REVIEW ARTICLE

Hormonal profiles behind the heart of a man

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Abstract

This study focuses on the role of sex steroids on the libido, sexual life, emotional and physiological heart of men of all ages. Sex steroids play a significant role throughout a man's life, with a gradual decline in old age. The foetal testis secretes testosterone and dehydroepiandrosterone at about nine weeks gestation. At puberty, testosterone increases dramatically in boys. Changes in weight and height of boys across this period are associated with increasing testosterone concentration and sex hormone binding globulin (SHBG). Romantic thoughts, fantasy, and sexual pleasure-seeking behaviour in adolescents are associated with exposure to high androgens secretion. Thus, the libido and sexual life of a man is initiated and maintained by testosterone and SHBG.

Lower testosterone levels are associated with erectile dysfunction among other risk factors: diabetes, hypertension, heart disease, psychological stress and obesity. Men with proven coronary atherosclerosis have lower levels of testosterone and SHBG, which have negative correlation with very low-density lipoprotein, triglycerides, body mass index and body fat mass. These are some of the risk factors for cardiovascular diseases. Thus, in men, endogenous sex steroids impart beneficial effects on the heart. How exactly endogenous sex steroids act on the heart is not clear. Further study is needed to understand the interaction between endogenous sex steroids, higher centers in the brain and the heart of a man. (Cardiol J 2009; 16, 4: 300–306)

Key words: sex steroids, testosterone, libido, sex life, erectile dysfunction, atherosclerosis, cardiac risk factors

Introduction

The love/lust essence of the emotional heart was felt and recognised by men and women long before the discovery of the physiological heart in the body, at the same time as the evolution of the god or goddess of love at the dawn of civilization. Ever since, people have expressed their romantic heart in various ways through art, literature and culture, blending their feelings and imaginations.

In European tradition, the heart symbol is drawn in a stylised shape in red, signifying both blood and, in many cultures, passion and strong emotion. Though there is disagreement about the genesis of the heart-shape, the typical heart shape as depicted on the playing card may have been adopted from Greek culture, because the heart shape formed by the back and wings of a dove is associated with Aphrodite, the ancient Greek goddess of love. Even today, young men and women want to know the reality of the romantic or emotional heart.

What is behind this heart? How does romance emanate from the heart? Are the emotional heart and the physiological heart the same? How does the heart change with age? What are those factors that

influence both the emotional and the physiological heart? These have been very important questions down the ages because of the association between libido, sex life and some bio-elements regulating the relationship between the heart and lifestyle. In this article, an attempt has been made to answer those queries with elucidation of the interacting facets and trajectories of the emotional and physiological human heart in the light of the findings of modern medical science.

Method and design

Data was extracted from the literature though the MEDLINE database service from the years 2000 to 2008 to answer these queries. A search was made with key words 'testosterone' and 'heart'. Surveys, reviews, community-based and clinical investigations pertinent to the theme of this article were included in this review. This article is a multidisciplinary approach following a traditional review pattern.

During foetal life

The endogenous male sex hormones, testosterone and its derivatives, not only create a man but also maintain manliness, along with other metabolic factors. These hormones function throughout life, with a gradual decline in old age. The 'androgen' generally denotes testosterone, its precursors and derivatives that function like testosterone and are anabolic in nature. The foetal testis secretes the androgens testosterone and dehydroepiandrosterone at about nine weeks gestation. Testosterone and its derivative dihydrotestosterone (DHT) stimulate the development of accessory sexual organs as well as other important functions of foetal development with the influence of chorionic gonadotropin hormone. As the foetal pituitary-hypothalamic axis develops, testosterone secretion by foetal testis comes under the influence of foetal luteinizing hormone (LH) and follicle stimulating hormone (FSH). The highest testosterone levels are reached at about 16–20 weeks gestation, coincident with maximal secretion of foetal LH and FSH. However, these hormone secretions become significantly lower at birth and remains so until the advent of puberty [1].

Pubertal changes

At puberty, testosterone secretion increases and produces growth and maturation of the male accessory organs and secondary sex characteristics such as deepening voice and characteristic pattern of hair distribution. The spurt in growth as measured by height occurs some two years later. No precise point in time comparable with the onset of menstruation in the female exists to indicate the attainment of maturity in the male [1].

Sex steroids exhibit an increase in concentration, mainly from the adrenal glands, after the age of 7 to 9 years in both boys and girls. A rise in gonadal function with age may contribute to this. Testosterone concentration increases more dramatically in boys [2]. In boys, changes in weight and height are accompanied by increases in testosterone and sex hormone binding globulins (SHBG). In girls, anthropometric variables do not change and are not correlated with oestradiol concentration [3].

Mechanism of pubertal changes

Neurons that produce gonadotropin-releasing hormone (GnRH) reside in the basal forebrain and drive reproductive function in mammals. A family of neuropeptides encoded by the Kiss-1 gene, the Kisspeptins, and their cognate receptor, GPR54, have been implicated in the regulation of GnRH secretion. Kisspeptins are potent secretagogues for GnRH. The Kiss-gene is a target for regulation by gonadal steroids e.g. oestradiol and testosterone, metabolic factors such as leptin, environmental factors such as photoperiod, and season in animal. Kiss-1 neurons in the arcuate nucleus may regulate the negative feedback effect of gonadal steroids on GnRH and gonadotropin secretion in both sexes. The expression of Kiss-1 gene in the anteroventral periventricular (AVPV) nucleus is sexually dimorphic, and Kiss-1 neurons in the AVPV nucleus may participate in the generation of preovulatory GnRH/LH surge in the female rodent. Thus the Kiss-1 neurons have emerged as primary transducers of internal and environmental cues to regulate the neuroendocrine reproductive axis in mammals [4].

The G-protein-coupled receptor, GPR54 and its ligand, Kisspeptins, encoded by Kiss-1 gene, are thought to be involved in the molecular mechanism underlying the re-awaking of GnRH neurons at puberty as GPR54 mutations cause hypogonadotropic hypogonadism in humans and mice. Kisspeptins induced GnRH secretion but not gene expression. An interplay between metabolic and sex hormones may trigger the Kisspeptins/GnRH signalling to GnRH neurons, suggesting a new mechanism which regulates the onset of puberty [5].

Hormonal rhythmicity at puberty

As to the diurnal and seasonal rhythms of cortisol, testosterone, and dehydroepiandrosterone (DHEA) associated with the pubertal development, the study indicated those hormones showed diurnal fluctuations. The peak time of cortisol occurred earlier than that of testosterone or DHEA and showed a seasonal effect, with the peak time occurring earlier in spring than in summer. The peak time of cortisol also occurred later in the day for boys than for girls during later puberty. Seasonal effects were found only for cortisol with higher concentration in the spring and summer. Cortisol concentrations were relatively stable across pubertal maturation, but significantly lower concentrations were observed at pubertal stage 3 (Tanner stages) compared to the other stages. Morning cortisol levels were also higher in boys at pubertal stage 2. Testosterone concentrations were higher in boys at pubertal stages 3 and 4, and DHEA was lower at pubertal stage 1 than 3 and 4 for both boys and girls. There was a positive correlation between DHEA and testosterone during early puberty (stages 1–3) but not later puberty (stages 4–5). Awakening secretory activity correlated with daytime secretory activity for testosterone and DHEA, but not for cortisol [6].

Behavioural change

Adolescence is associated with an increase in pleasure-seeking behaviors, which, in turn, are shaped by the pubertal activation of the hypothalamic-pituitary-gonadal axis. In the animal model of naturally rewarding behaviors such as sex, testicular androgens-testosterone and DHT contribute to the development and expression of the behavior in males. The brain undergoes significant remodelling during adolescence to modulate behavioral maturation and many of the changes are likewise sensitive to androgens, presumably acting through androgen receptors. Given the delicate interaction of gonadal hormones and brain development, it is no surprise that disruption of hormone levels during this sensitive period significantly alters adolescent and adult behaviors [7].

Does sexual abstinence influence the neuroendocrine response to the masturbation-induced orgasm in males? The study showed that the orgasm increased blood pressure, heart rate, catecholamines, and prolactin concentration in the blood. These effects were observed both before and after sexual abstinence. In contrast, although plasma testosterone was unaltered by orgasm, higher testosterone concentrations were observed following the period of abstinence, thus indicating that acute abstinence did not change the neuroendocrine response to orgasm but did produce elevated levels of testosterone in males [8].

Sexual desire

Sexual desire or libido is the expression of neurohormonal interplay or interaction. In men, testosterone and DHT have a significant role to initiate and maintain sexual desire. The German community survey of 2,341 men and women aged 18–93 years showed that sexual desire declined with advancing age. Overall, men reported more frequent and stronger sexual desire than women. However, there were important interactions between gender and age indicating an earlier decline among women. For both men and women, sexual activity in the older group was mostly an issue in the presence of a partnership. There were additional social and personality determinants for lack of sexual desire and sexual inactivity: in man, sexual desire was compromised by social factors such as unemployment or low income, while in women these were previous sexual traumas, e.g. childhood sexual abuse, rape [9].

Several pharmacotherapeutic approaches have confirmed the influence of neuroendocrine parameters on sexual desire, function and fantasies in men. A substantial increase in plasma prolactin level following orgasm in healthy men in fact suggested a feedback mechanism for peripheral prolactin in the control of acute sexual arousal. A comparative study confirmed that sexual offenders demonstrated higher sexual desire as well as action and a more positively perceived refractory period. However, both offenders and non-offenders displayed a prolonged, significant increase in plasma prolactin levels after orgasm, thereby indicating that factors other than peripheral hormones influence deviant sexual behaviour [10].

Sexual activity also induced transient increase of plasma epinephrine and norepinephrine levels during orgasm, with a rapid decline thereafter. In contrast, prolactin levels increased immediately after orgasm and remained elevated for a long duration. Although oxytocin was acutely increased after orgasm, these changes were not consistent and did not reach statistical significance. Vasopressin, LH, FSH, and testosterone concentrations remained unaltered during sexual arousal and orgasm. Thus, the findings reinforced a role for prolactin

either as a neuroendocrine reproductive reflex, or as a feedback mechanism modulating dopaminergic systems in the central nervous system that are also responsible for appetitive behavior [11].

Emotional response

Does sex hormone influence the emotional response of a man? The study showed that fathers hearing the cry stimulus felt more sympathetic and more alert compared to groups who did not hear the cries, or to non-fathers who heard the cries. Fathers and non-fathers with lower testosterone levels felt more sympathy and/or a greater need to respond to the infant's cries than fathers with higher testosterone levels. Fathers with higher, as compared to lower, prolactin levels were also more alert and more positive in response to the cries. Fathers hearing cry stimuli showed a greater percentage increase in testosterone levels than fathers not hearing the cry stimuli. Experienced fathers hearing the cries showed a greater percentage of increase in prolactin levels compared to first-time fathers or to any group of fathers hearing control stimuli. Finally, partial correlations with parity and experience entered as covariates indicated that both experience and testosterone contributed to the variance in fathers' effective responses to infant cries [12].

In another study, an influence of age on reaction time and reaction time variability was observed in men aged 46–77 years with respect to men aged 18–29 years in simple alert and complex reaction time tests (go/not-go and working memory). Younger men showed divided attention with the highest reaction time. The difference in frontalis electromyography increased with age, while the autonomic response (skin conductance and heart rate) did not vary. In most attentional tests, the age-related reduction of reaction time was associated with increased testosterone and decreased cortisol levels [13].

Penile erection and dysfunction

Penile erection occurs when the soft spongy tissue (corpora cavernosa and corpora spongiosa) in the shaft of a penis fills with blood causing the penis to enlarge, stiffen and become erect. This occurs in response to physical and/or psychological stimulation associated with neuro-hormonal mechanism involving spinal nerves, higher centers in the brain and androgens such as testosterone, DHT.

The prevalence of erectile dysfunction (ED) among Korean men aged 40–79 years was 13.4%. ED was more prevalent in subjects of older age,

lower income, lower education and in subjects without a spouse. The risk factors associated with ED are diabetes, hypertension, heart disease, psychological stress and obesity. Levels of triglycerides, testosterone and DHEA-sulphate were significantly different between the ED and non-ED control groups [14]. However, men with idiopathic ED had evidence of endothelial dysfunction in forearm resistance vessels, increased pulse pressure and impaired heart rate variability. This supports the theory that erectile dysfunction is a predictor of cardiovascular dysfunction and a precursor of clinical cardiovascular disease [15]. This also shows how sexual life is related to the emotional and physiological heart of a man.

There was a significant association between ischemic heart disease and increased severity of ED. Furthermore, a higher degree of ischemic heart disease was significantly associated with severe ED. Overall, 92.1% of patients with ED had one or more coronary artery risk factors. Thus, coronary artery risk factors are significantly associated with erectile dysfunction [16].

In the Saudi community in Egypt, 20% of affected patients had a psychogenic cause and 80% had an organic cause of ED. A significant association was found between increased severity of ED and the presence of diabetes, hypertension, dyslipidemia, ischemic heart disease, myocardial infarction, psychological disorders, increased values of end diastolic velocity, decreased values of peak systolic velocity, resistive index, regidometer and decreased response to intracavernosal injection [17]. The low-testosterone level is usually found to have association with those risk factors.

The pattern of age-related testosterone depletion indicated that the mean age was significantly higher in patients (55.3 ± 7.3 years) with decreased testosterone than in patients (50.8 ± 10.2 years) with a steady testosterone level. However, a significant decrease in mean testosterone level was observed throughout the study period in all age groups older than 30 years at any visit in comparison to previous visits, and this was also significantly associated with increased severity of ED at baseline visits [18]. This also confirms the significant role of testosterone to maintain the romantic and erectile function in the sexual life of a man.

Role of sex steroids

In Massachusetts, the study showed that normal healthy men aged 40–79 years, non-smokers with a body mass index not exceeding 29 kg/m^2 and

alcohol consumption ≤ six drinks/day had significantly higher median hormone concentrations at most times as compared to non-healthy controls. About 95% of normal healthy men in their 40s, 50s, 60s and 70s would be expected to have total testosterone in the range of 2.51–9.14, 2.16–8.76, 1.96––8.59, and 1.56–8.18 ng/mL serum, respectively. Chronic disease and high body mass index significantly decreased (whereas smoking tended to increase) total, free and bio-available testosterone concentration. The study also showed approximately 2.5% of men aged 40–79 years had abnormally low testosterone levels [19].

There is evidence for autonomic nervous system dysfunction such as circadian autonomic activity in the patient with coronary artery disease, especially after myocardial infarction. The 24-hours Hotler monitoring in such patient showed that testosterone levels were associated with increased heart rate variability measure of parasympathetic activity. This association remained significant after adjustment for age, ejection fraction, and other relevant clinical covariates. Thus, this finding suggested that testosterone beneficially influenced autonomic regulation of the heart of a man [20].

Are endogenous sex steroids levels associated with risk of premature death? A study showed that higher free testosterone and lower DHT levels were significantly associated with ischemic heart disease mortality, although the later association was not robust. Free testosterone level was significantly associated with respiratory mortality. However, total testosterone level was unrelated to mortality and SHBG was not found significantly associated with mortality. Thus, in man, endogenous sex steroid levels seem to have a relatively weak association with mortality [21].

Low endogenous testosterone levels in man were found to have association with increased risk of cardiovascular disease and atherosclerosis. In men, long-term hyperglycaemia (higher sugar level) as measured by glycosylated haemoglobin (HbAlc) was related to cardiovascular mortality and HbAlc across its normal range was also positively related to coronary heart and cardiovascular disease mortality. Therefore, HbAlc was found inversely associated with total testosterone and SHBG. HbAlc was also positively associated with body mass Index and waist circumference. Further analysis showed that testosterone, SHBG, age, number of cigarettes smoked, body mass index, and waist circumference were independently associated with HbAlc level. Thus, low testosterone levels in man are found to be associated with cardiovascular

problems, thereby indicating that sex hormone may have some role in the maintenance of a healthy heart of a man [22].

Men with proven chronic heart disease had significantly lower levels of testosterone, free testosterone, free androgen index and oestradiol. The level of testosterone was negatively associated with the DUKE index. The most essential negative correlation was found between SHBG and atherogenic lipid profile such as low high-density lipoprotein (HDL), high triglycerides, free testosterone, free androgen index and blood pressure, especially with diastolic pressure. Men with proven coronary atherosclerosis had lower levels of endogenous androgens than the healthy control group [23]. Thus, coincidence of low sex steroids levels and different heart diseases was noted. However, it is still unknown whether this low sex hormone level detected in heart disease represents an effect of the illness or one of the causes.

Deficiencies in DHEA-sulphate, total testosterone and free testosterone (defined as serum levels at or below 10% of that found in healthy peers), were seen across all age categories in men with chronic heart failure. Men with chronic heart failure and normal levels of all anabolic hormones had at least three years' survival rate as compared to those deficient in one or more anabolic steroids. This indicates the beneficial effects of endogenous sex steroids on the ailing heart of a man [24].

In healthy men aged 41–72 years, SHBG and oestradiol were positively associated with HDL, while free androgen index was negatively associated with HDL. Testosterone and SHBG were negatively associated with very low-density lipoprotein (VLDL) and triglycerides, while free androgen index was positively associated with VLDL and triglycerides. Testosterone and SHBG were negatively associated with body mass index and body fat mass, while free androgen index and oestradiol were positively associated with body mass index and body fat mass. Thus, atherogenic lipid profile in men is associated with low SHBG, low testosterone levels and a high free androgen index. Therefore, SHBG has emerged as a key factor in the association between sex hormones and plasma lipids of a man [25]. Thus, testosterone may influence the cardiovascular function of men.

Testosterone was confirmed to be an acute concentration-dependent vasodilator at concentration ≤ 1 μmol/L. The dilating effect of testosterone was augmented in the patient with androgen deficiency prior to treatment and this effect was abrogated following appropriate testosterone replace-

ment [26]. This is why androgen replacement therapy is now under consideration for the androgen-deficient patient.

Besides the renin-angiotensin-aldosterone system, most endocrine glands are affected in chronic heart failure cases. Occurrence of these disorders depends on the degree of heart failure. Elevated serum prolactin and decreased testosterone concentration were the most frequent hormonal changes observed in this disease. Chronic heart failure was often accompanied by disturbance in pituitary and gonadal secretion. The frequency of these disturbances rose with the degree of clinical advance of chronic heart failure [27]. How these sex hormones or endocrine glands are associated with the heart ailment of a man is not yet clearly understood, except their co-existence.

In men over 50, a significant positive correlation was found between testosterone and HDL-cholesterol. Interestingly, the older subjects were associated with increased levels of SHBG and decreased free testosterone Index (T/SHBG), suggesting the role of low testosterone level in the pathogenesis of atherosclerosis in elderly people [28].

Dobrzycki et al. [29] however, opined that the male gender itself is an independent coronary artery disease risk factor, because androgens, especially testosterone, are considered responsible for the much higher rate of coronary artery disease in men. There is controversy on this aspect due to lack of authentic data about the functional correlation between sex hormones and the heart. Further research is needed for a deeper understanding and elucidation of the dynamic relationship between sex hormones (especially testosterone) and the heart of a man. However, it appears that a man is naturally vulnerable at heart, in the domain of love as well as in life.

Mode of action of sex steroids

The cardiomyocites (heart muscle cells) are known to be androgen targets. The changing of systemic steroid levels is thought to be associated with various heart ailments. However, how sex steroids act on the human heart is not yet clearly understood. The immuno-localization test showed presence of androgen binding protein (ABP) or androgen receptors in the heart muscle cells, thus providing evidence of an intrinsic expression of ABP in the human heart. The ABP might be secreted from heart muscle cells in a paracrine manner, perhaps to influence the bioavailability of gonadal steroids in the myocardium (heart muscle), thereby indicating the role of sex steroids on the cardiovascular function [30]. A study also showed the inverse relationship between thoracic artic intima media thickness and testosterone levels [31].

Conclusions

The role of sex steroids for maintenance of the emotional and physiological heart of a man is preliminarily identified. How this steroid interacts with the nervous system and the heart to bring about these effects is not yet clearly understood. More study is required to explore how sex steroids act on the heart of a man.

Acknowledgements

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