

ANDROPAUSE

A CLINICAL ENTITY *Bansal V.P.

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INTRODUCTION

"You can't help getting older, but you don't have to remain so if you desire".

Nepal population is exploding. According to The World Fact Book the population has already reached nearly 30 million in July 2012. The life expectancy is increasing and the fertility rates are decreasing. Due to these facts the people above the age of 65 years of age are 613,905 males and 705,181 females. Collectively the males and the females above the age of 65 constitute about 4.4 % of the total population. It may be worth noting that in year 2007, the population of the people above the age of 65 years was 3.8 %. Thus it is expected that in future increase of population growth will occur in this group. All these people are liable to have old age diseases. Hence it should be a matter of concern for doctors of this country.¹

Andropause medically referred to as Androgen Deficiency Amongst Men (ADAM). The synonyms are Male Menopause; Male Climacteric and Veropause. Andropause may also be referred in the literature as Aging male Hypogonadism or late onset hypogonadism. Typically Andropause is a syndrome affecting the various organs of the body and producing varying symptoms. Overall the quality of life is decreased over the period of years and the individual considers this as aging. It has been my experience that if in an old man a physician is unable to diagnose a particular disease based on the history, clinical examination and laboratory investigations; where multiple systems are involved and where the physician himself is confused as to what he should do, he should think of Andropause. The understanding of Andropause amongst the medical profession dealing with old age population has not been kept in pace with the developments in this field.

Andropause being the multidisciplinary disease of the old age is not clearly defined in the medical books when the modern medical science is divided into specialties and super specialties. The ultimate sufferer is the patient who is treated by a specialist depending upon dominance of symptoms related to the particular specialty but that is no treatment since deficiency of testosterone is not treated. In such cases one single investigation ie testing of the male hormone particularly the free testosterone shall clinch the diagnosis.

During the last nine years, the author has treated more than two hundred cases of Andropause. In all of these cases, total and free testosterone levels along with other hormones and the blood investigations relevant to the system involved was assayed. Seventy three percent of the patients had testosterone levels below the normal values. Eighteen percent of patients did not have the testosterone below normal; however had levels along the lower limits of normal values. The variety of presentations makes it difficult to create a clinical typeset for Andropause and it is usual for physicians to get patients who have symptoms which are different from what they have learnt and practiced.

Physiology of Testosterone

Testosterone, one of the most important androgens, is synthesized from cholesterol. It was first isolated by a Dutch scientist in 1935 from mice testicles and successfully synthesized by the German biologist Adolf Butenandt. Although it was the first hormone to be discovered, yet its overall role is still not completely defined.² Testosterone is primarily produced in the Leydig cells of testes. It is also produced in small quantities in the adrenal gland in both men and women.

The regulation of testosterone in blood is a complex system, through an inter-relation between hypothalamus, anterior pituitary and the testes. It happens through a feedback mechanism. The hypothalamus secretes Gonadotropic Releasing Hormones (GnRH) which further controls the Luteinising Hormones (LH) having a direct effect on the production of testosterone by the Leydig cells in the testes. Another hormone secreted by the anterior pituitary gland is Follicle Stimulating Hormone (FSH) that has got direct effect on spermatogenesis.

Both testosterone and FSH act synergistically on some of the testicular cells to stimulate the secretion of Androgen-Binding Protein (ABP). This protein binds to testosterone and keeps the concentration of testosterone high near the area in the testes where the sperms are produced. Testosterone is liquid soluble which diffuses out of the different cells/tissues of the testes into the blood. The testosterone that is secreted by the Leydig cells of the testes also affected by some target cells in the prostate gland where the enzyme 5 alpha reductase converts testosterone to even more potent androgen called Di Hydro Testosterone (DHT).

Therefore there are two types of androgens available in the body, one is testosterone and the other is DHT. Both these androgens bind to the same receptors, which are found within the nuclei of target cells. The hormone-receptor complex acts to regulate gene transcription, turning on transcription of some genes and turning off transcription of other genes. As a result of these changes in gene activity, following are some of the effects amongst many on the male body.³

1. Testosterone plays a crucial role in the development of the male excretory ducts and the descent of testes in the embryo. Formation of the external genitalia, on the other hand, is influenced by DHT. Testosterone also plays a role in the development of certain regions that typifies a male brain.
2. The development and enlargement of male sex organs and the development of masculine secondary sexual characteristics that are seen during puberty are due to Testosterone and DHT. These include physical changes like wide shoulders and narrow hips; pubic, axillary, facial, and chest hair; thickening of the skin; increased sebaceous (oil) gland secretion; and enlargement of the larynx thereby deepening of the voice.
3. Androgens promote sexual behavior including libido in both males and females and spermatogenesis in males.

4. Androgens stimulate protein synthesis. This obviously brings about heavier muscle and bone mass of most men as compared to women.

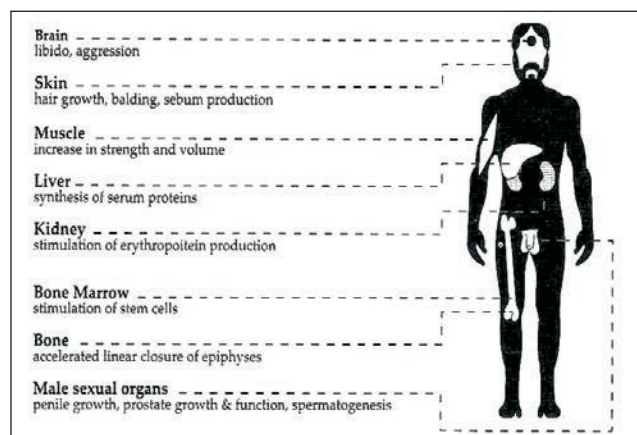


Fig. 1: Effect of testosterone on body organs

Testosterone helps to build protein and is essential for normal sexual behavior and producing erections. It also affects many metabolic activities such as production of blood cells in the bone marrow, bone formation, lipid metabolism, carbohydrate metabolism, liver function and prostate gland growth. Fig.1 summarizes the effect of testosterone on different organs of the body. It is not essential that in an individual with low testosterone all the target organs are involved, rather this never happens..

Testosterone and the females

It is a common misconception that testosterone is solely a male hormone. However, testosterone is also present in the blood of females. The central biological difference between adult men and women, then, is not that men have testosterone and women don't. It's that men produce more of it than women do. An average woman has 40 to 60 nanograms of testosterone in a deciliter of blood plasma. An average man has 300 to 1,000 nanograms per deciliter.²

The major female hormone is 'estrogen' which is more concerned with the reproduction in the female and is the correlate of testosterone in males.

At the time of conception even the embryo is a female and until and unless this is altered by the testosterone, the embryo shall develop into a female child.² Therefore, in embryo it is the testosterone that makes the real boy in its form to make the masculine body and brain. In men, there is flood of testosterone twice first at six weeks after conception and then at puberty. The burst of testosterone in embryo primes the

brain and the body sensitizing the male features with its instinctual knowledge to respond to the latter's flood of testosterone when the changes of puberty are brought in the boy. Without testosterone the human would revert to the formation of female. Anybody based on this scientific ground may believe in the statement that it is not women who are made out of men but it is men who are made out of women.

Besides its control on body and brain, the big T also co-relates with energy i.e. self-confidence & competitiveness having strength and sexual drive. Testosterone is elevated in response to short-term confrontational situations e.g. street-fights, high-level debates and also in response to highly charged sexual environment, pornographic websites. However, in long-term stress situation like war, testosterone levels decrease. It is higher in working women than those housewives. There are many more studies on record that the all lawyers who are habitual to combat have testosterone at higher level than other lawyers. Testosterone levels have also been studied amongst criminals who have high level of testosterone than the normal males of same age.

Causes of Male Hypogonadism

The causes of the deficiency of testosterone in the male body can be innumerable. Some of them are described below:

- The effects of aging on testosterone production - Andropause
- Testes-Based Conditions
- Pituitary/Hypothalamus-Based Conditions
- Genetically-Based Conditions
- Miscellaneous causes

The effects of aging on testosterone production Andropause

As men age, their ability to produce testosterone declines.^{3,4} Some men's production of LH decreases with aging, which lowers testosterone production. Moreover, a protein called sex hormone binding globulin (SHBG) increases in older men, which reduces the amount of free (unbound) testosterone in the blood that is available to tissues, such as muscles. Aging also causes changes in the daily cycle of testosterone production. For example, younger men show a peak of testosterone in the morning, but this finding is blunted in older men.

Testes-Based Conditions

Men whose testosterone deficiency is caused by an abnormality in the testes often display increased FSH levels, increased LH levels and impaired sperm production. Various conditions are trauma to the testes, orchitis, radiotherapy,

chemotherapy and testicular tumors.

Pituitary/Hypothalamus-Based Conditions

Men whose low testosterone levels result from defects in the pituitary or hypothalamus generally have a low or low-normal FSH level and low or low-normal levels of LH. These conditions include pituitary tumors. HIV/AIDS, viruses or other infectious agents may directly or indirectly affect the hypothalamus, pituitary or testes and can decrease testosterone levels; as many as 50 percent of men infected with HIV may have low testosterone.

Genetically-Based Conditions⁵

Men may have low testosterone as a result of chromosomal abnormalities or genetically-based conditions. These conditions include Klinefelter syndrome, Kallmann syndrome, Prader-Willi syndrome and Myotonic dystrophy.

Miscellaneous Causes

- Generalized vascular diseases such as diabetes and perhaps even problems caused by heavy smoking.
- Diseases when the immune system attacks and destroys the testis such as variations of Systemic Lupus Erythematosus
- Viral infections such as mumps.
- Stress, excessive alcohol, overweight and lack of exercise add to the general effect of ageing⁶

Environment:⁷

Xeno-estrogens, which are primarily petrochemical, have a very potent estrogen like activity. They are in our air, fuels, pesticides, herbicides, fungicides, plastics, clothing, bug / mosquito sprays and personal care products. Such synthetic hormones have molecular structures that are not compatible with our physiology. We do not have enzymes designed to modify their effects, nor can they be efficiently excreted. Therefore, these synthetics can have an unnatural and far more potent hormonal effect on our body systems than natural hormones.

Our diet is also contaminated with Hormones. Synthetic estrogens are used now-a-days to fatten cattle, as well as other meat-producing animals, and to increase milk and egg production. These are innocently ingested by us through our meals.

All these synthetic estrogens cause Estrogen Dominance where the level of Testosterone is already compromised and causes precipitation of the Andropause symptoms.

Surgical Causes

Surgical removal of or surgical injury to the testis and male reproductive tract (including hernia repairs, prostatectomy etc). Vasectomy however needs special reference.

Vasectomy seemingly a simple operation, is often presented as the ideal and infallible solution to family planning. No sperm - No problems. It is widely thought that since the blood vessels are not cut and testosterone levels in the blood remains normal, vasectomy will not have any effect on sexual desire and performance. Unfortunately, it's not quite that easy. The testicles are very delicate and sensitive structures. They are very complex organs, with a rich nerve, blood and lymphatic supply. Also they are under intricate hormonal and temperature control to regulate sperm and testosterone production. So that the man doesn't produce antibodies to his own sperm, which to the rest of the body is foreign protein. All these systems can be disrupted, even when the vasectomy seems to have gone smoothly, and there can be an alarming variety of short- and long-term complications, which can sometimes be serious⁴

- (a) Short Term Complications: Post vasectomy pain syndrome - This complication can turn a previously fit man into a chronic invalid because of the post-operative discomfort which may be for weeks, months or years after the operation. Sometimes tender cysts or granulomas can arise around the cut ends of the vas which may be painful.
- (b) Long Term Complications: Vasectomy reduces testosterone production thereby contributing directly to the onset of Andropause. A consistent opinion amongst doctors advocating testosterone treatment for Andropause is that vasectomy brings about male menopause at an earlier age. It is believed that the incidence and prevalence rate of Andropause after vasectomy is twice as high as that in the general population. However the mechanism of this reduced hormonal production is not clear. The most likely cause seems to be an auto-immunity to sperm released into the tissues after the vasectomy.⁸⁻¹⁰

Effect of Testosterone on Metabolism

The physicians in general are ignorant about the role of testosterone in metabolism. By virtue of its influence on gene transcription, the primary role of testosterone is in protein metabolism. However, it also regulates sugar metabolism and through this pathway it influences the fat metabolism as well.¹¹

Protein metabolism

The anabolic action of androgens upon the skeletal muscle is well known for many years that have promoted its misuse in not only body builders and wrestlers, but also other sportspersons.^{12,13}

Some authors through experimental studies have proven the effects of androgens on the assimilation of amino acids like leucine into muscle proteins. Incorporation of uridine into ribonucleic acid of muscle has also been shown to increase under the influence of testosterone.

Carbohydrate metabolism.¹¹ The decrease of male hormone with age leads to chronic intolerance to glucose and thus, diabetes. Now, this is recognized as the leading cause of maturity-onset diabetes after the age of 40 years. An intramuscular injection of 5 to 25 milligrams of testosterone propionate provokes a significant decrease of glycaemia within two or three hours following the injection and its action lasts four or five hours.

Fat metabolism¹¹

Through the pathway of sugar metabolism testosterone influences the fat metabolism. When there is hyperglycemia, it can't be burned enough through the Krebs' cycle and there is overproduction of acetyl-coenzyme A which is the initial compound for making cholesterol and lipids.

Because every man, some time or other, will have a lack of testosterone production after forty, the investigation of triglycerides and cholesterol is important in old age.

CLINICAL PRESENTATION

The preceding paragraphs particularly figure 1. appreciates the role of testosterone on different organs of the body and the paragraph on metabolism are convincing that if there is deficiency of the male hormone in the body, certain systems are likely to be affected and depending upon the involvement of organs the patient may present with a mixed clinical picture thereby leading to a combination of symptoms of different diseases. In Orthopedic practice that old patients presenting with the symptoms related to bone and joints often suffer from osteoporosis. On taking their detailed medical history it would be evident that these patients suffer from some other disease invariably like diabetes, affection of the cardiovascular system, the kidney disease or symptoms of the thrombo-embolic phenomenon. Further most of these patients have loss

of libido and or Erectile Deficiency. It is not uncommon in such patients to have some other generalized effect anywhere on the rest of the body or on brain. Table 1 mention in short about the involvement of different systems in the body.

<p>General:</p> <ol style="list-style-type: none"> 1. Reduced general well being 2. Impaired cognitive function 3. Skin alterations 4. Decrease in body hair 5. Thinning of body hair 6. Sleep Disturbances 7. Slower recovery to injury 8. Reading Difficulty (small print) 9. Reduced interest in Sex 10. Weight gain 11. Abdominal obesity 12. Reduced haemopoiesis 13. Reduced immunity 14. Cancers 	<p>Brain and Psychology:</p> <ol style="list-style-type: none"> 1. Anxiety and Fear - about losing sexual potency 2. Depression 3. Forgetfulness 4. Indecisiveness 5. Irritability 6. Loss of purpose and direction in Life 7. Loss of self-confidence 8. Poor concentration / memory lapses 9. Short term memory loss 10. Senility 11. Stroke/Paralysis
<p>Sexual:</p> <ol style="list-style-type: none"> 1.Reduced libido 2.Erectile Dysfunction <p>Prostate enlargement</p>	<p>Heart and Blood Vessels:</p> <ol style="list-style-type: none"> 1.High blood pressure 2.Atherosclerosis <p>Coronary Artery Disease</p>
<p>Bones and Muscles:</p> <ol style="list-style-type: none"> 1. Muscle weakness 2. Muscle soreness and Stiffness 3. Muscle tenderness 4. Reduced muscle mass and strength 5. Osteoporosis / Reduced Bone Mass 6. Fatigue (less endurance for physical activity) 7. Osteoarthritis 	<p>Metabolic Disturbances</p> <ol style="list-style-type: none"> 1.Diabetes <p>Hyperlipidemia</p>

TABLE 1: SYMPTOMS ASSOCIATED WITH "ANDROPAUSE"

HEART, BLOOD AND BLOOD VESSEL

Generally you are as young as your heart and brain. This all is based on how good is circulation to these vital organs of the body.

Involvement of blood vessels¹¹

As the age advances, arteriosclerosis and atherosclerosis sets in different vessels all over the body. The muscle fibres are replaced by collagen tissue/fibrous tissue making the arteries inelastic. Now strong evidence is coming forward that muscular fibre of the arteries need testosterone to maintain their activity. Therefore deficiency of testosterone may accelerate arteriosclerosis. This is the consequence of cholesterol and lipid accumulation in the body through the impaired sugar and fat metabolism when testosterone is low in the body.

Therefore arteriosclerosis and atherosclerosis are two general involution phenomena increasing with the decrease of testosterone secretion.

Ischemic Heart Disease

For the last nearly 50 years, most of the doctors including the Cardiologists are of the view that testosterone is bad for the heart which is based on two reasons, one is that heart-attack in men under 50s is five times more common than in women in most of the western countries Though the women catch up soon after that age unless they are on Hormone Replacement Therapy (HRT). According to this line of reasoning, therefore, Testosterone is bad for the circulation and estrogen is good. The second reason that the Testosterone is bad for heart is because of the bad affects of the methyl testosterone orally and its use by athletes taking the wrong drug in wrong doses for the wrong reason and all this gives bad propaganda in the papers.¹⁴

Recent researches, however, beg to differ. Good numbers of papers are now available to convince that individuals with low testosterone have higher incidence of developing heart disease. These observations on deficiency of testosterone and its affect on heart and coronary vessels and usefulness of testosterone is further authenticated by various workers.¹⁵⁻¹⁷

Georges Debled has quoted similar studies and showed a positive correlation between lower Testosterone levels and coronary heart diseases. However, he points out, elevated estradiol levels pose greater risk for developing CHD; Table2¹¹

Hormone	Plasma level	Correlation with coronary heart disease
Total Testosterone	Low	+
Free Testosterone	Low	+
DihydroTestosterone	Low	+
Estradiol	Elevated	+

That Testosterone has beneficial effect on the heart can be discerned from its vasodilatory effect on blood vessels thereby increasing the much required blood supply and nutrition to the muscles of the heart^{14,18,19} It has also been found that Testosterone can prevent the type of spasm of coronary arteries that causes angina.

High cholesterol levels (with the exception of HDL-cholesterol) are disadvantageous for the heart as the risk of developing CHD is greater in such individuals and which is all the more evident from Georges Debled's work,¹¹ Table 3.

Testosterone has anti-atherogenic properties. This is by virtue of its influence on the fat metabolism whereby it causes reduction in cholesterol and body fat in general.

High level of	Correlation with coronary heart disease
Total cholesterol	+
LDL Cholesterol	+
Triglycerides	+
HDL Cholesterol	-

Blood Hypercoagulability

In patients with coronary artery disease and particularly those patients having blockade of the coronary vessels the blood is hypercoagulable. Keeping in view this analogy all such patients are prescribed dispirin. The main question about blood is not how it coagulates but keeping it fluid. The dissolution of the blood clot is under the influence of fibrinolytic agents. Such fibrinolytic agents of the blood are under the influence of testosterone as reported in the Lancet of the 21 July 1962 by Fearnley G R and Chakrabarti R¹¹ Therefore, the use of Testosterone in cases where the blood is hypercoagulable cannot be overstressed.

Anaemia

The number of red blood cells decreases by 10% in castrated men. This is similar in men with low testosterone levels in blood. The ischaemic heart disease is of course aggravated by this phenomenon.

The erythropoietic function of the kidneys is somehow under the control of Testosterone. Lack of testosterone therefore, can produce anaemia.

In 1981, Nagean Y et al. reported in the American Journal of Medicine the improvement of anaemia in a serial of 137 patients when treated by male hormones. Anaemia recurs when the therapy is stopped and improves again with

androgens²¹ The family physician may think of low Testosterone as cause of unexplained anaemia in old age. Varix, Hemorrhoids and thrombosis

The veins and the arteries are constituted by muscle fibres. The strength and tone of these muscle fibres is maintained by Testosterone. Lack of Testosterone produces involution of the muscular tissue of the vessels. Such situation in veins and arteries can cause varix, haemorrhoids and even thrombosis that have their own complications subsequent to dislodgement of the thrombus to vital organs like brain¹¹

MIND AND MATTER

"Age is a question of mind over matter. If you don't mind, it doesn't matter." Satchel Paige

What men do and how they do things depends on an intricate relationship between testosterone, mind and matter. This cannot be better explained than Andrew Sullivan's excellent article, which was published 12 years ago. His observation are as true today as they were when he wrote the article, and would probably remain true till mankind exists on Earth until a revolution is brought into the chemical nature of testosterone more affectionate to women to favor them against their own estrogens.

Andrew Sullivan, who himself is HIV positive noticed to have extreme fatigue and weight loss. He noticed that his body was producing far less testosterone than it should have been at his age. Therefore he used to give himself the injections of testosterone and experienced the true effects of testosterone himself.² The effects of injection testosterone were that his weight increased from around 165 pounds to 185 pounds. His collar size went from 15 to 17 1/2 in a few months. His chest went from 40 to 44. His appetite improved. Going from napping two hours a day, he rarely slept in the daytime and had enough energy for daily workouts and a hefty work schedule. He could squat more than 400 pounds. Depression, once a regular feature of his life, was now a distant memory.

He mentioned in his monograph that Men and women differ biologically mainly because men produce 10 to 20 times as much testosterone as most women do, and this chemical, no one seriously disputes, profoundly affects physique, behaviour, mood and self-understanding. Within hours following injection testosterone he felt a deep surge of energy. His attention span shortened within two or three days after the shot, he found it harder to concentrate on writing and felt the need to exercise more. His wits were quicker, the mind faster, but the judgment was more impulsive.

Mental abilities

Testosterone affects verbal ability and mental focus. The female style of thinking has been described as "web thinking" and the male style "step thinking". And it's mostly due to testosterone's effect on the brain.²²

The physical effects of testosterone are well documented but the awareness of its profound effects on the psyche is limited. Since it is unethical to experiment with human embryos by altering hormonal balances, what we do know today of the testosterone impact on mind is based on research conducted on animals, personal experiences and/or surveys. There are subtle differences in individual interpretation of testosterone effects on mind however, majority agree upon the notion that testosterone endows the individual with energy, self-confidence, competitiveness, tenacity, strength and sexual drive. This is irrespective of caste, creed and even gender.

Yes, women are also affected by testosterone similar to men. The animal experiments have shown that newborn female rats, injected with testosterone developed penises and indulged in aggressive sex like male rats. Animals with female dominance demonstrate high testosterone levels in females like hyenas and sea snipes. Typical "male" behaviour, in other words, corresponds to testosterone levels.

As mentioned in previous paragraphs both men and women produce testosterone and the physical differences between both the sexes arise due to the huge difference in production levels of testosterone. Women with higher testosterone levels have high sex drive and are usually the dominant partner during sex. Although libido is not entirely testosterone endowed, individuals with low testosterone levels exhibit lesser sexual arousal and activity. Around the age of 25-30 years, when the testosterone levels are highest, men are prone to promiscuity. The zest for satisfaction is not a physical one but a hormonal one. It is interesting to note that testosterone levels are higher in bachelors than in married men that further substantiate the idea of sexual gratification not being superficial.

Women in business exhibit higher testosterone levels than general female population. They are confident and energetic to the extent that they even subdue the "supposedly" dominant male species. Men or women engaged in fiercely competitive professions like sports persons or lawyers have a higher testosterone level than those in docile jobs like ministers and general merchants. Male and female inmates with higher testosterone levels have frequent altercations with the prison officials and are more likely to get into trouble.

It won't be altogether incorrect to say that testosterone is a "Booster" hormone. It not only boosts the musculo-skeletal system presenting with enhanced muscle bulk, strength, power and stamina but also has anti-depressant properties. A recent Australian study on men with suicidal tendency shows that about 30% of such men had low testosterone levels. When these individuals were managed with Testosterone, their views about life were radically altered, from extreme pessimism to optimism. This has given firmness to belief as mentioned by TASA coordinator, Linda Byart- "Suicide in older men is often hormonally based and can be prevented by appropriate hormone replacement therapy" and the same is supported by Alison Mc Cook who has found that men suffering from Andropause are four times likely to suffer depression than other males with normal Testosterone levels.^{23,24}

Women have a greater incidence and prevalence of depression than men. How this happens is not known exactly, but it has been hypothesised that testosterone increases the physical activeness, thereby allowing lesser time for retrospection. The concentration level also increases with testosterone making it more lucrative for use (and misuse for that matter).

Irritable Male Syndrome (IMS) with its various symptoms of irrational anger, depression and loss of control is triggered by a sudden drop in levels of testosterone.²⁵ Introduction of testosterone results in mood stabilization, the person becoming easier to be around, more able to socially relate to others and many other positive characteristics.²⁶ Stresses such as bereavement, divorce or life-threatening illnesses lowers testosterone levels. Based on this assumption psychiatrists do use testosterone therapy for the patients under depression.

Psychological Challenges in the Andropause

Some psychological aspects have been dealt with in the preceding pages, however the views of Robert S Tan on the role that testosterone plays on our psychology needs attention. The male in his life faces several psychological challenges and these are often amplified during Andropause.²⁷

The sexuality of a youthful man aged between 15 to 30 years when his testosterone was at an all time high, drops to the ebb during the Andropause. Young men often have testosterone levels exceeding 1000ng/dl. Compare this with 80 year-old men, whose average testosterone is 200ng/dl. You might say the sexuality of a man in the Andropause is down 80%, a seemingly disastrous event.

The older men tend to be closer to their family and are more interested in domestic issues than when they were younger. It

is as if the lack of testosterone makes them more "feminine". They take on more homely roles of cooking, cleaning and looking after children. More often than not, they devote much more time and attention to their grandchildren than they had previously to their own children when they were parents themselves. Perhaps it is because they have more time during the andropausal years as they have probably retired by then. They usually also have more disposable income, having saved most of their lives, and are more willing to enjoy little pleasures around them, stopping to smell the roses. Their emotions become less "fiery" and take on a gentler aspect, so in a sense, the decline of testosterone enhances domestication skills.

In the andropausal years the mind becomes less sharp and nimble. The older male becomes less swift in mental calculations and his judgment is not as accurate as before. Perhaps he used to make razor-sharp business deals, but now he makes blatant mistakes and incurs painful financial losses. It is often attributed to aging, but it may be partly due to the decline of testosterone. In more severe cases, the memory may get impaired, leading to dementia. It is not uncommon for older individuals to report misplacing a key or forgotten important details. Often the memory loss is so minor that it does not affect everyday functioning. This memory loss has sometimes been referred to as "age related memory loss" and is not as severe as Alzheimer's disease. Demented hypogonadic men who had low testosterone were administered testosterone and improvements in their visual-spatial cognitive abilities were demonstrated. However, more research is needed before recommending testosterone as a possible treatment of certain dementia.

Alzheimer's Disease

Alzheimer's disease is a chronic, incurable, and unstoppable Central Nervous System disorder that occurs gradually, resulting in memory loss, unusual behaviour, personality changes, and a decline in thinking abilities. These losses are related to the death of specific types of brain cells and the breakdown of connections between them.

Alzheimer's disease is characterized by the age-related deposition of -amyloid (A) 40/42 peptide aggregates in vulnerable brain regions. Testosterone reduces neuronal secretion of Alzheimer's -amyloid peptides. Testosterone supplementation, therefore, in elderly men may be protective in the treatment of AD.^{28,29}

Muscle cramps and Numbness.

In old age muscle cramps in different muscles is a common complaint. Some patients have even complained difficulty in swallowing water. It was as if the muscles in the food-pipe had gone into spasm. Cramps in some muscles of hands, back, legs and the feet is also not uncommon. The severity and duration of these cramps varies. After starting the treatment with oral testosterone, in most of the cases cramps disappear.

Some of the patients of Andropause complain about paraesthesia of the distal parts in both hands and the feet, which invariably happens in the early hours of morning. Besides testosterone some of these patients required injections of vitamin B12.

MUSCLES, BONES AND JOINTS

Testosterone is an anabolic Hormone that helps in building muscles, bones and connective tissues. This effect of Testosterone is known to the general public and has been often misused by professional weight-lifters and other sports persons to improve their performance by increasing their muscle mass, strength and stamina.

A deficiency in Testosterone reverses these positive effects and brings about weakness in muscles, bones and connective tissues. With ageing connective tissue loses its elasticity and its constitution is changed for worse. "MIDDLE AGE MAN BECOMES STIFF".

Effect on Posture

The onset of Andropause brings about progressive rounding of the shoulders and loss of height. Simultaneous reduction in bone density may lead to vertebral collapse and kyphosis. Altered posture also affects the overall alignment of the structures in and around the spine. Back pain is a frequent complaint amongst people with low testosterone levels.

Another important aspect of Andropause is the abdominal enlargement, particularly when the muscles of the rest of the body are wasted *en masse*. This is due to excessive fat deposition in and around the abdomen that is added on to the already weak emaciated muscles of the abdomen.

Effect on Muscles

Most of the Andropause patients present with mild to severe pain in muscles that is not relieved by rest. The muscles also lose their normal conformation because of wasting; most apparent in the thighs and calves. These muscles become weak losing their strength, power and endurance. Many people

would have experienced a gradual slowing down of their walking speed. They would also have experienced difficulty in climbing stairs, getting up from low seats or have a feeling of instability in legs while walking. This however, could be because of lowered testosterone level that is normally not appreciated as a causative factor in the society as a whole. Overall, the muscles not only have a reduced working capacity, but also their "reaction time" to contract increases thus causing slowed movements. It is important to note that group of muscles all over the body are tender. The muscle tone in Andropause men also goes down resulting in flabbiness. It is not only the muscles of the limbs are affected. The muscles all over the body are affected so much so that affection of the levator ani and the other pelvic muscles may be the cause of constipation. The weakness of the abdominal muscles along with the other factors is the cause of abdominal enlargement.

Effect on Tendons

The tendons lose their elasticity and stretchability. This is particularly felt on Tendo-achilles. On walking for a short distance the tendons of the lower limbs become painful. In cases of tendon ruptures in old people are investigated lack of testosterone may be one of the important causes.

Effect on Ligaments

In Andropause ligaments lose their elasticity. Therefore it may be one of the causes of stiffness of the joints. In foot small bones join together through ligaments. Since the ligaments become stiff the brunt is on the bones to bear the strain on walking. This whole process makes the feet painful on walking a short distance.

Effect on Joints.

Early - The Andropause male usually has morning stiffness of various joints particularly that are used for weight bearing or carrying loads specially the knee joints. At this stage usually, there is no limitation of movements of these joints. The pain in the neck and back is due to multiple factors namely, osteoporosis, receding muscle support and changes in posture.

Late - If Andropause remains undiagnosed and untreated, the resultant effect is on the joints wherein the joint cartilages are subjected to abnormal shearing forces. With concomitant alteration in the basic composition of the joint cartilage, the resultant effect is Osteo-arthritis of various joints particularly knee joints. Testosterone also potentiates the immune system of the body thereby reducing the risks of developing autoimmune disorders like Rheumatoid Arthritis of old age and other autoimmune diseases that may affect the joints.

Effects on Bones

In a healthy individual, bone tissue is constantly being broken down and rebuilt. In men, testosterone is thought to play a role in helping to maintain this balance. In an individual with osteoporosis, more bone tissue is lost than is regenerated and it is estimated that between the ages of 40 and 70 years, male bone density falls by up to 15 percent. Wrists, hips, spine and ribs are most commonly affected. Due to this, the individual may have severe pain in the bones adjoining the joints or anywhere including generalized tenderness of some bones or the other.

Osteoporosis and its ramifications are clearly mentioned in women after menopause. Unfortunately, with advancing age and declining testosterone levels, men, like women, seem to demonstrate a similar pattern of risk for osteoporosis. What's more, approximately one in eight men over the age of 50 years suffer from osteoporosis.

The incidence of hip fractures rises exponentially in ageing men, as it does in women, starting about 5 to 10 years later. Administration of Testosterone with usual fracture management is likely to decrease the morbidity and mortality, thereby adding on to a comfortable old age.

SEX AND SEX ORGANS

Testosterone secretion decreases with ageing. This effect leads to sexual involution in men, characterized by weak libido, weak penile erection, poor frequency of sexual intercourse, impotency, ejaculation problems, phimosis, sclerosis of penis and sometimes gynaecomastia.

Testosterone plays a major role in the development of secondary sexual characters including the development of the size of the penis. Testosterone is the hormone of 'Performance' as it excites desire, causes a strong erection to perform the sexual intercourse successfully and satisfactorily, provides lubrication prior to ejaculation, causes ejaculation and is responsible for orgasm.

Dwindling testosterone levels take away the libido and performance. Due to lack of Testosterone the penis is deficient in erection. It may have weaker erections or may not erect at all. The penis in flaccid position may also reduce in size thereby affecting the overall length.

Loss of libido is the earliest sign of Andropause and if low level of testosterone continues for long time it affects the erection and the size. Because of these reasons some of the patients of Andropause may not have Erectile Deficiency though they may have loss of libido.

The sexual problems and the level of testosterone is tabulated as follows [table 4]

Prostate³⁰

Testosterone works directly on many tissues of the body. But, Dihydrotestosterone (DHT) a hormone derived from testosterone is much more potent than testosterone and acts on prostate gland and the other sexual organs. DHT is produced within the prostate gland and some other organs from testosterone by the enzyme 5-alpha reductase. Without DHT a male would not develop his external sexual organs or his prostate. DHT is necessary for the normal growth and development of the prostate. Its presence is also necessary for the pathologic enlargement of the prostate, known as Benign Prostatic Hyperplasia (BPH) in older men.

Table 4 Sexual Problems and the testosterone

Age	Symptoms	Total T Level	Free T Level
54	1. Inadequate erection 1-2 years 2. Unsatisfied sex because of premature ejaculation	2.97 ngm/ml (1.95-11.50)	3.0 pg/ml (5.5-42.0)
43	1. Loss of erection 2. decrease in timing and duration of sexual intercourse and weakness	2.32 ngm/ml (1.95-11.50)	1.70 pg/ml (5.5-42.0)
34	1. Tiredness and general bodyache 2. Lack of interest in work at shop 3. Early discharge and low erection	3.50 ng/ml	7.0 pg/ml
26	1. Loss of erection 2. Low interest in sex 3. Poor sex performance	2.4 ng/ml	-----

Because the presence of DHT is necessary for the development of BPH, a recent therapeutic approach to treating this condition is to reduce the formation of DHT by blocking the enzyme 5-alpha reductase. This can be done by the new, highly promoted drug finasteride (or Proscar), which has been approved by the FDA for this purpose. The herb serenoa repens (or saw palmetto) also has this effect, as one of its actions..

.Dr. George Debled who specializes in sexual dysfunction and prostate problems has an experience of treating approximately 2,000 patients since 1970. He orders a battery of blood tests, which he calls a male hormonal profile and concluded that young men with impotency or libido problems often have hormone profiles similar to older men with similar problems and BPH. Testosterone and especially free testosterone levels are reduced and other hormones, such as estrogen and prolactin are increased.

Dr. Debled points out that testosterone is necessary to nourish all of the tissues of the male urinary and reproductive systems, including the prostate. It nurtures the development of muscles and is necessary for proper muscular functioning. When the muscles of the bladder and the prostate do not receive sufficient testosterone, they tend to function poorly, atrophy and fibrose. This may then help to explain some of the symptoms of BPH. Rather than trying to inhibit the formation of DHT, testosterone is administered to all these patients. Having successfully treated over 2,000 patients with impotency and prostate problems over the past 15 years, he believes that he can forestall BPH surgical procedures for at least 10 years by giving men the testosterone. He has also noticed that his patients have a much lower incidence of prostate cancer than would be expected, suggesting that testosterone rather than causing cancer may actually be a preventive.

GENERAL BODY EFFECTS**Universality of the androgen receptor**

The androgen receptor is identified in a variety of organs: the seminal vesicles, the hair follicle, the sebaceous glands, the foreskin glands and more generally all secondary sexual organs, the testicles and the epididymis, the uterus and the ovary, the kidney, the submaxillary glands, definite cerebral areas as the hypothalamus, the pituitary gland and the cerebral cortex, the levator ani muscle and the skeletal muscle, and the bone marrow. In reality small quantities of androgens' receptors have been observed in numerous organs.

In Andropause overall the health goes down. The stamina for work goes down. One loses interest in the work. The agility is reduced. It is often noted that the senior officers few years before their retirement may be seen dozing off on the chair. People have been seen dozing off during the course of the meetings.¹¹

Andropausic gait

The elasticity and the stretchability of the both muscles and the tendons is reduced. When this is coupled with the weak muscles of calf, thigh and the foot muscles, the normal springiness of the gait is lost. One would be walking on a wider base in a slow and painful pace. The pain is felt earlier on the tendons than the muscles, particularly the Achillis tendon (not normal gait of heel strike, foot flat and toe off).

Hair

The growth of hair is reduced, the hair become thinner and grey. An andropausic individual may complain that he goes to the barber less often than earlier. Similarly it be noticed that he may not feel the necessity of shaving the beard daily and regularly. The hair on the rest of the body is also reduced.

Skin

The skin all over the body becomes dry. The thickness of the skin also reduces. It reduces its elasticity and the shine. The skin rather looks darker. Since it loses its elasticity and proper thickness it starts getting wrinkled all over the body but this is more evident on the face. If one lifts up the skin over the back of the hand it can easily be pinched; since it has lost its elasticity, it takes time to gain its original tenor.

There are more chances of getting skin infections because the usual protection of the connective tissue to the skin is dampened. The loss of skin elasticity also takes its toll on the skin covering the glans of the penis leading to phimosis.

Due to the combined effect of the amyotrophy of the muscles and loosening of the skin, different facial crease of the forehead and the face become prominent. The cheeks also pucker in. Physicians experienced in managing the aged would be able to appreciate the facial changes of the andropausal male better.

Obesity

Obesity follows fat accumulation. It has been seen that obese men have lower testosterone levels in the blood, which is directly related to the degree of obesity.^{11,31}

Table 5: Low plasma testosterone in massively obese men

Obese group (200-280% of ideal body weight)	223 ngm/100 ml testosterone level
Control group (85-135% of ideal body weight)	599 ngm/100 ml testosterone level

Because the testosterone secretion decreases with age it seems logical to believe that this phenomenon is a leading cause of fat deposits everywhere in the body and that being overweight is a clinical sign of Andropause.

Lungs

Normal breathing is a result of good elasticity of connective tissue of the lungs. Respiratory muscles in good condition are also necessary for a good respiration. Connective tissue deterioration and amyotrophy of the respiratory muscles in Andropause leads to breathing problems.¹¹

It is a common observation that some men become breathless after climbing some flight of stairs or walking even short distances. It has been my observation that Andropause is the main reason behind this. In some of the cases after TRT their have been improvement on this score which of course needs confirmation through respiratory function tests..

Immunity

Testosterone stimulates immunity. A decrease of androgens' secretion induces a lack of production of lymphocytes leading to chronic infections and cancer. Testosterone therapy may gain importance in cases of HIV positive patients.²

Another role of testosterone is to help regulate the immune system. Patients with autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus and

multiple sclerosis appear to benefit from testosterone. It has been used to improve appetite, increase weight in malnourished patients, improve wound healing and increase resistance to infection.³⁰

Eyes

The acuity of vision is disturbed particularly the peripheral vision. Moreover it has also been observed that lack of testosterone causes dryness and itching in the eyes as if the secretion of lacrimal glands is reduced. This issue needs further investigations before being authenticated.

George W. Drach pointed out that fundoscopic examination of the retina of the eye may have bearing in diagnosing the cases of Erectile Deficiency (ED), which may be related to generalized atherosclerosis which afflicts the penile vessels as well.³¹

VIAGRA

In most men suffering from Andropause, low sexual performance or Erectile Deficiency is the chief concern. Although the last problem to be revealed by the patient, this is the most disturbing aspect of Andropause for most of them. However, in some of the patients high doses of Testosterone may be required to achieve the desired effects. There may be some other patients who do not improve in their sexual performance in spite of taking Testosterone. Such patients may have Erectile Deficiency probably due to causes other than Andropause. For such patients Viagra seems to be a more pertinent choice.

Viagra is one drug that has gained tremendous popularity in this field. Although a recent entrant into the field, it has already benefited more than 16 million men globally. With an efficacy rate as high as 80% as propagated by the manufacturer, it has been shown to work in Erectile Deficiency irrespective of the cause and frequency of the problem and age of the patient.³³

However, as a word of caution needs mention here that the improved effectiveness corresponds to the dosage of the medicine administered. As a study done on 1448 patients shows, almost 100 mg of Viagra is required to achieve 80% success rate, Chart 1.³⁴

DIAGNOSIS

“Hormones do not decline because we age we age because hormones decline.” -Anonymous

After the age of 50, the average testosterone level decreases at

a rate of approximately 1% per year.³⁵ However, if only absolute testosterone levels are evaluated, many patients with Andropause will be missed. There may be an increased level of sex hormone-binding globulin that binds the testosterone and makes less of it available to the tissues. Also, as men get older, there is less of a daily rhythm to the secretion of the testosterone. Younger men have higher testosterone in the morning, which then decrease as the day wears on. In older men, this curve is flattened, leading to steady low levels of testosterone throughout a 24-hour period.

It is well accepted that if total testosterone is less than 200 ng/dL, a man will be considered as having a low testosterone level. If his total testosterone is greater than 600 ng/dL, low testosterone may be ruled out.

At this point in time, it appears that the best measurement of androgen status is either “free testosterone” or “bioavailable testosterone”. The normal laboratory values are mentioned in Table 6. The importance of free testosterone has already been stressed in the preceding paragraphs.

Table 6: Laboratory Values Of Hormones

	Gender	Age	Normal Range
Total Testosterone	Men	20-50 yrs	245 1600 ngm/dl
		>50 yrs	181 722 ngm/dl
	Women	Ovulating	0-81 ngm/dL
		Post -menopausal	0 74 ngm/dl
Free Testosterone	Men	20-50 yrs	5.5 4.2 pg/ml
		>50 yrs	10.8-24.6 pg/ml
	Women	Ovulating	0.0 4.1 pg/ml
		Post -menopausal	0.1 1.7 pg/ml

TREATMENT

"You can't turn back the clock. But you can wind it up again."
- Bonnie Prudden

It is established that Andropause is due to deficiency of bio available or free Testosterone. Therefore, the obvious treatment would be to replace Testosterone to the afflicted individuals.

Before replacing testosterone, a total hormonal assay of these individuals is essential. This is to provide the baseline value of different hormones that may also change after giving Testosterone. Moreover the dosage of Testosterone would depend upon the baseline level of Testosterone. Both to

establish the diagnosis and to monitor the treatment properly, laboratory measurements of the sex hormones and the complex range of factors regulating their action, together with tests of blood fat, liver, kidney, and prostate function and hematology profile, all need to be checked before treatment and at each follow-up assessment.

The role of treatment actually is that rest of the endocrine system should be balanced. This may involve the administration of thyroid hormone, DHEA or physiologic doses of cortisol. Some recent studies on ageing indicate that the administration of optimal doses of human Growth Hormone (hGH) may also be extremely useful when it is deficient. Male Andropause is largely a preventable and treatable condition.

Besides the medicines *per se* a comprehensive approach that emphasizes lifestyle, including an optimal diet, nutritional supplements, exercise, stress management, reduction of smoking and alcohol, detoxification procedures and energy balancing is more important. Recently anti-oxidants have outweighed all other treatments claiming that even the serious diseases can be controlled with anti-oxidants alone.³⁰

Testosterone Replacement has been shown to be very effective in improving the physiological and psychological functions of the individual, as enumerated below.³⁶

- Improvement in mood and sense of well-being
- Increased mental and physical energy
- Decreased anger, irritability, sadness, tiredness, nervousness
- Improved quality of sleep
- Improved libido and sexual performance
- An increase in lean body mass, a decline in fat mass
- An increase in muscle strength (hand grip, upper and lower extremities)
- Potentially, a decrease in the risk of heart disease

With Testosterone therapy, one's attitude improves, reinforcing self-esteem and self-confidence at work, as well as an increased energy at home and in social activities. Most men will feel more vigorous, experience improved energy levels, mood, concentration, cognition, libido, sexual performance and an overall sense of well-being. These effects are usually noted within 3 to 6 weeks.

Other potential benefits include maintenance or improvement in bone density, improved body composition, muscle mass and muscle strength, as well as improvement in visual-spatial skills.

Testosterone Replacement:

Pills

Methyl testosterone (Android, Virilon, Testred, Oreton) 10mg, 25mg (not recommended)

Testosterone undecanoate (Restandol, Andriol, Tetocaps, Cernos) 40mg, essentially a testosterone in oil preparation

Mesterolone (Proviron) 25mg -- less potent

I have experience of only using Testosterone undecanoate. I recommend that this may be used for TRT.

Transdermal Preparations (Testoderm, Testoderm TTS, Androderm)

In transdermal testosterone, the hormone is released slowly through the skin to deliver a constant level in the blood, again not a routine pattern, but convenient. Transdermal testosterone can be applied either to the scrotal area or to other areas.

Injections

The following forms of injectable testosterone are available.

1. Testosterone Cypionate (Cernos) 100 mg/ml
2. Testosterone Propionate in oil 100 mg/ml
3. Testosterone Enanthate 200mg/ml

The usual dose is 1cc injected weekly or bi-weekly. This route of administration eliminates the risk of liver damage which may be caused by methyl testosterone as well as eliminating the theoretical risk of changes in cholesterol caused by oral medications

4. Testosterone undecanoate depot (injection cernos by Sun pharmaceutical) 1000 mg in 5ml Usually one injection is sufficient for 12 weeks.

Side effects of Testosterone Replacement Therapy:

TRT can have undesirable side effects that include nausea, vomiting, jaundice, ankle swelling and frequent or persistent erections. Breast enlargement can also develop as Testosterone can be converted to estrogen via the enzyme aromatase. More serious complications include water retention, liver toxicity, cardiovascular disease, sleep apnea, and prostate enlargement. These risks are relatively uncommon when the dosage is closely monitored to that found physiologically in the body.

TRT is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate. A digital rectal

examination and laboratory test for prostate specific antigen (PSA) should be checked before initiation of therapy and every 3 to 6 months thereafter.

TRT also should not be considered in those with known hypersensitivity to the preparation or in patients with compromised cardiac, renal, or hepatic functions.

While there is no direct evidence that link Testosterone replacement to accelerated prostate enlargement, there is a correlation between Testosterone treated hypogonadal men and normal men with prostate volume and age.

Results of TRT may not be evident for several weeks. Impotence may not be corrected after several months of therapy despite improvement in other Andropause symptoms. For these patients, evaluation for causes of erectile dysfunction other than hypogonadism due to Andropause is indicated.

Nutritional Supports

Andropause is a syndrome of degenerative disease characterized by age related diseases such as cardiovascular dysfunction, cancer and arthritis. One of the primary mechanism of Andropause may be oxidative stress from free radicals. Through improper diet, external pollutants, stress of life, our body's cells are continually bombarded by millions of free radicals each day. The degree and the amount of free radicals present in the body are related directly to the speed of the aging process.

Therefore, one of the primary goals of preventing Andropause may be retarding the proliferation of free radicals through intake of food rich in anti-oxidants and antioxidants supplements.

While there is no established laboratory reference for the ideal intake level of antioxidants for anti-aging, many in the forefront of anti-Andropause research are advocating much higher levels of intake than the Recommended Dietary Allowance

Proper Exercise

Exercise, in addition to its cardiovascular benefits, also increases the level of hormones in the body, which include growth hormone, Testosterone, DHEA and pregnenolone. Performing strength-training exercise is a key component because of the above-mentioned effects.

Following an anti-aging exercise program incorporating flexibility training, cardiovascular training, and strength

training program in a balanced fashion is the key to preventing Andropause. It is strongly advised that none of the three components should be ignored.

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