Loss of Testosterone: Is Andropause Inevitable?

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All bodily systems undergo changes as we age. Aging is an inexorable process of cell alteration, cell death and consequent decreased anatomic and metabolic function. These changes are attended by progressively advancing signs and symptoms, which in many instances, are amenable to amelioration by appropriate intervention.

Endocrine changes: the four pauses

Although each of the terms mentioned below are misnomers since there is no actual "pause", these descriptors that are easily recognizable and commonly used in the medical literature.

Menopause

Menopause is a clearly delineated entity, which is inevitable in the life of every woman. For practical purposes, ovarian function does not pause, but actually ceases, never to recover again.

Andropause

Andropause is a clinical entity in which the falling levels of testosterone, in the aging male, induce symptoms that are in part or completely relieved by the administration of testosterone.

Adrenopause

Adrenopause is the term used to denote the decline in the adrenal gland's production of dehydroepiandrosterone (DHEA) with aging. Does this induce symptomatology that can be reversed by treatment with DHEA? The evidence of this in humans is not strong, except in cases where there is virtual absence of DHEA, such as in Addison's disease. In this circumstance, especially in post-menopausal women, there is increased energy and an increased sense of well-being when DHEA is administered. DHEA is not available for sale in Canada, but can be purchased over the counter in the US.

Somatopause

The decline in growth hormone secretion with aging is referred to as somatopause. There is an increasing body of literature suggesting that individuals with overt adult growth hormone deficiency may demonstrate a variety of metabolic benefits from growth hormone administration; however, the role of growth hormone in promoting the growth of malignancies has yet to be clearly resolved. It remains to be determined whether growth hormone therapy will be recommended on a wide-scale basis.

The physiological importance of testosterone

Although testosterone is predominantly acclaimed as the leading male sex hormone, promoting libido and to a lesser extent, erectile function, its physiological importance extends far beyond the sexual realm.

Erythropoietin

Testosterone enhances the secretion of erythropoietin from the kidneys. Erythropoietin stimulates hematopoiesis, red blood cell and hemoglobin production. Unexplained anemia in a

male could be due to testosterone deficiency. In some men treated with testosterone, this stimulatory effect is so significant that the hemoglobin and the hematocrit may rise above the upper limit of normal. If this happens, the dose of testosterone has to be reduced, or if this reduction induces undesirable side-effects, periodic phlebotomy may be undertaken.

Protein synthesis in muscles

Testosterone retains nitrogen and induces protein synthesis in muscles, which causes an increase in lean body mass, by enhancing muscle development. At the same time, testosterone treatment causes a reduction in fat mass. Therefore, hypogonadal men tend to:

- fatigue more readily,
- have decreased energy and
- decreased strength.

All of this can be reversed when treatment with testosterone is initiated.

Bone physiology

Testosterone has a significant positive impact on bone physiology. It stimulates the formation of osteoid and periosteal bone. This effect of testosterone operates through its conversion to dihydrotestosterone (DHT) under the catalysis of the enzyme, 5-α-reductase. Testosterone also interferes with bone breakdown by inhibiting osteoclast differentiation through the action of estradiol, to which testosterone is converted in the presence of the enzyme, aromatase. Hypogonadal men with osteoporosis show increased bone mineral density when treated with testosterone.

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Testosterone's receptor sites

Testosterone has receptor sites in the vascular smooth muscle fibres and in the heart. Men with the most severe degree of coronary artery obstruction tend to have reduced serum testosterone levels. Testosterone injected directly into coronary arteries induces vasodilation and hypogonadal men, with chronic stable angina treated with testosterone, take longer to demonstrate 1 mm ST depression during a stress test, when compared with men treated with placebo.

Treatment with testosterone tends to lower LDL-cholesterol and triglycerides levels. When put together, these findings strongly suggest that testosterone has a cardioprotective effect.

Testosterone in the brain

Testosterone is active in the brain, not only to stimulate libido, but to support functions in other brain centres as well. Using a standard depression scale (Beck's Depression Inventory [BDI]), studies have shown an increase in BDI with advanced age. This, of course, is not due solely to the falling levels of testosterone in the aging male but it may, in part be because higher BDI scale are also associated with lower testosterone levels. Hypogonadal men treated with testosterone have a reduction in various scales which measure depression. In tests of cognition, hypogonadal men tend to score lower on memory tests, visuospatial functioning and visual memory.

Hypogonadism

As men age, they become hypogonadal. Hypogonadism is defined as a reduced state of testicular function, both with respect to the secretion of testosterone and the production of

sperm. Hypogonadism may be induced by pathological states affecting the testes (primary hypogonadism). Examples of such pathology include:

- Klinefelter's syndrome,
- orchitis,
- trauma,
- irradiation and
- chemotherapy.

Secondary hypogonadism is induced by pathological states of the hypothalamic-pituitary axis. Examples of these include:

- insufficiency of gonadotropin releasing hormone (GnRH) due either to an absence of GnRH or an abnormality of its receptor (Kallmann's syndrome is GnRH insufficiency plus anosmia),
- hypothalamic or pituitary tumour, which is either functioning or non-functioning (the most common functioning tumour is a prolactinoma),
- hypopituitarism (idiopathic or surgically induced),
- hyperprolactinemea and
- hemochromatosis.

GnRH can be suppressed by a number of different factors including:

- excess cortisol,
- systemic illness,
- malnutrition,
- excess exercise,
- estrogens,
- cyproterone acetate,
- opioid drugs and
- AIDS.

The most common form of hypogonadism in the aging male is andropause, a state of reduced (not necessarily subnormal) testosterone production and availability.which induces symptoms. Several changes of aging reduce both testosterone production and availability. These include:

1. Decreased Leydig cell numbers, hence decreased testosterone production
2. Vascular changes in the testes
3. Decreased Leydig cell responsiveness to LH as evidenced by decreased testosterone secretion after the administration of human chorionic gonadotropin (hCG), which has the biological activity of LH
4. Decreased GnRH pulse frequency and amplitude, hence decreased production of LH, which stimulates testicular Leydig cells to produce testosterone
5. Increased production of sex hormone binding globulin (SHBG) giving rise to decreased free and bioavailable testosterone
6. Loss of the diurnal variation of testosterone secretion (in younger men testosterone is higher in the morning)
7. Obesity—adipose tissue contains high concentrations of aromatase, thus enhancing the conversion of testosterone to estradiol

The most reliable measure of testosterone is bioavailable testosterone. Assays for total testosterone are generally reliable, as opposed to assays for free testosterone, which may not give accurate results. SHBG binds 50% to 60% of total testosterone very avidly, making SHBG-bound testosterone unavailable for immediate biological activity. Albumin-bound testosterone (about 40% of a male's total testosterone) and free testosterone (about 2% of total testosterone) together constitute bioavailable testosterone. Unfortunately, most provincial jurisdictions will not cover the cost of this reliable assessment of biologically available testosterone.

Table 1

Testosterone preparations available in Canada

Generic name or description	Route	Usual starting dose
Testosterone enanthate	Intramuscular	200 mg every two weeks
Testosterone cypionate	Intramuscular	200 mg every two weeks
Testosterone undecanoate	Oral	80 mg b.i.d with food
Testosterone patch	Transdermal	5 mg per day
Testosterone gel	Transdermal	5 g of 1% gel per day

Managing the older male

The male who complains of the following may have a number of possible pathological processes as the primary etiology of his complaints. These are the potential complains:

- weakness,
- fatique,
- lethargy,
- mood changes,
- cognitive changes,
- osteopenia or osteoporosis,
- anemia,
- loss of muscle mass,
- frailty,
- sexual dysfunction,
- decreased motivation and
- decreased self-esteem.

Pathological processes which can induce these symptoms include:

- chronic disease,
- cancer,
- cardiovascular disease,
- various systemic diseases,
- depression,
- anxiety,
- thyroid dysfunction and
- poor life-style factors.

A significant number of men, however, may have the above symptomatology because of reduced levels of testosterone, particularly bio-available testosterone.

Management of the older male, regardless of the etiology of his symptoms, should include general life-style changes as applicable. These include:

- weight reduction,
- cessation of smoking
- cessation of illicit drug use,
- decreased alcohol intake or total abstinence and
- increased exercise.

Psychosocial factors may also be playing a role in symptomatology and may need specific counselling or psychotherapy, irrespective of other pathologies. Such factors include:

- relationship issues,
- facing retirement,
- family dysfunction,
- anger management, *etc.*

If there are no absolute contraindications (*i.e.,* prostate or breast cancer, very severe urinary obstructive disease, polycythemia), men with symptoms and a low or low normal level of testosterone are candidates for a four month to six month trial of testosterone therapy. There is no evidence that testosterone therapy will cause a *de novo* prostate cancer, but it may theoretically exacerbate an existing one. Prostate monitoring by both a digital rectal examination and a prostate specific antigen (PSA) measurement are essential.

Four testosterone treatment modalities are available in Canada, these are:

- Injections
- Pills
- Patch
- Gel

Table 1 explains the testosterone preparations that are available in Canada and gives the usual starting doses of these preparations. If the patient's symptoms are, in part or in total, related to reduced testosterone availability, there should be an amelioration or elimination of the symptoms within three months to four months. If there is not, then the clinical state will dictate whether to increase the dose, change to another form of testosterone, or discontinue it altogether. If this is done, in retrospect, some patients recognize a beneficial effect. If there is no clinical response, but testosterone levels are very low, a bone mineral density study is recommended to elicit an objective measure of testosterone insufficiency and that is osteopenia or osteoporosis.

Conclusion

Aging brings with it multiple bodily changes. The progress to death is inevitable, in other words, the anti-aging movement is a fruitless effort. But, what is not fruitless is intervention that is safe and effective to delay the inevitable, to reduce symptomatology and to improve the quality and perhaps even the quantity of life.

This article has focused on hypogonadism in the aging male, andropause and other hypogonadal states; however, there are many other areas of changes in the aging male that need more study, both within and outside of the endocrine system.

Within the endocrine system, we need a better understanding of the etiology and treatment of the increased incidence of hypogonadism in diabetes mellitus in the metabolic syndrome, in HIV positive men, in obesity and in depression.

Treatment with testosterone is certainly not the answer to all of the ills that befall aging men, but for a subset of those men, under carefully monitored circumstances, such therapy may certainly improve life from several perspectives. There is now an ever-increasing focus on the systemic and metabolic functions of the aging male and the years to come will bring a better understanding of how we can intervene to prevent and treat the common complaints of this growing population.

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