2) (Gabrielsen et al., 2016). The reasons among others for this misuse of testosterone were inappropriate prescribing practices by so-called ‘Low T clinics’ as well as direct-to-consumer advertising for testosterone in the public media (Storrs, 2014) —developments considered unacceptable in Europe.

This commercialization of testosterone prescriptions and the steeply increasing number of testosterone users caused the FDA to intervene based on several controversial and partially flawed studies (Xu et al., 2013; Vigen et al., 2013; Finkle et al., 2014; Baillargeon et al., 2014) and issued safety statements and warnings for testosterone use: ‘Based on our findings, we are requiring

Table 2 Percentage of men in the USA undergoing accurate or inappropriate pre-treatment evaluation before prescription of testosterone. Data are based on records from insurance companies and summarized by Gabrielsen et al. (2016) (with permission by RightsLink)

| Study | Database type | Men | n | Number of pre-treatment tests % |
|-------|---------------|-----|---|-------------------------------|
| Layton et al. (2014) | Insurance | >18 years | 410,029 | 40 | 50 | 10 |
| Muram et al. (2015) | Insurance | >18 years | 63,534 | 29 | 31 | 40 |
| Jasuja et al. (2015) | Veteran Affairs | >20 years | 111,631 | 16.5 | 83.5 | |
| Baillargeon et al. (2015) | | >40 years | 61,474 | 24.6 | 57.4 | 18 |
labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Healthcare professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy' (FDA 2014). The controversy about this issue and the respective paper prompted 30 societies to call for the retraction of the paper by Vigen et al. (Morgentaler et al., 2015).

In contrast, but based on the same papers and a European meta-analysis (Corona et al., 2014) the European Medicine Agency (EMA) concluded their evaluation of the situation: ‘The PRAC review did not find consistent evidence that the use of testosterone in men who do not produce enough testosterone (a condition known as hypogonadism) increases the risk of heart problems’ (EMA 2014). Nevertheless, the FDA warnings achieved their goal and resulted in a significant reduction of new and total testosterone users in the USA.

BACK TO EVIDENCE-BASED MEDICINE

Meanwhile, a number of studies and meta-analyses of the effects and side effects of T substitution in hypogonadal men, including those with LOH, have been undertaken and published. Among these, the placebo-controlled so-called ‘Seven T trials’ of testosterone substitution in men over the age of 65 years with LOH play a prominent role. As will be discussed in a separate chapter of this issue (see this issue of ANDROLOGY) the trials revealed, that in these LOH patients testosterone substitution had a positive effect on libido and sexual function, on walking distance, on bone mineral density of lumbar spine and hip, and on hemoglobin in otherwise unexplained anemia. All results from the ‘Seven T trials’ and other studies are reflected in the recent Practice Guidelines of the US Endocrine Society (Bhasin et al., 2018); the guidelines not only list advanced age as a cause of organic hypogonadism, but also conclude: ‘in men ≥65 years who have symptoms or conditions suggestive of T deficiency and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussions of the potential risks and benefits’. This confirms the original LOH recommendations of 2005 and 2008 and describes what responsible physicians/endocrinologists would do anyhow, namely prescribe testosterone only to hypogonadal patients with symptoms of testosterone deficiency and documented low testosterone.

Thus LOH has overcome various doubts negating its existence and has reached maturity as a pathophysiological entity. However, questions remain to be answered: how much does organic LOH cause various comorbidities such as erectile dysfunction, loss of libido, obesity, metabolic syndrome, diabetes type 2, anemia, and sarcopenia and to what extent do comorbidities cause functional LOH (Corona et al., 2016).

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