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PERKENI CABANG SURABAYA

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Naskah Lengkap

Joint Symposium

SURABAYA DIABETES UPDATE - XXII (SDU-XXII)

&

SURABAYA OBESITY UPDATE - 5 (SOBU-5)

Theme:

DIABETES UPDATE IN CARDIO-METABOLIC PREVENTION AND TREATMENT OF OBESITY AND ITS ENDOCARDIOMETABOLIC CONSEQUENCES

(Challenges in Prevention and Innovative Management)

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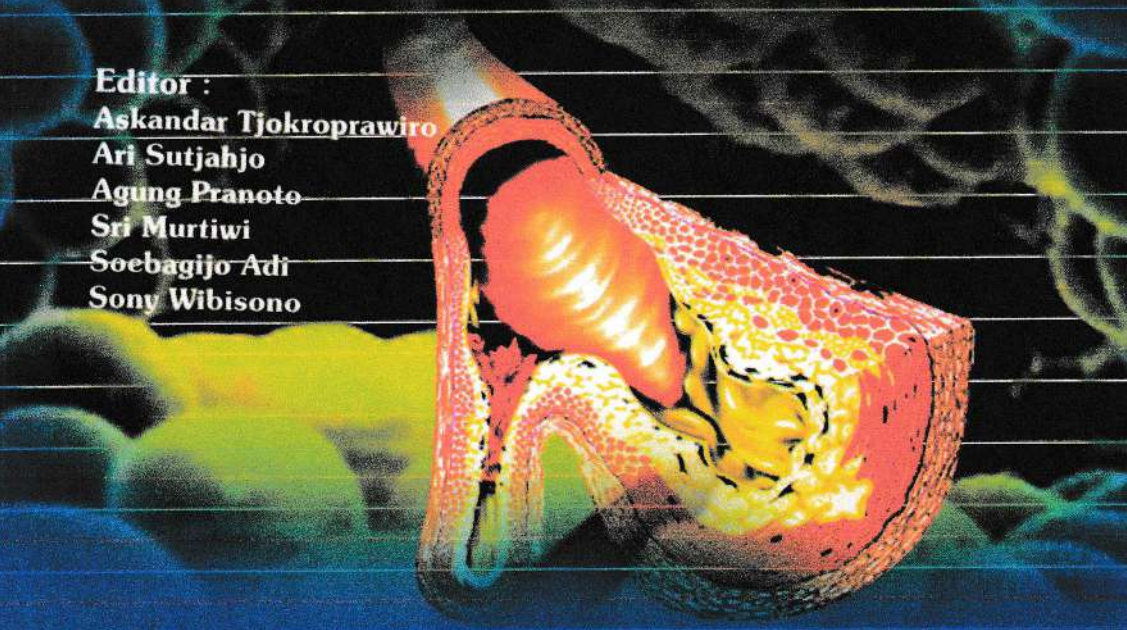

The Role of Testosterone on Sex Dysfunction in T2DM

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Abstract

Testosterone plays a significant role in glucose and lipid metabolism. Metabolic syndrome is clustering of risk factors predisposing to diabetes mellitus type 2, atherosclerosis and cardiovascular morbidity and mortality. The main component of metabolic syndrome are insulin resistance, visceral obesity, glucose tolerance, dyslipidemia, hypertension, and pro inflammation or prothrombotic state. Epidemiology studies showed a direct correlation plasma testosterone and insulin sensitivity and low testosterone increased risk of T2DM. Insulin resistance could diminish release GnRH due to insulin and the GnRH decrease, gonadotropin secreation low, sel Leydic testosterone secretion low. Besides above in visceral obesity cause aromatase increased, HPA axis decreased, inflammation in insulin resistance. That multi factors can decrease testosterone secreation by leydic cell.

In men with T2DM have low testosterone is associated with a high prevalence of symptomatic hypogonadism, frequently due to hypogonadotrophic hypogonadism. Between 55 and 58% of our diabetic men with ED had low testosterone levels. This represents a much higher prevalence than that seen in normal men with ED. As previously mentioned, about 35% of men with ED have been reported to have reduced or border- line low androgen levels. The findings of ourselves and others, especially in light of the effect of testosterone replacement therapy in sildenafil non-responders, demonstrate that testosterone levels should be assessed in type 2 diabetic men with ED. Sexual dysfunction is one of symptom of hypogonadotrophic hpogonadism.

Testosterone replacement in hypogonadal men with T2DM and or Metabolic syndrome in TIMES 2 study was associated with beneficial effect in not only sexual health but also insulin resistance, and lipid profiles.

Introduction

Sexual problems can occur in men with diabetes, these consist erectile dysfunction and retrograde ejaculation.

Erectile dysfunction is a consistent inability to have an erection firm enough for sexual intercourse. The condition includes the total inability to have an erection and the inability to sustain an erection. Estimates of the prevalence of erectile dysfunction in men with diabetes vary widely, ranging from 20 to 75 percent. Men who have diabetes are two to three times more likely to have erectile dysfunction

than men who do not have diabetes. Among men with erectile dysfunction, those with diabetes may experience the problem as much as 10 to 15 years earlier than men without diabetes. Research suggests that erectile dysfunction may be an early marker of diabetes, particularly in men ages 45 and younger.

In addition to diabetes, other major causes of erectile dysfunction include high blood pressure, kidney disease, alcohol abuse, and blood vessel disease. Erectile dysfunction may also occur because of the side effects of medications, psychological factors, smoking, and hormonal deficiencies. Men who experience erectile dysfunction should consider talking with a health care provider. The health care provider may ask about the patient's medical history, the type and frequency of sexual problems, medications, smoking and drinking habits, and other health conditions. A physical exam and laboratory tests may help pinpoint causes of sexual problems. The health care provider will check blood glucose control and hormone levels and may ask the patient to do a test at home that checks for erections that occur during sleep. The health care provider may also ask whether the patient is depressed or has recently experienced upsetting changes in his life.

Treatments for erectile dysfunction caused by nerve damage, also called neuropathy, vary widely and range from oral pills, a vacuum pump, pellets placed in the urethra, and shots directly into the penis, to surgery. All of these methods have advantages and disadvantages. Psychological counseling to reduce anxiety or address other issues may be necessary. Surgery to implant a device to aid in erection or to repair arteries is usually used as a treatment after all others fail.

Retrograde ejaculation is a condition in which part or all of a man's semen goes into the bladder instead of out the tip of the penis during ejaculation. Retrograde ejaculation occurs when internal muscles, called sphincters, do not function normally. A sphincter automatically opens or closes a passage in the body. With retrograde ejaculation, semen enters the bladder, mixes with urine, and leaves the body during urination without harming the bladder. A man experiencing retrograde ejaculation may notice that little semen is discharged during ejaculation or may become aware of the condition if fertility problems arise. Analysis of a urine sample after ejaculation will reveal the presence of semen.

Poor blood glucose control and the resulting nerve damage can cause retrograde ejaculation. Other causes include prostate surgery and some medications.

DM had low testosterone levels. This represents a much higher prevalence than that seen in normal men with ED. About 35% of men with ED have been reported to have reduced or border- line low androgen levels. The findings of ourselves and others, especially in light of the effect of testosterone replacement therapy in sildenafil non-responders, demonstrate that testosterone levels should be assessed in type 2 diabetic men with ED.

Sexual problems can occur in women with diabetes. Many women with diabetes experience sexual problems. Although research about sexual problems in women with diabetes is limited, one study found 27 percent of women with type 1 diabetes experienced sexual dysfunction. Another study found 18 percent

of women with type 1 diabetes and 42 percent of women with type 2 diabetes experienced sexual dysfunction.

Sexual problems may include

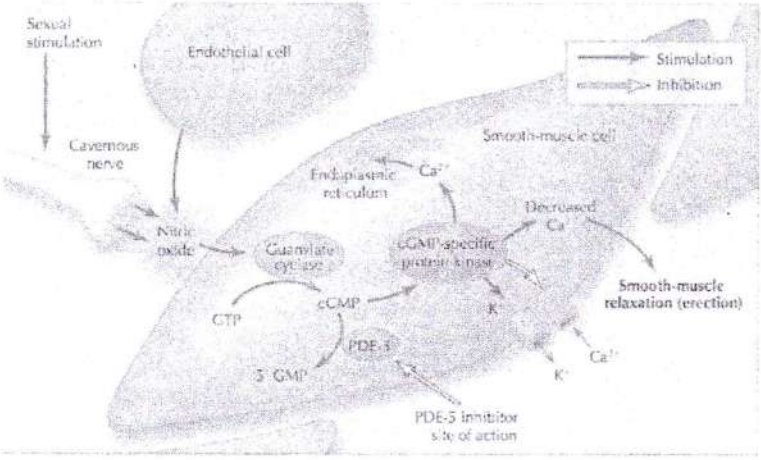
- decreased vaginal lubrication, resulting in vaginal dryness
- uncomfortable or painful sexual intercourse
- decreased or no desire for sexual activity
- decreased or absent sexual response

Erectile dysfunction

Erectile dysfunction can be defined as the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. Erection involves the integration of neural and vascular functions. In essence, an erection occurs when blood flow to the penis exceeds flow out of the penis. The cavernosal arteries supply blood to the corpora cavernosa of the penis (through the pudendal artery); the emissary veins running through the tunica albuginea allow drainage. During erection, relaxation of trabecular smooth muscle results in increased blood flow to the corpora cavernosa and expansion of the sinusoids therein. This distension causes mechanical compression of the emissary veins, which impedes their ability to drain blood and thereby results in penile rigidity. Penile blood flow is controlled by the autonomic erecion centre, which provides parasympathetic (S2–S4) and sympathetic (T12–L2) input to the pelvic plexus, including the cavernous nerves that innervate the cavernosal arteries and trabecular smooth muscle. These nerves are responsible for the delivery of high local concentrations of nitric oxide to the trabecular smooth muscle, which results in relaxation. Nitric oxide diffuses across the smooth-muscle membrane and activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP); the biochemical cascade that ensues results in altered potassium and calcium ion channel permeability; ultimately, the decrease in cytosolic calcium concentration causes smooth- muscle relaxation and increased regional blood flow. Phosphodiesterase enzymes (PDEs) regulate this pathway by inactivating cGMP, which results in elevated cytosolic calcium concentrations and smooth-muscle contraction. PDE type 5 is the most important isoenzyme in the corpora cavernosa.
The somatic motor nerve supply arises from the sacral spinal cord, whose fibers join the pudendal nerve innervating the bulbocavernosus and ischiocavernosus muscles, active during ejaculation and climax. Adrenergic stimulation is responsible for cavernous smooth-muscle contraction and detumescence. Cholinergic nerves may contribute to the erectile process through adrenergic inhibition as well as by causing release of nitric oxide from the endothelium.

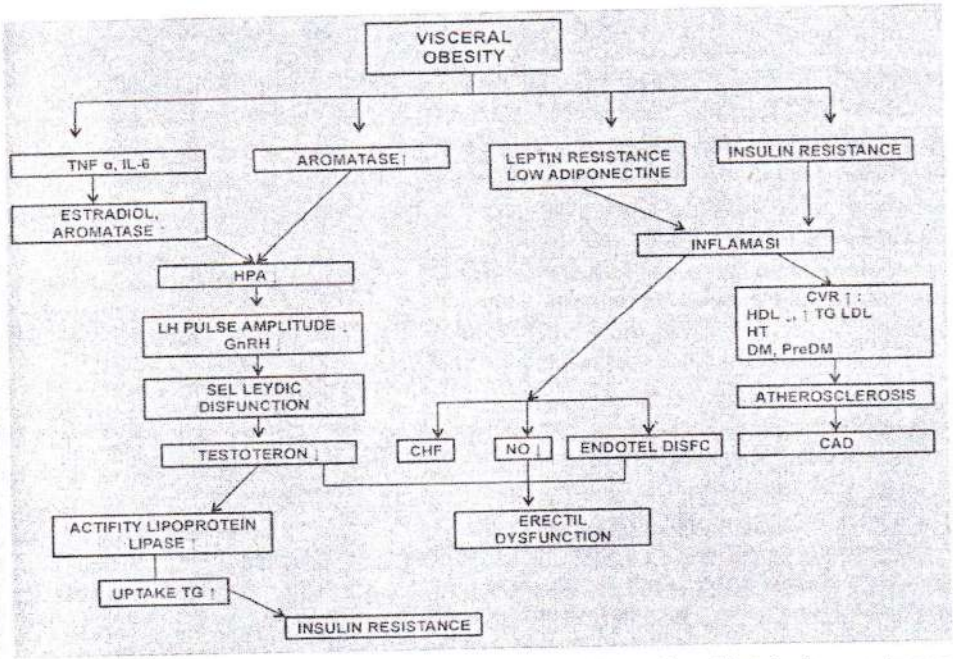
Three mechanisms trigger these vascular changes: psychogenic, reflexogenic and centrally originated (nocturnal erections). Psychogenic erections occur through stimulatory pathways (e.g., sound, smell, sight and touch) that travel from the spinal erection centres (T11–L2 and S2–S4) and induce a dopaminergic initiation of erection from the medial preoptic area. Reflexogenic erections, induced by direct genital stimulation, send ascending messages to the central erection centres

and direct messages to the autonomic nuclei, which explains residual erectile activity in patients with upper spinal cord injuries. Nocturnal erections, initiated in the pontine reticular formation and amygdalae, are seen during REM sleep and are believed to be caused by a relative decrease in sympathetic inhibition with augmentation of the pro-erectile centres.



Erectile dysfunction Low Testosterone in T2DM

The first time that ED was more prevalent in men with a higher WC. This is an important finding, as visceral adiposity is more strongly linked to the development of impaired glucose tolerance and cardiovascular disease and is an essential component of metabolic syndrome. The volume of visceral, but not subcutaneous, fat has been shown to be directly correlated with the degree of insulin resistance. Furthermore, testosterone levels are also lower in men with visceral obesity. This is because with increase in abdominal adipose tissue, there is an increased aromatase activity (which has the highest activity in visceral fat), leading to a decrease in testosterone levels in men through conversion to oestradiol. The resulting low testosterone increases lipoprotein lipase activity and triglyceride uptake, leading to an increased visceral adiposity which further decreases testosterone levels. Testosterone levels are also lowered as a result of leptin resistance at the hypothalamic-pituitary and testicular levels, resulting in reduced LH release and testosterone secretion. Furthermore, low-grade pro-inflammatory adipocytokine activation (increased TNF-α, IL-6) may also inhibit the hypothalamic-pituitary-testicular axis, resulting in low levels of testosterone. Visceral adiposity could also explain the lower SHBG levels seen in our men with ED. Other studies have reported that the waist-hip ratio in men was significantly inversely correlated with TT, free testosterone and SHBG.



Testoteron replacement in Hypogonadal with T2DM and or Metabolic syndrome

Diagnosis of hypogonadism

Hypogonadism is defined as a clinical syndrome that must comprise symptoms and biochemical confirmation with low circulating testosterone levels. The more common symptoms of hypogonadism include reduction or loss of libido, decreased erectile strength, fatigue, reduced physical strength and endurance, impaired cognitive function, and mood disturbances, including sadness, irritability, grumpiness, and depression.

Two major sets of guidelines has provided some help in making the diagnosis. Recommendations for the diagnosis and management of late-onset hypogonadism (symptomatic men with low testosterone levels associated with ageing) were published by a group of international experts under the auspices of the International Society for Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association for Urology (EAU). These recommendations state that in the presence of symptoms a total testosterone level < 8 nmol/l requires testosterone substitution therapy, whereas a level > 12 nmol/l does not. In symptomatic men with total testosterone levels between 8 and 12nmol/l a trial of testosterone therapy can be considered. The guidelines of the Endocrine Society of America recommend that testosterone levels < 10.4 nmol/l are consistent with hypogonadism. Blood drawn for testosterone analysis should be taken before 1100 h because the hormone has a diurnal variation with levels reaching a peak between 0600 and 0800h and a nadir between 1800 and

2000 h. It has been demonstrated that in some normal men testosterone levels can fall into the hypogonadal range in the afternoon. Therefore, blood for testosterone should not be taken during an afternoon clinic visit because this could lead to misdiagnosis. In some older men, but not all, the rhythm is less pronounced or lost, so it is still important to assess testosterone only in the morning. Testosterone levels can be low in the presence of intercurrent infection, infarction, and injury including the postsurgical period and can be higher the morning after sexual intercourse.

Traditionally, hypogonadism has been classified as primary (testicular failure with elevated luteinising hormone (LH) or secondary hypogonadism (hypothalamic-pituitary failure with low LH).

The original insights into the mechanisms of action of androgens on sexual function indicated a prominent role of testosterone on sexual interest while the effects of testosterone on erectile function were less apparent from these investigations. There is growing insight that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological D biochemical substrate of erectile capacity, reversible upon androgen treatment. An improvement of nocturnal erections [tumescence and rigidity, spontaneous and sexually related erections was found in men with androgen deficiency upon treatment with transdermal testosterone and eugonadal circumstances].

Several studies have indicated that the administration of phosphodiesterase inhibitor type-5 (PDE-5) inhibitors is not always sufficient to restore erectile potency in men, and that administration of testosterone improves the therapeutical response to PDE-5 inhibitors considerably. There is increasing insight not to view ED as a single entity but as part of the ageing process. Circulating levels of testosterone are closely related to manifestations of other aetiological factors in ED, such as atherosclerotic disease and diabetes mellitus. The latter are correlated with lower-than-normal testosterone levels. Erectile difficulties provide often a window into the presence of pathology in these areas. Rather than a disease in itself, ED is, particularly in elderly men who have enjoyed normal sexual function earlier in life, a manifestation of pathologies of the biological systems involved in erectile function. There is now ample evidence from animal studies that androgen deprivation produces changes in the histological properties of penile structures. Shabsigh could demonstrate that castration caused apop- tosis in the rat corpus cavernosum smooth muscle after only 3 days. Administration of testosterone restored DNA synthesis already after 4 days. In a rat model Shen et al. [reviewed in demonstrated that androgen deprivation leads to loss of elastic fibres in the tunica albuginea and of smooth muscle fibres in the corpus cavernosum [reviewed in which were replaced by collagenous fibres in both structures. Singh et al. [reviewed in found that the mesenchymal pluripotent cells follow a myogenic lineage or adipogenic lineage depending on circulating levels of testosterone. In hypogonadal men with type 2 diabetes, testosterone therapy increases physical activity and improves libido, ED, muscle strength, and mood. Testosterone substitution in hypogonadal men also improves insulin sensitivity.

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