

Roles of Testosterone in Men with Type 2 Diabetes: A Review

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Abstract— Androgen deficiency has recently come to the forefront of the medical literature after being ignored for decades. The prevalence of hypogonadism is greater than previously thought. Important associations are being developed and confirmed in the literature between androgen deficiency and metabolic disorders, specially in type 2 diabetes [1]. The prevalence of type 2 diabetes is increasing on over the world and directly effects the quality of sexual life of men [2]. However, in men with type 2 diabetes, besides the effect of erectile improvement, testosterone replacement therapy also reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes. Improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk. The objective of this paper is reviewing the roles of testosterone in men with type 2 diabetes.

Keywords— Testosterone, hormone of men, type 2 diabetes, erectile dysfunction.

I. INTRODUCTION

The prevalence of type 2 diabetes is increasing on over the world and directly effects the quality of sexual life of men. Androgen deficiency is the main cause of this circumstance because it may leads to erectile dysfunction and decreased libido, specially more in men with type 2 diabetes [3]. If we recognize the problems of the mechanism, we can fix them appropriately in time and the patient will get more benefit from appropriate treatment. The living quality, therefore, will become better.

II. TESTOSTERONE

Testosterone is one of a hormone whose nature is lipid (steroid hormone). The main place where it is produced is the interstitial cells: Leydig cells. Besides, a small amount of testosterone is produced by the adrenal cortex and ovary (androgen is produced by the reticularis of the adrenal cortex). Testosterone is transported in the blood by combining with globulin: globulin binds to sex hormone (sex hormone binding globulin: SHBG) because the lipid hormone is insoluble in plasma. More than 70% of testosterone is combined with protein; the proportion of free hormone is insignificant [4].

The main functions of testosterone are making the primary and secondary sex of male formation; taking part in protein metabolism; sperm producing and cause the sexual

desire of male. In the fetus, the Y chromosome triggers the sexual germ-cells to produce a little amount of testosterone, which encourages the fetus develop its male sex (the development of male sexual organ). This is called the primary sex of male. When reaching the puberty, testicles (Leydig cells) begin to produce testosterone that forms the secondary sex of male such as: the gait, muscular development, bear-raising, armpit hair, pubic hair, bass voice ... Besides, testosterone takes a role in strengthen the process of synthesizing protein, which results in muscular development. It increases the transcription of gene, DNA molecule in the cellular nucleus to create message RNA (mRNA) and increases the translation of gene on endoplasmic reticulum containing ribosomes to synthesize the protein molecules. With doping in sport, the athletes have overused the testosterone products, which makes the muscles develop rapidly and the power of muscles become stronger in order to gain high results [5,6]. Moreover, testosterone is also important in reproductive fuction. It combines with FSH hormone (Follicle Stimulating Hormone) of the anterior lobe of pituitary gland to produce sperms and cause the sexual desire of male. This is extremely important because it is a motivation for species survival of both human and animal [7,8].

III. TYPE 2 DIABETES

There are 2 types of diabetes. Type 1 diabetes or insulin dependence diabetes refers to the failure of the pancreatic endocrine glands that is unable to produce insulin, which causes the deficiency of insulin. Type 2 diabetes or insulin independence diabetes refers to the pancreatic endocrine glands whose function has not failed. It is still able to produce insulin [9]. However, why does diabetes occur? It is due to the sensitive level of the cells to insulin. When the cells want to get insulin, the membranes have to contain receptors whose nature is protein. The cells once get the insulin; they have to increase the process of synthesizing protein or exactly, synthesizing receptors. It is a pity for these people because the ability of synthesizing protein is low. As a result, there are no receptors to get insulin although the pancreas is able to produce insulin. We often use the phrase insulin resistance or lower the sensibility to insulin. Diabetes not only causes disorders in glucid metabolism but also in lipid and protein metabolism. The lipid metabolism is more important [10].

In lipid metabolic disorder, Insulin has an effect in speeding up the transportation of glucose from plasma into the cells through the membranes. The deficiency in insulin makes the process of transporting glucose into the cells lower as much as 20 times. Therefore, glucose is unable to go into the cells; it will stay in the blood, which pushes the blood sugar up. 180mg/dL is the blood sugar level that is much higher than the renal tubular absorption threshold, which causes diabetes.

In lipid metabolic disorder [11,12], insulin has an effect in inhibiting the lipase enzyme in the adipose tissue. The deficiency of insulin, thus, releases the lipase enzyme. The enzyme, then, starts its function is to digest triglyceride to form fatty acid and glycerol. The lipase enzyme digests the stored fat of the body and releases the saturated fatty acid into the blood. The liver will keep the fatty acid and increase the process of synthesizing triglyceride and cholesterol. These substances are transported into the circulation under a very low density lipoprotein (VLDL) that will transform into the low density lipoprotein (LDL) in the blood. In conclusion, the lipid blood will increase in diabetes. There is a significant increase in plasmatic level of triglyceride (fat), total cholesterol, low density lipoprotein (LDL); except for the high density lipoprotein (HDL), it decreases. LDL is the substance causing the atherosclerosis while HDL is the substance against forming the atherosclerosis. LDL brings cholesterol into the artery walls, which create many cholesterol crystal plaques on the inner walls. The fibroblasts will cover the cholesterol crystal and calcium precipitates to the cholesterol plaques to harden the walls. These factors cause many serious consequences. Firstly, the artery walls become thick as a result of some reactions: smooth muscles layer become aneurismal, the cholesterol plaques, the invading of the fibroblasts and the precipitated calcium. Then, the walls harden and lose their elasticity due to the fibroblasts and calcium. These cause high blood pressure. Secondly, the inner walls are narrow, which reduces the pump of the blood to the organs because of thicker arterial walls and the cholesterol plaques protruding inner arteries. Thirdly, The blood is easy to be clotted in the inner wall to form many thrombi, which cause artery obstruction throughout the body. Especially, when it happens in the heart and the brain, it causes cardiac infarction and stroke. The blood is clotted easily in the inner due to the cholesterol plaques protruding inner that help the thrombocytes stick on to trigger the process of clotting blood. Finally, the blood vessels are degenerated easily because of the sclerosis of the arterial walls, which press the blood vessels feeding the arterial wall cells. These cells that are cut off the feeding, will be degenerated and die. This easily lead to arterial aneurysm and fragile arteries. It is sometimes extremely dangerous because of breaking big blood vessels such as:

abdominal aorta. The stroke is due to breaking the cerebral blood vessels results in cerebral haemorrhage. There are two reasons: high blood pressure and the arterial walls are sclerosing and degenerated. All of the above changes of the blood vessels are called atherosclerosis.

In protein metabolic disorder, insulin induces protein synthesis and inhibits protein metabolism. It increase protein synthesis by three methods. The first one is increase of amino acids transported from interstitial fluid into the cells, amino acids are ingredient for protein synthesis. In the absence of insulin, the level of amino acids transported decrease by twenty times. Without amino acids, the cells stop producing protein. The second one is increase of gene replication in the nucleus to reproduce mRNA and the last one is increase of transcription in the endoplasmic reticulum to synthesize protein. Besides, insulin also inhibits protein metabolism by inducing glucose metabolism to acetyl-CoA. Acetyl-CoA inhibits protein metabolism in the negative feedback mechanism. In the absence of insulin, glucose is not metabolized, therefore there is no acetyl-CoA to inhibit protein metabolism. In the other hand, in the lack of glucose, the cells have to metabolize protein to produce energy in the form of ATP (Adenosine Triphosphate) [13]. Therefore, without insulin, the body will decrease protein synthesis and increase protein metabolism.

Diabetes causes many complications overall the body [2,10,11,14]. They are atherosclerosis (lipid metabolism disorder increase blood LDL); cardiovascular complications (hypertension, stroke, myocardial infarction, cerebral infarction, cerebral hemorrhage); nervous system damage (both central and autonomic nervous systems are affected due to metabolism disorders), renal failure and proteinuria; severe infections caused by decreased protein synthesis and increase protein metabolism weaken the immune system and macrophage which require protein to function; limb necrosis (peripheral vessels occlusion due to thrombi); eye injury (retinal hemorrhages, or retinal vessels occlusion leading to injury to receptor cells: rods and cones, and vision loss subsequently); and erectile dysfunction, decreased libido.

IV. ERECTILE DYSFUNCTION AND DECREASED LIBIDO IN DIABETES – ROLES OF TESTOSTERONE THERAPY

Mechanism of erection is penis need a full erection to penetrate the vagina [16]. Erection is the process in which the arterioles dilate causing the erectile tissues (corpora cavernosa and corpus spongiosum) filled with blood. The veins of the corpora cavernosa are compressed restricting the egress and circulation of this blood, causing the penis erecting and firm (four times than normal). Erection regulation center is located in the spinal cord and is triggered by

the stimulation from the genital organ. Erection is also caused by sexual desire stimulation from the cerebral cortex. The outlet of the signal is the pelvic nerve branches. The sympathetic stimuli constrict the arterioles, restricting blood to the erectile tissues, erection then subsides. Substances that block sympathetic receptor, like yohimbin, may cause erection. In normal person, erectile dysfunction can be affected by various factors: age, depression, exhaustion, anxiety,... In people with diabetes, beside those factors above, the main cause of erectile dysfunction [3,17,19] is the complication of diabetes, namely 4 factors below:

a – Male genital organ deficiency, where testosterone is synthesized by Leydig cells. There are two reasons of this deficiency: (1) Decreased protein synthesis cannot compensate for the normal protein loss. (2) Atherosclerosis of the supply vessels reduce blood to the organ. The male genital organ deficiency cause decreasing in testosterone production, therefore decrease sperm production.

b – Atherosclerosis narrows the lumen of arteries supply to erectile tissues, blood is not pumped enough to cause erection.

c – The decrease of testosterone level in plasma leads to libido, affects severely the quality of sexual life. They are parallel and have a closed relationship. Infact, plasma level of testosterone has never higher than physiology normal level because of negative feedback mechanism. This means whenever testosterone level over the physiological level, the anterior pituitary gland will be inhibited and the secretion of LH hormone (Luteinizing Hormone, stimulating testicles secrete testosterone) from it is delayed [20].

d – The transmitted way for sexual signals from brain to sexual organ is damaged because of atherosclerosis caused by diabetes. The rate of sexual transmittance is slower and slower and finally there is no signal transmittance. There is approximately 60% of diabetes patient faced to this complication. So, the more early diabetes is diagnosed and treated, the more effective of treatment and the better of life quality are. Erectile dysfunction often appears 3 years after the patient has diabetes [1].

In men with type 2 diabetes, besides the effect of erectile improvement, testosterone replacement therapy also reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes. Improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk [11,22,23,24].

Testosterone is a hormone increasing the synthesis of the cell. That includes insulin receptor protein, which is a membrane receptor protein. The cause of type 2 diabetes mellitus is lacking of protein receiving insulin, not lacking of insulin. Therefore testosterone increases receptor protein, the cell is more sensitive and reduce in resistance with insulin. That mean insulin is put into the cell easily, then it will be involved in the metabolism of: protein, lipid, glucide. Then symptoms and complications of diabetes will not appear. Moreover, when insulin was present in the cell, it is also a hormone increasing the synthesis protein strongly. The effect increasing synthesis protein is double, so the effectiveness of treatment is also more powerful [3,25]. Expect from the treatment of diabetes, testosterone has two another important effect: increased libido, a factor that improve the quality of life and increased sperm production, the main role in the reproductive. Expect from directly putting testosterone into the body, there is another method that is stimulation production of testosterone male genitalia organ by herbal medicine which seems to stimulate Leydig cells to produce testosterone naturally, no need to bring from the outside, no side effects, easy to use and no contraindications. But there is still not much evidence about this.

V. CONCLUSION

World Health Organization (WHO) has considered diabetes such as a epidemic disease in the 21st century in the world [2]. This disease has increased rapidly, exceeding over more than the predicted rate of the health sector, causing high costs for patients in treatment, especially dangerous complications threatening their lives. The principles of diabetes treatment are early and comprehensive treatment: appropriate medication to control blood sugar levels strictly. Keep the HbA1C level below 6.5%; testosterone replacement therapy; adhere to the diet strictly; sports, exercise regularly; no alcohol and tobacco; keep healthy, comfortable and happy life.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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