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Subclinical male hypogonadism

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Male hypogonadism is traditionally defined as the inadequate production of testosterone and impaired spermatozoa generation in the presence of elevated or reduced levels of gonadotropins. A more frequent measurement of testosterone levels and the development of highly sensitive and specific assays have led to the detection of less clinically evident gonadal dysfunction, in which small biochemical alterations may or may not be accompanied by signs and symptoms. This condition is called “compensated” or “subclinical” hypogonadism. To determine whether subclinical hypogonadism is a paraphysiological state, a clinical condition in itself, or a precursor to overt hypogonadism, we carried out a literature review with the aim of establishing a practical approach to subclinical hypogonadism.

Introduction

Male gonadal function is regulated by a complex feedback loop that originates from the pulsate release of gonadotropin releasing hormone (GnRH), produced in the hypothalamic neurons, followed by secretion of gonadotropins by the anterior pituitary gland. Leydig cells and Sertoli cells in the testes are stimulated respectively by the pituitary gonadotropins – luteinising hormone (LH) and follicle-stimulating hormone (FSH) – producing sex steroids and inhibin, which in turn exert a negative feedback on GnRH, LH and FSH secretion. In addition to this regulated hormone secretion, gonads also produce the spermatozoa necessary for reproduction. The loss of one or both of these functions is

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named male hypogonadism.[1] This is traditionally defined as the inadequate production of testosterone (T) and a subnormal number of spermatozoa in the presence of elevated or of reduced levels of gonadotropins. The former, hypergonadotropic hypogonadism, is due to primary testicular failure, while the latter, hypogonadotropic hypogonadism, is caused by a secondary hypothalamic–pituitary dysfunction. Clinical features of hypogonadism differ according the age of presentation, genetic background and associated risk factors.[2]

A more frequent measurement of T levels and the development of highly sensitive and specific assays have led to the detection of less clinically evident gonadal dysfunction and the recent emergence of the concept of "compensated" or "subclinical" hypogonadism (SH).[3,4] However, while there have been numerous publications concerning other subclinical endocrine diseases such as subclinical hypothyroidism and subclinical Cushing's syndrome, SH has only recently begun appearing in the literature, and the few reports are often inconclusive. It is unclear if SH is a paraphysiological state or a distinct clinical entity, or even a transitional state preceding overt primary hypogonadism. This review will focus on the definition and diagnostic approach to SH, providing indications for its screening and management.

Literature sources

A search of MEDLINE articles, textbooks and article references revealed few studies attempting to identify a subclinical alteration of the hypothalamus–pituitary–gonadal axis, its consequences, or its evolution. The definition of SH in various studies ranges from a characterisation of biochemical features of elevated gonadotropins in the presence of normal T,[5–7] to a description of these features in the absence (or almost) of signs and symptoms,[4] and finally to the condition of impotent patients with psychosomatically reduced T and increased LH without overt signs of androgen deficiency.[3] Given these different definitions, to avoid misunderstanding we suggest diagnosing SH on a biochemical basis, as with subclinical endocrine diseases,[8] but with some additional features that we discuss below.

In recent decades the diagnosis of SH has gained momentum through large-scale screening for partial androgen deficiency of the ageing male (PADAM). In addition, evaluation of T levels when monitoring conditions such as cardiovascular and metabolic diseases has increased in clinical practice. These circumstances have led to a rise in the detection of subtle alterations of gonadal function and male sex hormones that could be described as SH.

Normal hypothalamic–pituitary–gonadal axis function

The hypothalamic–pituitary–gonadal (HPG) axis is highly regulated. GnRH hypothalamic neurons receive excitatory and inhibitory signals which influence the release of GnRH. The "GnRH pulse generator" controls the release of gonadotropins – LH and FSH – from the anterior pituitary gland.

Once released in the systemic circulation, LH and FSH bind testicular receptors on the Leydig and Sertoli cells respectively, stimulating sex steroid production, spermatogenesis and inhibin B production. In turn, sex steroids and inhibin B exert a negative feedback on GnRH, LH and FSH secretion in the hypothalamus and pituitary gland respectively.[9] This mechanism acts to maintain testicular output. The loss or modification of one of these regulatory loops affects the whole system and can be influenced by various physiological and pathological conditions.

HPG set point

The relationship between T levels and gamete production in the testis with respect to LH and FSH stimulation appears to be regulated by a complex, genetically determined individual set point.[10] The most well known examples include androgen receptor sensitivity, genetically determined by CAG triplets,[11] and aromatase gene polymorphism,[12] affecting the conversion of androgens to oestrogens. Healthy men with CAG repeat polymorphism in the androgen receptor (AR) have been found to have impaired androgen feedback and a relative increase in circulating T. These mechanisms lead to individual differences in the LH-to-T ratio, further complicating diagnosis.