

PHYSIOLOGICAL ASPECTS OF TESTOSTERONE ADMINISTRATION IN ANDROPAUSE

Rina Judiwati^{*)}, Reny I'tishom^{*)}, Hudi Winarso^{*)}

ABSTRACT

Testosterone is a hormone which belongs to the androgen group. It is a misnomer to classify them as these "male hormone" as they are present in both male and females, albeit in different amounts. Andropause is : A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. Metabolic and endocrine effect of testosterone on the human body exist are effect of testosterone on glucose homeostasis, effect of testosterone on body composition, effect of testosterone on lipid regulation, effects of testosterone on the cardiovascular system. Andropause is a syndrome characterized primarily by : (1) The easily recognized features of diminished sexual desire (libido) and erectile quality and frequency, particularly nocturnal erections, (2) Changes in mood with concomitant decreases in intellectual activity, cognitive function, spatial orientation ability, fatigue, depressed mood and irritability, (3) Sleep disturbances, (4) Decrease in lean body mass with associated diminution in muscle volume and strength, (5) Increase in visceral fat (6) Decrease in body hair and skin alteration, (7) Decreased bone mineral density resulting in osteopenia, osteoporosis and increased risk of bone fracture.

Keywords : testosterone and andropause

INTRODUCTION

Testosterone is a hormone which belongs to the androgen group. It is a misnomer to classify them as these "male hormone" as they are present in both male and females, albeit in different amounts. There is undeniable evidence that aging result in lowering androgens. When testosterone is measured, 20% of men above 55 years are hypogonadal (Tenover, 2000; Meigs et. al., 2000). However, when bioavailable testosterone is measured 50% of men above 50 years are defined as hypogonadal. Ninety-eight percent of circulating testosterone is bound to plasma proteins, the remaining 2% of free testosterone is responsible for biological activity. Approximately 40% of the bound testosterone readily available to tissue when needed. Bioavailable testosterone includes free testosterone and that loosely bound to albumin (Morales et. al., 2001).

As the decline in androgen is gradual, the alternative term of Andropause was "Androgen Decline in Aging Males "[ADAM]. Partial Androgen Decline in Aging Male " [PADAM] has also been suggested, because the androgen deficiency in older men is generally moderate and not a complete deficiency. There is often confusion that andropause

^{*)} Biomedical Department, School of Medicine, Airlangga University

is a symptomatic state. It must be stressed that like menopause, there could be presence or absence symptoms. Transitory symptoms can include changes in mood and sexuality. The long term effects of hypogonadism can result in osteoporosis, muscle atrophy and cognitive changes. Symptomatic hypogonadism is sometimes referred to as the "Andropause Syndrome" (Laaksonen et. al., 2003).

Patient andropause with metabolic syndrome are at high risk for cardiovascular disease, diabetes mellitus and chronic renal insufficiency (Yue et. al., 1995). In men with any of these chronic medical illness their already compromised quality of life is often further decreased by erectile dysfunction or voiding dysfunction. Currently treatment modalities focus on treatment focus on treating the primary disease.

DEFINITION

Andropause is : A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ system.

PHYSIOLOGICAL ASPECT

Since the concept of hypogonadism as a critical component of metabolic syndrome is only in its infancy, testosterone as a treatment option for metabolic syndrome has not been thoroughly studied. However, numerous studies of the individual metabolic and endocrine effect of testosterone on the human body exist.

Effect of testosterone on glucose homeostasis. At physiological doses testosterone is known to have beneficial effects on glucose regulation. In experimental non diabetic rats exposed to subtherapeutic or supratherapeutic doses of testosterone marked insulin resistance developed. When serum testosterone was normalized, insulin sensitivity was fully restored. In human studies of obese, diabetic and hypogonadal men testosterone administration resulted in decreased fasting glucose, increased insulin sensitivity and decreased glycosylated haemoglobin A_{1c}. In studies of patients with prostate cancer undergoing androgen deprivation therapy increased serum insulin has been noted despite no change in glucose (Dockery et. al., 2003; Singh et. al., 2003). This suggests an underlying resistance to insulin and a subsequent need for higher serum levels to achieve euglycemia.

Effect of testosterone on body composition. The age related decrease in testosterone normally seen in aging men is associated with a progressive loss of muscle mass and increase in body fat. The

principle of testosterone therapy and hyponadal elderly men is base on supposition that correcting testosterone level should result in an increase in muscle mass and a decrease in fat mass. Multiple others studies of oral testosterone therapy in men have documented increase lean body mass, weight loss decreased percent of body fat an decrease n waist to high ratio (Marin, 1995; Li et. *al.*, 2002). In a double blind study of men with central obesity treated with transdermal testosterone marine found a decrease in visceral fat but not in femoral fat. In men with treated with testosterone (Smith et. *al.*, 2001). Rajan *et al* hypothesized that testosterone may regulate body composition by preferentially inducing pluripotent mesenchymal cell diffentiation toward myogenic lineage and away from an adipogenic lineage (Lempiane et. *al.*, 1999).

Effect of testosterone on lipid regulation. While observational studies have shown a consistent association between low testosterone and high cholesterol, studies of testosterone therapy have yielded inconsistent results. It has been suggested that testosterone may actually decrease HDL concentration and have a potentially atherogenic effect.

Effects of testosterone on the cardiovascular system. Testosterone has been shown in vitro and in vivo to hav direct vasodilatory effect on coronary arteries. Yue *et al* observed that testosterone administrated to rabbit induces relaxation of the coronary arteries and aorta (Webb et. *al.*, 1999). They proposed that the site of action of testosterone may be an adenosine triphosphat insensitive potassium channel. In a study of elderly men with coronary artery disease (Webb et. *al.*, 1999) reported coronary artery dilatation and improved coronary blood flow with the direct intra coronary infusion of physiological amount of testosterone for three minutes (Boyanov et. *al.*, 2003).

In study of obese hypogonadal and diabetic men treated with oral on transdermal (Marin, 1995; Smith et. *al.*, 2001; Li et. *al.*, 2002). Testosterone was shown to decreases favorable. Conversely men treated with androgen deprivation therapy for prostate cancer have been found to have increased arterial stiffness (Dockery et. *al.*, 2003; Singh et. *al.*, 2003). In one this studies an interval improvement in arterial compliance was not take during period when androgen deprivation therapy was halted.

PATHOGENESIS

To our knowledge a central unifying theory to explain the relationships among the various components of metabolic syndrome

remains to be elucidated. However, the ongoing obesity epidemic in the western world has been suggested as a major causative factor in the pathogenesis of this increasingly more prevalent disease. In the particular abdominal or central obesity has been linked to hypertension, increased serum low density lipoprotein (LDL), low serum high density lipoprotein (HDL) and hyperglycemia.

Excessive hepatic gluconeogenesis, impaired peripheral glucose use and increased lipolysis leading to increased free fatty acids are the hallmarks of insulin resistance found in metabolic syndrome. Examining the multiple physiological effects of insulin in the human body helps us understand metabolic abnormalities that result from insulin resistance in metabolic syndrome. In the vascular system insulin stimulates the growth of endothelial cells and pericytes. In the kidney insulin has a role in volume and, hence blood pressure regulation by activating mechanism of sodium reabsorption. Insulin also facilitates wound healing by promoting effective platelet aggregation and fibrinolysis.

When normal insulin regulation is disrupted, as in metabolic syndrome, abnormalities in endothelial function, blood pressure regulation and coagulation result. These abnormalities cause atherosclerosis, chronic inflammation and unstable plaque formation, which predispose to acute thrombosis in the cardiovascular system (Basaria, 2001; Walker, 2001).

In addition to central obesity and insulin resistance, several other endocrine factors have been implicated in the pathogenesis of metabolic syndrome. It has been suggested that alterations in the peripheral metabolism of glucocorticoids, brought about that alterations in the peripheral metabolism of glucocorticoid, brought by changes in expression of 11 β hydroxysteroid dehydrogenase, type I, may be responsible for the abnormalities in body fat distribution seen in patient with obesity and/ hypoglycemia (Laaksonen et. al., 2003). Laaksonen et al reported that low total testosterone (T), free testosterone and sex hormone binding globulin (SHBG) correlate strongly with metabolic syndrome (Holmang, 1992). Given the multiple metabolic and endocrine axes involved in metabolic syndrome and the large number of complex interactions among them, it is clear that much remains to be understood about the true pathogenesis of this disease.

RECOMMENDATION

Andropause is a syndrome characterized primarily by :

- The easily recognized features of diminished sexual desire (libido) and erectile quality and frequency, particularly nocturnal erections.

- Changes in mood with concomitant decreases in intellectual activity, cognitive function, spatial orientation ability, fatigue, depressed mood and irritability.
- Sleep disturbances
- Decrease in lean body mass with associated diminution in muscle volume and strength : Increase in visceral fat, decrease in body hair and skin alteration, decreased bone mineral density resulting in osteopenia, osteoporosis and increased risk of bone fracture.

In patients at risk or suspected of hypogonadism in general and andropause in particular a thorough physical and biochemical work-up is mandatory and especially, the following biochemical investigations should be done :

1. A serum sample for total testosterone determination and sex hormone binding globulin (SHBG) should be obtained between 07.00 and 11.00 hours.
2. There is however general agreement that total testosterone levels above 250 pmol/L (72pg/mL) do not require substitution.
3. If testosterone levels are below or at the lower limit of the accepted normal adult male values, it is recommended to perform a second determination together with assessment of serum luteinizing hormone (LH) and prolactin.

Testosterone administration is absolutely contra-indicated in men suspected or having carcinoma of the prostate or breast. Clinically benign prostate should not be treated with testosterone. Moderate obstruction represents a partial contraindication. After successful treatment of the obstruction, the contra indicated if lifted.

For the present time mid to lower young adult male serum testosterone levels seem appropriate and should be the therapeutic goal. Supraphysiological levels must be avoided.

Digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA) are mandatory in men over the age of 45 years as baseline measurements of prostate health prior to therapy with testosterone, at quarterly intervals for the first 12 months and yearly thereafter.

REFERENCES

- Basaria S, Dobs A.S. 2001. Hypogonadism and androgen replacement in elderly men. *AM j Med.*110:563-572.
- Boyanov, M.A., Boneva, Z., and Christov, V.G. 2003. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male*, 6:1.

- Dockery, F., Bulpitt, C.J., Agarwal, S., Donalson, M and Rajkumar, C. 2003. Testosterone suppression in men with prostate cancer leads to increase in arterial stiffness and hyperinsulinemia. *Clin Sci*, 104 : 195.
- Holmang, A. and Bjorntorp, P. 1992. The effect of testosterone on insulin sensitivity in male rats. *Acta Physiol Scand*. 146:505.
- Laaksonen, D.E Niskanen , L., Punnonen, K., Nyyssönen, K., Tuornainen, T.P., Salonen, R. 2003. Sex Hormone, inflammation, and the metabolic syndrome : a population- based Study . *Eur J Endocrinol*, 149:601.
- Laaksonen, D.E., Niskanen, L., Punnonen, K., Nyyssönen, K., Tournainen, T.P Salonen, R. 2003. Sex Hormone, inflammation, and the metabolic syndrome : a population, and the metabolic syndrome : a population- based study. *Eur J Endocrinologi*. 149: 601.
- Lempiane, P., Mykkanen, L., Pyorala, K., Laasko, M. and Kuusisto, J. 1999. Insulin resistance syndrome predict coronary heart disease events in elderly nondiabetic men. *Circulation*, 100:123.
- Li, J.Y., Zhu, J.C., Dou, J.T., Bai, W.J. Deng, F.M., Huang, W. 2002. Effect of androgen supplementation therapy on partial androgen deficiency in the aging male : a preliminary study. *Aging male*. 5:47.
- Marin, P. 1995. Testosterone and regional fat distribution. *Obes Res*, suppl. 3:609.
- Meigs, J.B., Mittleman, M.A., Nathan, D.M., Tofler, G.H., Singer, D.E, Murphy- Sheehy, P.M. 2000. Hyperinsulinemia, hyperglycemia, and impaired hemostasis : the Framingham offspring Study. *JAMA* 283 :221.
- Morales A, Heaton J.P, Carson C.C. 2001. Andropause : a misnomer for a true clinical entity. *J urol*. 110:563-572.
- Singh, R., Artaza, J.N., Taylor, W.E., Gonzales- Cadavid , N.F. and Bhasin, S. 2003. Androgens stimulate myogenesis differentiation and inhibit adipogenesis in C3H 10 T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*. 144:5081.
- Smith K.W, Feldman HA, McKinlay J.B. 2000. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in aging men. *Clin Endocrinol*. 53:703-711.
- Smith, J.C. Bennett, S., Evan, L.M., Kynaston, H.G., Parmar, M., Mason, M.D. 2001. The effects of induced hypogonadism on arterial

- stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab.* 86: 4261.
- Tenover J.S. Androgen Administration to aging men. *Endocrinol.* 2000;53;703-711.
- Walker, B.R. 2001. Steroid metabolism in metabolic syndrome X. *Best Pract Res Clin Endocrinol Metab.* 15; 111.
- Webb, CM., McNeill, J.G., Hayward, C.S., de Zeigler, D. and Collin, P. 1999. Effect of testosterone on coronary heart disease. *Circulation*, 100:1690.
- Yue, P., Chatterjee, K., Beale, C., Poole-Wilson, P.A and Collins, P. 1995. Testosterone relaxes rabbit coronary arteries and aorta. *Circulation*, 91:1154.