
Introduction

In the past decade, several peer-reviewed studies have been reported in the medical literature, which have advanced our understanding of the management of male hypogonadism. However, many of these findings have not been put into routine clinical practice up to now. This book brings together key areas where our understanding and knowledge of hypogonadism have progressed. These include the diagnosis and management of hypogonadism and the role of testosterone deficiency in specific tissues and organ systems and its adverse effect on mortality.

Although male hypogonadism is an established clinical condition which can be treated, many men suffering from it are not diagnosed. There are several reasons for this, which include a lack of general clinical awareness, the non-specificity of its symptoms, biochemical tests which are not always easy to interpret, concerns over the safety of testosterone replacement therapy especially in older men, and the false perception that testosterone is a sex hormone which has no other specific health benefits. This is compounded by the fact that men in general see their doctors less often than women and are less likely to discuss their sex problems. Tiredness is a common symptom of hypogonadism which can be profound but there are not many medical practitioners who include the assessment of testosterone levels in the clinical workup of this symptom. Hypogonadism impairs well-being and quality of life and puts relationships and employment at risk. Guidelines for the diagnosis and management of hypogonadism [1] and late-onset hypogonadism [2] were published in 2006 to assist clinicians [Arver and Lehtihet, p. 5].

The diagnosis of hypogonadism in the presence of symptoms is dependent on the measurement and interpretation of the serum testosterone level. Total testosterone is widely used and threshold levels below which hypogonadism can be diagnosed (in the presence of symptoms) are provided in the published guidelines mentioned above. Levels in the lower-to-normal range can be consistent with the

diagnosis of hypogonadism. The biologically active fractions of testosterone, free and bioavailable testosterone levels, in borderline cases can be helpful to the clinician when making the diagnosis. A working knowledge and current understanding of these tests is therefore important for the clinician to be able to interpret the values [Diver, p. 21].

One of the major recent advances has been new formulations of delivery with improved dosing schedules that allow replacement of testosterone to physiological levels [3]. These primarily include dermal gels, buccal tablets and depot injection therapy [Gooren, p. 32]. These formulations also allow therapies to be tailored to individual patient's preferences and needs.

There is evidence to support the notion that the level of tissue androgenization is not only dependent on the circulating testosterone level but also on the sensitivity of the androgen receptor. A polymorphism of the androgen receptor involving the number of CAG repeats in exon 1 is associated with differences in the biological actions of androgens [Zitzmann, p. 52]. These include effects on the prostate, spermatogenesis, bone density and psychological traits. Potentially further knowledge of this and other androgen receptor polymorphisms may lead to more accurate dosing of testosterone replacement therapy, i.e. pharmacogenetics.

Late-onset hypogonadism has now become the recognized terminology to describe symptomatic testosterone deficiency associated with aging. There is increasing evidence that its diagnosis and treatment is safe and improves well-being and quality of life [Gooren, p. 62]. There is also evidence that testosterone substitution has beneficial effects on specific conditions that are related to age which include frailty, osteoporosis, diabetes and cardiovascular disease. The importance of testosterone in normal bone turnover has been recognized for some time; however, testosterone levels are not always assayed in men with osteoporosis [Tuck and Francis, p. 123]. Frailty, including the risk of falls, is associated with low testosterone levels and studies are underway to determine if testosterone replacement therapy may be of clinical benefit [Srinivas-Shankar and Wu, p. 133]. Testosterone deficiency has significant adverse effects on cognition and is associated with the development of Alzheimer's disease. Only small studies have been conducted but they do signify that larger studies are indicated to investigate if there is a role for testosterone replacement therapy [Cherrier, p. 150].

Over the last 2 years, four population-based epidemiological studies have reported that low circulating testosterone levels are associated with an increase in mortality [4-7]. These studies have found the more positive link with all-cause mortality; however, in some studies there are specific correlations with death from respiratory disease, cardiovascular disease and cancer. A large follow-up study of men with locoregional prostate carcinoma has found that men treated with androgen suppression therapy have an increased hazard ratio for sudden cardiovascular death, myocardial infarction and diabetes [8]. The obvious question is whether or not these correlations with low testosterone levels are causative or a consequence of the disease

process itself. Any inflammatory state results in an increase in the production of cytokines which are known to suppress the hypothalamic-pituitary axis. The associations and effects of testosterone deficiency in ageing, obesity and chronic disease must be taken in context with changes in other hormones such as growth hormone, glucocorticoids and cytokines.

To understand this in more detail, a wider knowledge of how testosterone deficiency affects these tissues is required. The major areas where such work has been performed are the metabolic syndrome and diabetes [Stanworth and Jones, p. 74] and coronary heart disease [Nettleship et al., p. 91]. Early evidence suggests that testosterone may have important beneficial effects in these conditions. Diabetes and the metabolic syndrome is associated with a high prevalence of hypogonadism, and testosterone substitution therapy can improve insulin resistance. Male gender is a major cardiovascular risk factor; however, there has been no adequate explanation for this phenomenon. There has been the perception that testosterone is bad for the heart and that the difference between sexes may also be that oestrogens are cardioprotective. There is recent evidence that testosterone deficiency is associated with the presence and degree of atherosclerosis and studies in animal models demonstrate that testosterone is atheroprotective. The role of testosterone substitution in chronic diseases including HIV, COPD and renal failure has been studied, albeit in small trials [Bhasin and Storer, p. 163]. Evidence has also been found that testosterone has a beneficial effect on the function of the immune system.

Erectile dysfunction is not only a symptom of hypogonadism but may be the first symptom of diabetes and/or cardiovascular disease. It has been stated that sexual health is a portal to men's health, particularly cardiovascular disease. In addition, we are only now beginning to understand the importance of the role of testosterone deficiency and its replacement in erectile dysfunction [Blute et al., p. 108].

One of the main concerns of testosterone replacement therapy has been whether or not it increases the risk of men developing prostate cancer. This concern is addressed by Morgentaler and Schulmann [p. 197] and their conclusion is that 'the available evidence strongly suggests that testosterone therapy is safe for the prostate'; however, 'it is strongly recommended that men undergoing testosterone therapy undergo regular monitoring for prostate cancer'. Testosterone therapy is contraindicated in men with heart failure but recent evidence using physiological testosterone substitution has shown that it has a beneficial effect in men with moderate chronic heart failure [Malkin et al., p. 183].

The current knowledge acquired from recent research on testosterone in several fields suggests that testosterone replacement may have significant benefits on quality of life and life expectancy. These findings underline the need for doctors to have an increased clinical awareness of hypogonadism and its diagnosis and treatment. However, larger and longer-term studies are needed to further evaluate these benefits and the safety of testosterone replacement therapy. Until further studies have become available for treating these novel indications, it is mandatory that the clinician

first makes a sound diagnosis of hypogonadism before commencing testosterone therapy. In borderline cases where there is clinical suspicion as advised by the guidelines, a 3-month clinical trial of testosterone replacement therapy can be performed.

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References

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