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Andropause and the development of cardiovascular disease presentation—more than an epi-phenomenon

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Abstract

Andropause refers to a generalized decline of male hormones, including testosterone and dehydroepiandrosterone in middle-aged and aging men. This decline in hormones has been associated with changes such as depression, loss of libido, sexual dysfunction, and changes in body composition. Aging has been associated with an abundance of concomitant diseases, in particular cardiovascular diseases, and although andropause is correlated to aging, a causal relationship between reduction of androgens and the development of chronic diseases such as atherosclerosis and heart failure has not been convincingly established yet. On the other hand, increasing data has emerged that revealed the effects of low levels of androgens on cardiovascular disease progression. As an example, low levels of testosterone have been linked to a higher incidence of coronary artery disease. Whether hormone replacement therapy that is used for andropausal men to alleviate symptoms of "male menopause" can halt progression of cardiovascular disease, remains controversially discussed, primarily due to the lack of well-designed, randomized controlled trials. At least for symptom improvement, the use of androgen replacement therapy in andropausal men may be clinically indicated, and with the appropriate supervision and follow up may prove to be beneficial with regard to preservation of the integrity of cardiovascular health at higher ages.

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1 Introduction

"The secret to staying young is to live honestly, eat slowly, and lie about your age."—Lucille Ball, American Actress. The "male menopause" or "andropause" has gained widespread attention more recently, especially in the media and supported by those who advocate the use of products such as male hormones to overcome the effects of declining androgens in middle-aged and older men. To date, the terms "andropause" and "treatment" reveal 907 000 hits on the internet by a Google search which are mostly by sponsored links through companies that hardly have any scientific reputation or clinical background whereas most academic institutions do not have any links to the condition, which is in sharp contrast to other conditions of the aging individual such as "osteoporosis" with more than 16 400 000 internet hits that are led by well established institutions such as the Mayo clinics or medical advising website such as WebMD. The scientific community as such has not yet accepted "andropause" as a disease condition that may require treatment. On the other hand, aging itself is heavily associated with an abundance of concomitant diseases, in particular cardiovascular diseases with very high morbidity and mortality that is increasing with older age. Andropause is correlated to aging but a causal relationship between the development of chronic diseases such as cardiac failure or atherosclerosis and reduction of androgens has not widely accepted in the practicing medical community whereas several correlations have been well established by the scientific community. Of note, more attention has recently been focused on women's health secondary to the issues with hormone therapy for post-menopausal women and the under-treatment of women with heart diseases, especially the less aggressive therapeutic approaches towards older women. In contrast, hormone therapy in older men has been neglected from many scientific studies and research proposals and thus, lacks supportive attention. Still, in particular heart diseases appear more prevalent among older men, but the majority of studies performed in men with cardiovascular

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diseases enroll patients between the ages of 18 and 75 years, whereas the septuagenarians at higher ages and octogenarians are excluded from most large scale randomized trials. Based on these considerations, it seems obvious that there is a lack of reproducible data assessing a causal relationship between androgen deficiency and cardiovascular diseases. In attempt to discuss potential common denominators between low testosterone levels and symptoms of cardiovascular insufficiency, we present some evidence from experimental and clinical studies that support the association between andropause and heart disease.

2 The clinical phenomenon of andropause

Andropause relates to the slow but steady reduction of the production of testosterone and dehydroepiandrosterone (DHEA) in middle-aged men, and the reasons for that reduction including a decrease in Leydig cells. It is often referred to as late onset hypogonadism, male menopause, male climacteric andropause or viropause. In contrast to menopause in women, however, the reproductive capability is preserved (*i.e.*, older men can still father a child), even though there is a decline in sexual performance capacity as well as libido with increasing age. Of interest, the term andropause is not included by the World Health Organization in its medical ICD-10 classification system, which is in contrast to menopause. Even though andropause or "Androgen Decline in the Aging Male (ADAM)", by definition is associated with a decline in male sexual hormone production, in particular testosterone, the condition has not been used synonymously with hypogonadism. Hypogonadism in males is defined as a state of reduced testosterone and its sequelae that are identified by below normal testosterone blood levels (normal total testosterone levels range from 300–1000 ng/dL). Low testosterone levels can result in defective primary or secondary sexual development among children and young adults, as well as withdrawal effects among older adults. The term hypogonadism is usually applied to permanent rather than transient or reversible defects, and implies deficiency of reproductive hormones with or without defects in fertility. In primary hypogonadism, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are usually elevated, suggesting a primary defect with the testes whereas in secondary or central hypogonadism, LH and FSH levels are normal or low, suggesting the problem is in the pituitary gland.

In contrast to the term hypogonadism, andropause is used in a more general manner to refer to middle-aged and aging men with signs and symptoms of a generalized decline of male hormones that is often associated with conditions such as depression, loss of libido, sexual dysfunction, and changes in body composition such as increased abdominal body fat and loss of muscle mass and tone. The entire state sometimes referred to as male mid-life crisis or "puberty in reverse", usually with changes in hormonal, psychological, interpersonal, social, sexual and spiritual life. It is estimated that at least 25 million American males between ages 40 and 55 are experiencing some degree of male menopause. Even though this is almost the number of diabetics in the USA, only a relatively small number of scientific publications deal with the syndrome of andropause, with the majority of these papers being review articles rather than randomized controlled trials.

The loss of testosterone can occur in men as young as 35 years of age, is gradual, with testosterone levels dropping just 1% to 1.5% annually. Unlike the precipitous loss of estrogen women face when reaching menopause, the gradual loss of testosterone can take years to create symptoms in men, many of which are similar to menopausal symptoms women experience. Simultaneously, levels of thyroid hormone, growth hormone and DHEA begin to decline in men in their mid 20s, with the first signs showing in the mid 30s to 40s, and by the age of 80, most male hormone levels decrease to pre-puberty levels.

The first signs of decline in testosterone are generally vague: diminished subjective energy levels, increase in irritability, decline in mood, decline in cognitive performance, loss of early morning erections. These symptoms often mimic other conditions. Complaints include infertility, decrease in beard and body hair, increase in body fat, decrease in muscle mass, gynecomastia, changes in size or firmness of testicles, and signs of osteoporosis. Whether or not the decline of hormone levels is directly correlated to the development of disease presentation such as cardiovascular diseases among older men, is still controversially discussed.

3 Andropause and cardiovascular disease

Aging per definition is defined as a natural process that is represented by accumulation of changes in an organism over time and usually refers to a process that involves the physical appearance by changes in the morphologic structure, the multi-organ system function by changes in metabolism and energy expenditure, psychologic and social well being by changes in mobility, behavior, and physical and mental capabilities. Even though late in a human's life a potential to physical, mental and developmental growth exists, senescence is usually associated with a decline in functional capacity of each organ system, a reduced ability

to respond to stress, increased homeostatic and metabolic as well as hormonal imbalances that finally result in the death of an organism. It is hypothesized that many diseases such as progressive heart failure represent an early form of cellular senescence which is attributed to the shortening of telomeres with each cell cycle. When telomeres become too short, the cells die. The length of telomeres is therefore the "molecular clock" according to Hayflick. Hayflick also proposed that the "anti-aging concept is an oxymoron" and that aging per se should not be conceptionalized as a disease state.[1–3] In men, there is debate of whether an age-dependent decline in androgen levels directly leads to health problems that might affect or alter the quality of life and physical and psychological functioning. Moreover, the usefulness and/or necessity for hormone replacement therapy which may possibly reverse these changes are controversially discussed. The primary reasons behind the use of hormone replacement therapy are as follows: (1) the uncertainty of accepting age as a natural process of a "non-restitutio ad integrum" once organic function declines, (2) safety concerns associated with long-term hormone therapy, similar to hormone therapy in postmenopausal women, and (3) there is a loss of trust by potential patients towards many providers of substitution therapy due to the commercialization of hormone therapy and "age management" among thousands of (pseudo-medical) entities that do not have the scientific background, clinical expertise or academic recognition required for an adequate care model for the aging male in andropause.

Of note, it is estimated that each day 100 000 people die of age-related causes around the globe. With the increasing number of patients belonging to the baby boomer generation, this number is expected to rise as well as the demand for health care that provides ways and techniques to cope with age-related conditions and diseases. Increased age is associated with an increased demand in health care in general. Among middle aged men and women facing the steady competition from younger and stronger competitors (whether it is in sport competitions, the runway, or in Hollywood, which all determines the headline in the yellow press influencing the overall attitude towards external presentation), however, there is now an increased consumer demand and patient-directed activities in order to prevent age-related changes.

If age-related changes can be prevented or delayed, then this can result in improved well being and quality of life among the elderly. Especially in this population, self-ratings of health conditions have been correlated with well-being and mortality. Of interest, positive ratings of well being are correlated with reduced mortality (*i.e.*,"the better you feel, the longer you live"). Several reasons have been postulated for this association. People who are objectively healthy may naturally rate their health better than that of their ill counterparts, even in studies which have been controlled for socioeconomic status, psychological functioning and health status. This finding is generally stronger for men than for women.[4–6]

Andropause in its extreme presentation, often leads to frailty, a syndrome characterized by a reduced functional reserve and impaired adaptive capacity that results from cumulative declines of multiple subsystems, and causes increased vulnerability to adverse outcomes.[7] Chronic heart failure is an example of a disease that is associated with higher age and andropause but a causal relation, though it might appear obvious, has neither been clearly established nor widely accepted. Approximately 50% of all heart failure patients in the USA are above 75 years of age, which is identical in most European countries as well as in the Middle and Far East. Although aging is an independent molecular process with a multitude of genetic predetermination and biochemical mediations, aging itself does not automatically result in cardiac contractile insufficiency that ultimately results in the clinical syndrome of heart failure. Moreover, there is no evidence that andropause directly leads to cardiac failure, even though the association appears perceptible in several experimental studies and clinical trials. It is well established that cardioprotective mechanisms in response to stress are lost with increasing age, and progressive cardiomyocyte degeneration with replacement fibrosis is often seen in older hearts, even though the exact triggers are not completely understood.[8]

Aging has been associated with left ventricular hypertrophy, dilation of the cardiac chambers, and reduction of contractile material with subsequent replacement fibrosis.[8] These structural changes are oftentimes associated with a reduction in function and other pathologic conditions. As demonstrated by echocardiography in a special set of high aged rats, Walker *et al*.[9]showed left ventricular chamber dilation, increased wall thickness and a higher incidence of arrhythmias compared to younger rats. Re-expression of the fetally expressed beta-myosin heavy chain (beta-MHC) gene is a well documented marker of pathological cardiac hypertrophy and normal aging in many experimental models and in the aging heart it seems to be a marker of fibrosis (rather than of cellular hypertrophy).[10]

Paternostro *et al*.[11] have demonstrated in a drosophila model, that aged fruit-fly cardiac structure has a lower maximal heart rate in response to temperature stress while arrhythmias increase compared to younger flies. In addition,

the same drosophila model demonstrated an increase in the development of electrical pacing-induced heart failure and arrhythmias among aging flies.[12]

There are several more or less pre-determined processes in a cell's life that ultimately can result in either cell death (apoptosis, pre-determined cell death), cellular senescence, or malignant transformation. Several exogenous and endogenous factors seem to play a role in the change of metabolic and cellular equilibrium. These factors are considered a stress. If stress causes damage of the cellular DNA, this results in a cellular response with induction of stress response proteomes by certain checkpoint proteins. It is the task of these checkpoint proteins to stimulate a signal transduction cascade that evaluate the present damage of the genome before repair mechanisms take place. If the repair mechanism fails, *i.e.*, in the setting of malformation of checkpoint proteins or in overwhelming stress, then tissue degeneration, premature and accelerated aging and cancer transformation can occur. As known from studies in patients with ataxia teleangiectasia, abnormal DNA methylation can result in dysregulation of tissue specific epigenetic control over cell cycle checkpoints. Interestingly, this dysregulation has been shown to potentially result in degeneration such as calcification of aortic valves, atherosclerotic coronary artery disease, and heart failure caused in patients with diabetes mellitus. A recently published review focused on the "Disease Proteomics and Transcriptomics" that might serve as future diagnostic markers for these kinds of accelerated aging processes.[13] It is hypothesized that many of these cellular and biochemical alterations are augmented by low androgen levels.

In particular in forms of heart failure secondary to diabetic cardiomyopathy, increased levels of *O*-linked attachment of *N*-acetyl-glucosamine (*O*-GlcNAc) on nucleocytoplasmic proteins have been shown to be implicated in the development of cardiac dysfunction. A recently published experimental study in rats demonstrated a significant increase in *O*-GlcNAc levels in high-molecular weight proteins in older diabetic rats compared to age-matched lean controls and compared to younger diabetic rats, which also was associated with impaired cardiomyocyte function, indicating that both diabetes as well as age alter the levels of *O*-GlcNAc expression and their regulatory function.[14]

Moreover, the above mentioned drosophila model demonstrated that insulin receptors and associated pathways and altered ATP-dependent K channels change with age that seem to contribute to a reduction of cardioprotective mechanisms (for example, against ischemic-reperfusion injury) and also reduces cardiac performance.[12]

Aging also has been associated with a selective up-regulation of transcripts involved in inflammation and oxidative stress, and a down-regulation of genes involved in mitochondrial electron transport and oxidative phosphorylation.[15]

Another mediator that appears to contribute to preservation of structure and function in the heart is serum response factor (SRF). SRF is increased in both senescence and in heart failure. Interestingly, transgenic mice with lower levels of SRF were found to develop increased left ventricular (LV) wall thickness, decreased LV volumes, and increased LV stiffness with a 20% reduction in early diastolic LV filling, indicative of aging processes observed in human hearts.[16] Maintenance of SRF levels without age-related increase, on the other hand, was associated with preserved LV systolic pressure and lower levels of brain natriuretic peptide in response to isoproterenol stimulation with higher mRNA levels of SERCA2 and ryanodine receptor 2 in transgenic mice. These findings suggested that preventing the age-associated increase in SRF might be associated with preserved intracellular calcium handling and stress response.[17] To the best of our knowledge, a possible direct relationship between low testosterone and low SRF has not yet been studied.

It has been suggested that changes at the level of the "energy machines" within the cells, the mitochondria, determine processes of aging and cell death. Mutations in mitochondrial DNA such as base deletions or modifications are induced by oxygen-derived free radicals and are associated with aging and failing cardiac function. Mitochondrial alterations might result in impaired oxidative phosphorylation and defective electron transport chain activity that worsen further energy supply and creates more reactive oxygen species. Impaired respiratory chain function will then further augment free radical production and by thus, increase the rate of mitochondrial DNA mutation, which, in turn, will further compromise respiratory chain function, finally leading to cell death.[18] Mice models of oxidative phosphorylation and mitrochondrial diseases have demonstrated improved survival rates associated with higher testosterone levels.[19]

On the other hand, Trifunovic *et al*.[20] proposed that premature aging phenotypes in mitochondrial DNA mutator mice are not generated by a vicious cycle of massively increased oxidative stress but that respiratory chain dysfunction itself induces premature aging in these animals. Still, the chicken and the egg have not been clearly defined in the cellular processes of aging, andropause, and organic dysfunction.

4 Androgen effects

Testosterone is a steroid hormone produced by the leydig cells of the testes. Its synthesis, like that of many hormones, is the result of a signal-production-negative feedback loop. Like gonadotropins, testosterone, an anabolic hormone, is secreted in a pulsatile fashion which, in adult men, occurs throughout the entire day. Testosterone exerts its main effect on cells by affecting DNA transcription. Testosterone can freely enter a cell's cytoplasm, where it binds to androgen receptor proteins. Once bound, androgen receptor/androgen complexes form, which change the androgen receptor's conformation. The complex enters the cell's nucleus, where it can bind DNA receptor sites and act as a promoter for specific gene transcription. Testosterone can be converted intra or extra-cellular by 5-alpha-reductase, becoming dihydrotestosterone (DHT) and binding the androgen receptor in that form as well. DHT is the more biologically active form of testosterone. Once bound by either molecule, the net effect is pro-transcriptional, and moves a cell toward positive (or anabolic) nitrogen balance and protein synthesis. This effect is not limited to the sex organs; in fact, it plays an important role in maintaining general physiologic functions involving several organ systems.

Since 30% of testosterone is bound to sex hormone binding globulin (SHBG), it is not biologically available. Only the 1% to 2% of free testosterone is physiologically active. Its presence (or lack thereof) is manifested in multiple organ systems, with testosterone associated with retention of desirable values of actuarial disease risk and with well-maintained body composition. With increased age, there is a decline in the absolute number of Leydig cells in the testes; and the remaining cells shows a decline in testosterone production. Another factor affecting the functional availability of testosterone is the age-related increase in SHBG. SHBG levels increase with age and lower the amount of free or active testosterone. In men older than middle age, total testosterone levels may therefore be misleading because of the increase in SHBG levels.

Declining virility that accompanies the aging process is only reluctantly accepted as fate. Testosterone was the hormone that was identified as the cause and target for intervention in these cases. As early as in the 1800s different testicular extracts were prepared for human use with reported clinical responses, including the use of cadaveric transplants from younger male corpses into older men. By 1935, testosterone was purified.

As early as in the 1940, articles were published describing the clinical utility of using testosterone to treat symptoms of the "male climacteric." From then until the 1970s, testosterone was given according to subjective criteria and with generalized dosing regimens. Once plasma testosterone levels could be measured, it became possible to more accurately assess individual levels to implement and more precisely monitor therapy.

In assessing the changes that take place in the aging or diseased heart, the question arises whether androgen decline plays a role in the development of the propelled aging and, if so, whether testosterone replacement may counteract these conditions. A recently published experimental model demonstrated that testosterone and DHT pretreatment prevented cell death, primarily apoptosis, in hippocampal neurons induced by beta-amyloid, staurosporine, and apoptosis activator II.[21]

In an experimental model of adriamycin-induced cardiomyopathy in male mice, testosterone up-regulated Akt phosphorylation and Tfam expression in cardiac myoblast cells and exerted an antiapoptotic effect against Dox-induced cardiotoxicity.[22] In cultured rat cardiomyocytes, testosterone rapidly (1–7 min) led to an increase of intracellular Ca^{2+}, an effect that persisted in the absence of external Ca^{2+}.[23]

These newer experimental data are in contradiction to the widespread recognition that androgens might cause cardiomyopathy, heart failure, myocardial infarction and sudden death in case of abuse. On the other hand, older data showed a dose dependent induction of apoptotic cell death by testosterone in an in vitro model of rat cardiac myocytes, implicating the pathophysiology of anabolic steroid abuse and the development of cardiac remodeling and cardiomyopathy in these cases. Similar findings had been reported repeatedly in case series of individuals abusing anabolic steroids for athletic or aesthetic reasons.[24–27]

But there are several other potentially deleterious conditions that are at least associated with low (rather than high) androgen levels. The significant decrease of androgen levels in older men, causing quality of life impairment and increasing the risk of chronic disease, often is defined as Partial Androgen Deficiency of Aging Men (PADAM).[28]

As another example, in aging men, low testosterone levels are associated with a potentially atherogenic lipid profile including high triglycerides and low HDL-cholesterol.[29]

More data is now available on the effects of androgens on cardiovascular disease progression. Human observational studies have mostly concluded that men with lower testosterone levels tend to have higher incidence of coronary artery disease and that low androgen levels might predict cardiovascular risk. Whether adequate substitution therapy with testosterone in andropausal men, may be able to alter

their risk profile—although this may appears imperative—has not yet been convincingly established.[30]

In contrast to other data, a study done in 2000 on 189 men, ages 70 years and older, revealed that IGFBP-3, insulin and IGF-I have a statistically significant and independent associations with coronary arteriosclerosis in men as demonstrated by coronary angiograms.[31] On the other hand, andropausal men have a higher maximal intima media thickness (IMT) compared with controls in the common carotid artery (1.08 ± 0.34 *vs.* 1 ± 0.23, $P < 0.05$) and in the carotid bulb, which correlated inversely with serum testosterone and directly with LH. Middle-aged men with symptoms of andropause, together with absolute or compensated (as reflected by high normal to elevated LH) testosterone deficiency, showed increased carotid IMT. The authors suggested that normal testosterone levels may offer protection against the development of atherosclerosis in middle-aged men.[32]

In a mouse model of andropause, follitropin receptor knockout (FORKO) male mice which are testosterone-deficient, the diastolic and mean arterial pressures were significantly higher in FORKO compared to wild type controls, and resistance arteries of FORKO mice had greater media-to-lumen ratio (10.4 *vs.* 8.2; $P < 0.05$) and reduced relaxation responses to acetylcholine in pressurized preparations. Vasoconstrictor responses to angiotensin II were blunted, and angiotensin receptor 1 expression was decreased in FORKO mice. These data indicate that in androgen-deficient mice, blood pressure is elevated and resistance arteries exhibit endothelial dysfunction, structural remodeling, and vascular inflammation indicating that androgens may play an important role in modulating vascular function and regulation of blood pressure.[33]

In middle-aged men, testosterone (15.25 ± 5.43 nmol/L, mean ± SD, range 3.6–45.0 nmol/L) correlated directly with HDL-cholesterol ($r = 0.24$, $P < 0.0001$) and inversely with total cholesterol ($r = –0.06$, $P < 0.03$), triglycerides ($r = –0.30$, $P < 0.0001$) and body mass index ($r = –0.34$, $P < 0.0001$). In multivariate analyses, the significant determinants for serum triglycerides were testosterone (beta = –0.03, $P < 0.0001$), age (beta = –0.01, $P < 0.0001$), body mass index (beta = 0.039, $P < 0.0001$) and cardiovascular diseases (beta = 0.09, $P < 0.04$). The authors concluded that in aging men low testosterone levels are associated with a potentially atherogenic lipid profile including high triglycerides and low HDL-cholesterol.[8] The effects of androgens on sexual function and quality of life have been subject of debate for middle-aged and older males. Androgen deficiency often is associated with a decline in sexual activity and a loss of muscle mass. Testosterone replacement can reverse many of these effects. At present, no ideal form of testosterone replacement is available. Like the phosphodiesterase-5 inhibitors, testosterone replacement in older men in order to improve sexual function might significantly affect quality of life.[34]

Muscle strength determines mobility and physical functioning and thus, also does affect quality of life. Some studies suggest that aged men could benefit from testosterone replacement with regard to muscle mass preservation. The direct correlation of the therapy, however, and its direct impact on strength and functional status is unproven.[35]

Furthermore, low testosterone levels in middle aged men and older men has been associated with reduced activity, dissatisfaction with sexual function, negative self-concept of physical fitness, reduced sexual desire and hot flushes.[36] In addition, the slower, more subtle decline in total and bioavailable serum testosterone levels that occurs in aging men have been implicated in the pathogenesis of cognitive dysfunction prevalent in elderly adults.[37] In Japan, unlike in Western countries, late onset hypogonadism is diagnosed by measuring serum free testosterone levels because total testosterone did not show an age-related decrease in a large Japanese study. Patients with lower testosterone level undergo androgen replacement therapy. For those with normal testosterone, other treatments are recommended. Approval of more agents (*i.e.*, androgen gel or oral agents) for androgen replacement is awaited.[38] Potential consequences of age-associated decrease in plasma testosterone levels include long-term changes in diverse organ systems including changes of bone architecture, body composition, muscular strength, cognitive functions, and mood as well as negative effects on skin and hair. Indications and contraindications for a hormone replacement therapy as well as therapy monitoring are well-defined.

Replacement of testosterone in the case of late-onset hypogonadism is not a standardized therapy. Previous studies suggest that testosterone replacement therapy has positive clinical effects.[39] Animal experiments and cell biology studies have provided evidence that both estrogens and androgens can play a protective role against Alzheimer's disease (AD) related neurodegeneration. Males who become hypogonadal in later life often report problems with their memory. Lower than normal testosterone levels have also been detected in patients prior to the onset of AD, as well as in younger late-onset male AD patients, when compared to appropriate controls. There is no clinical evidence to date which suggest that the hormone DHEA can improve cognitive function. Rises in the levels of the gonadotropins, FSH and LH, have been associated with AD, but the clinical

effects of reducing their levels remain to be determined. It had been hypothesized that androgens, gonadotropin modulators, or perhaps selective androgen receptor modulators may be useful components of therapy aimed at preventing the onset or delaying the progression of AD in male patients.[40] Testosterone therapy can improve quality of life in aging men because aging is accompanied by declining testosterone levels that may contribute to decreases in muscle mass, bone density, libido, stamina, and cognition.[41]

5 Hormone therapy

A medicalised conceptualization of the body and the life-cycle had become widespread by the second half of the twentieth century. People especially in the Western world expect medicine to provide a cure for any ailment; in the wake of the development of the so-called wonder drugs, no affliction seemed beyond medical and pharmaceutical intervention.[42]

In this context, on June 13, 2010 a newspaper report stated that the global hormone therapy market is currently worth $2.1 billion, indicating a Compound Annual Growth Rate (CAGR) of −6.8% between 2001 and 2009. This decline in the market is mainly attributed to poor patient compliance as a result of the serious safety concerns associated with hormones. By 2016, the market is forecast to record $2.3 billion, with a CAGR of 1.2% between 2009 and 2016. The market is restrained by factors such as the poor acceptance of hormone therapies in patients as well as physicians.

Of interest, one study that defined symptomatic androgen deficiency as symptoms associated with low circulating androgens showed that the likelihood of andropause remission was at least 50%. The probability of andropause in this context was greater with older age and greater body mass index. Andropause was not considered a stable health state over a 15 year follow-up. However, in older men conditions other than pure andropause might take over a symptomatic state and a potential causal association might become less prominent.[43]

Also more recently (on June 30, 2010) a study of mobility-impaired aged men reported that more than one-fifth of patients using a testosterone gel developed cardiac problems. Those men who were using testosterone demonstrated increased strength in leg-press and chest-press strength and in stair climbing while carrying a load but among the 106 men using testosterone gel, 23 had cardiovascular-related events, compared with only five men in the 103-person placebo gel group.[44]

In contradiction, a longitudinal (18 year) study found that men over 50 years of age may not live as long if they have low testosterone levels. The study looked at death from any cause in nearly 800 men ages 50 to 91 years who were living in a southern California community and who participated in the Rancho Bernardo Study in the 1980s. At the beginning of the study, almost one-third of these men had suboptimal blood testosterone levels for men their age. The men with low testosterone levels had a 33 percent greater risk of death during the next 18 years than the men with higher testosterone. This difference was not explained by smoking, alcohol intake and level of physical activity or by pre-existing diseases such as diabetes or heart disease.[45] Similar data has also been more recently presented from Germany.[46]

6 Conclusion

In conclusion, there is a likely causal relationship between low androgen levels and aging, as well as its association with increased cardiovascular risk and the occurrence of cardiovascular events and progression of symptomatic disease. Neither the necessity of testosterone replacement nor the clear beneficial effects on the cardiovascular system in andropausal men has been widely accepted, in part secondary to the lack of convincing scientific data in randomized controlled studies, and in part because of fear of the development of side effects seen in uncontrolled use such as abuse by competitive athletes or uncontrolled substitution on commercial bases in patients at risk for prostate or breast cancers. Based on our experience, as well as published data, testosterone replacement therapy is clinically indicated in men with a clinical deficiency or absence of endogenous testosterone due to classical primary or secondary hypogonadism with related symptoms. Symptomatic men with total testosterone levels of less than 300 ng/dL may be candidates for testosterone replacement therapy. Once any testosterone intervention is initiated, adequate and ongoing follow-up is critical. Since optimal testosterone levels among older males might be different than the usual normal laboratory range for normality, testosterone substitution might be beneficial for symptom improvement for man with reduced libido, loss of muscle mass and strength and other symptoms of male climacterium.[47]

While experts from specialties such as endocrinology, urology, general internal medicine, cardiology, geriatrics, partition in age management medicine, the entire concept appears so complex that only a dedicated multi-disciplinary program might be able to provide adequate care for the symptomatic elderly male with proven hyogonadism.

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