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Case Report

How Low is Low Enough to be Given Testosterone Replacement Therapy in Patients with Late Onset Hypogonadism? What Should Be Evaluated?

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Abstract

Late Onset Hypogonadism (LOH) is a disease associated with advancing age, characterized by symptoms and a deficiency in serum testosterone. It is important to choose which patient suitable for testosterone replacement therapy (TRT), but there is no one consensus that fits for all. After treating patients with testosterone replacement therapy (TRT), several parameters need to be evaluated. A 74-years old male came with chief complaint of difficulty to maintain erection since 2 years ago. PADAM questionnaire was positive, and IIEF-5 score was 6. Physical examination showed an underweight condition. Total testosterone level was 3,65ng/mL, and patient chose to be given TRT instead of evaluating his free testosterone. PDE-5 inhibitor and non-pharmacologic treatment was also given. Follow-up showed that his erection was improved. At which level should testosterone be substituted is still debatable. Several consensuses issued by several organization still cannot be used universally. Study in Indonesia showed that symptoms of LOH had been occur when the testosterone level still in normal range. After giving TRT to our patients, routine follow up is needed. Non pharmacologic treatment also needs to be addressed to improve the outcome. Symptoms of LOH had been occurred even though testosterone level is still in normal range. The consideration made by clinician is the most important thing to be evaluated, whether to give TRT or not. Somatic and laboratory parameters mentioned in this study is important to be evaluated.

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1. Introduction

Testosterone played a significant role in males, as it is responsible for the development and physiologic function of the fetus through old age. Age-related testosterone changes occur in the elderly. Total and free testosterone decline gradually with age in the elderly.[1] Late onset hypogonadism (LOH) is defined as a disease associated with aging that is characterized by symptoms and a serum testosterone deficiency.[2] The prevalence of LOH among men aged 30-79 is 5.6% and increases significantly with age.[3] Several specific symptoms, such as decreased sexual desire, erectile dysfunction, and decreased morning erection frequency, are associated with low testosterone levels. The testosterone level of patients with a positive ADAM's questionnaire should be evaluated. Various consensuses have different threshold values for low testosterone levels. American Urological Association (AUA) defines low testosterone level as below 300ng/dL, whereas European Association of Urology defines low testosterone level as below 349ng/dL.[4] There is currently no consensus regarding the level at which testosterone should be substituted for the Indonesian or Asian population. Before administering TRT, it is essential to evaluate absolute and relative contraindications. Multiple routes of TRT administration were made available.[5] Clinician must comprehend the pharmacokinetics of TRT administered. Several somatic and laboratory parameters must be evaluated at different times.[1]

2. Case

A 74-year-old man who had been having trouble keeping an erection for the previous two years visited the andrology clinic at Dr. Soetomo General Hospital. He first believed that his erection's Erection Hardness Score (EHS) of 3 was sufficient for penetration, but it is now only EHS 1. Since two years ago, up until EHS 1, the EHS has been decreasing gradually but steadily. Additionally, he noticed that his body had less energy for normal daily activities. He lived in Surabaya throughout the past two years while his wife, who had heart illness, underwent routine exams outside of the city. Thus, they did not frequently meet or engage in sexual activity throughout these two years. He has occasionally claimed that his wife won't engage in sexual activity out of concern that her cardiac condition will worsen. Additionally, the patient admitted that he occasionally felt anxious before engaging in sexual activity with his wife out of concern that it could worsen her illness. When his wife returned from vacation a month earlier, her heart condition had stabilized. Since then, they have attempted but failed to engage in sexual activity. They attempted it seven times, but only once with the aid of his wife's hands was the penetration strong enough to pass to ejaculation. His wife asked him to check with the Andrology Clinic as a result of this failure. He could engage in sexual activity three to four times a week before this erection problem started. He had not had Nocturnal Penile Tumescence (NPT) at night in the previous 1.5 years. His libido had been declining for the past 1.5 years as well. Other than with his wife, he had never engaged in sexual activity. He also had no prior history of hypertension, diabetes mellitus, or any other chronic illnesses. About ten years ago, he underwent bilateral inguinal hernia surgery. In the last 40 years, he had smoked one pack of cigarettes. His wife was deemed to have neither a sexual history nor any current issues. He added that his wife still has a sexual attraction to him. The results of the PADAM survey were favorable, and the IIEF-5 score was 6. Blood pressure was 130/80 mmHg during a physical assessment, and all other vital signs were within the normal range. He is currently 39 kg overweight with a BMI of 14,7 kg/m2. He is 163 cm tall. The results of a subsequent physical and genital examination were normal. The results of his laboratory tests are listed below. We determined his severe erectile dysfunction to be et cause mixed (psychogenic and late-onset hypogonadism, or LOH) based on anamnesis, physical examination, and laboratory testing. We inform the patient about his condition and any potential causes, encourage him to change his lifestyle (doing regular exercise three to five times per week for at least 30 minutes, altering his diet, and getting enough rest), and most importantly, urge him to give up smoking because it affects his erectile function. In order to match his expectations for the outcome of the treatment we are about to deliver, we also educate him on the typical aging process of the sexual response and sexual changes in the elderly. In addition, we provide 50 mg of sildenafil on demand and instruct patients on how to use it. His total testosterone level was 3,65 ng/mL, which is still within the lower normal limit but still within the normal laboratory range. We gave the patient the option to get testosterone replacement medication without first measuring free testosterone level (TRT). Patient chose to be given TRT directly; 250 mg Sustanon® was given via intramuscular. He returned for control three weeks later. He claimed that he is stronger, healthier, and more energized to carry out his regular tasks. His erection receives a

positive response from TRT as well. Since the injection, NPT has been initiated, and the EHS score has increased (EHS 2). He still hasn't been sexually penetrated because he knows it will take time for his condition to get better. He started to alter his way of life by quitting smoking and beginning regular exercise. His total testosterone level increased to 4,81 ng/mL during the follow-up lab check, and his PSA level was 0.55 ng/dL. His total testosterone level increased to 4,81 ng/mL during the follow-up lab check, and his PSA level was 0.55 ng/dL. Due to his positive response, another intramuscular Sustanon® was administered.

Table 1. Baseline Laboratory Examination

Laboratory Examination	Results
Hb	11.8 g/dL
Hct	36.7%
Total Testosterone	3.65 ng/mL
PSA	0.09 ng/dL
Fasting Blood Glucose	125 mg/dL
2-hour Post Prandial	**153 mg/dL**
Total Cholesterol	145 mg/dL
Trigliseride	42 mg/dL
HDL	53 mg/dL
LDL	81 mg/dL

3. Discussion

The aging process affects a number of hormones. Some hormones grow, others remain steady, and still others decrease. The majority of hormone levels are lower in older people. Age-related increases in luteinizing hormones (LH) and follicle stimulating hormones (FSH), but only at extremely low levels. Cortisol, estradiol, estrone, and dihydrotestosterone are hormones whose concentrations never change (DHT). Thyroid hormones, Thyroid Stimulating Hormones (TSH), Prolactin, and Testosterone levels are dropped. Growth Hormones (GH), Insulin-like Growth Factor-1 (IGF-1), Dehydroepiandrosterone (DHEA), Melatonin, and Thyroid Hormones are also decreased. Both the total and free levels of testosterone decline. Sex hormone binding globulin is the particular protein to which testosterone is attached in human circulation (SHBG). SHBG levels are higher in the elderly. Increased SHBG levels result in higher serum testosterone concentrations in a number of illnesses, including hepatitis, estrogen use, antiepileptic medication use, and hyperthyroidism. Without a rise in physiologically active free testosterone, this disease develops.[1]

Testosterone is the main sex steroid produced by Leydig cells with a secretion rate of 7 mg/day. Adrenal also produced testosterone; about 5% of total testosterone was produced here. In plasma, testosterone is bound to SHBG, albumin and circulates freely. The Hypothalamic-Pituitary-Testicular axis is the main mechanism controlling the production of testosterone. Gonadotropin-Releasing Hormone (GnRH) secreted by the hypothalamus, will stimulate the pituitary to release LH, which later will stimulate the testis to produce testosterone.[6] Testosterone plays a major role in males. It is responsible for the development of primary sexual development in fetus, regulating secondary sexual male characteristics and skeletal muscle growth.[7] Testosterone is also important in regulating male sexual function; it is involved in every step of male sexual response. Impaired of sexual desire, morning erections, and erectile dysfunction (ED) is tightly related to low level of testosterone.[8] In the circulation, most of testosterone is bound to plasma proteins such as SHBG and albumin. Only a small amount of free testosterone is circulated. This free testosterone acts primarily at the androgen-dependent tissues, including seminal vesicles, muscle, bone, and prostate gland. Testosterone is converted to DHT by the enzyme 5-alpha-reductase to acts at the cellular level. Both testosterone and DHT bind to specific androgen receptor and regulate protein expression.[7] There were three factors that may cause the changes in serum testosterone levels in elderly. First, the incompetence of the feedback mechanism of Hypothalamus-Pituitary-Gonadal (HPG) axis in the elderly because testosterone level is regulated by HPG axis. Second, the decreasing number and spare capacity of the Leydig cells. This is marked by less increase in serum testosterone after stimulation with HCG. Third, the increase in SHBG. In younger age, the increasing level of SHBG is followed by the increasing level of testosterone. In elderly, the increasing level of testosterone is not happened because the insufficiency and incompetence of HPG axis.[1]

SHBG is a glycoprotein produced by hepatocytes. It is released into circulation as a homodimer of identical subunits, containing a single steroid-binding site for active androgens.[9]

When discussing testosterone level in elderly, it is important to mention and discuss the free testosterone. As the smallest fraction of testosterone found in circulation, it is not routinely checked in Indonesia. There were several methods that can be used in estimating the level of free testosterone. Nanjee-Wheeler equation (regression analysis of free testosterone calculated by the gel filtration method), Sodergard equation (based on law of mass action; including albumin in its equation), Vermeulen equation (based on law of mass action) and Ly and Handelsman equation (ultrafiltration). Study by Ho CK, et al analyze and compare the level of free testosterone counted by each equation. The result is that mean bias is quite high between these equations, ranging from 5.8% to 56%. Free testosterone can also be estimated using Free Androgen Index (FAI) equation, using total testosterone and SHBG. But study found that FAI is poorly correlated with free testosterone levels, showing that the free testosterone level is overly estimated in the condition when SHBG levels are low. So, it is not recommended to be routinely used in daily practice.[10] We applied this theory into our patient. Actually we can estimate the free testosterone level in our patients by evaluating SHBG and albumin level, since free testosterone is not routinely checked in our hospital. But as FAI and other equation have a high percentage of bias, we did not recommend this to our patient

Late Onset Hypogonadism is a term first described by International Society for the Study of the Aging Male (ISSAM) in 2002. It is clinically and biochemically defined as a disease associated with advancing age, characterized by symptoms and a deficiency in serum testosterone.[2] There are several symptoms that are associated with low testosterone levels and divided into more-specific symptoms, less-specific symptoms, and signs. More-specific symptoms of LOH are decreased libido, erectile dysfunction, and decreased frequency of morning erection. Less specific symptoms include decreased energy and motivation changes in mood, impaired memory, inability to concentrate, sleep disturbances, and hot flushes. Signs of LOH are decreased body/facial hair, central obesity, decreased testicular volume, decreased muscle mass, increase body fat, gynecomastia, and osteoporosis.[11] There are theories stated by Zitzman et al. in 2006 about the level of total testosterone and sign and symptoms of LOH. At first, the elderly will have their libido and vigor loss, followed by obesity. Later on, the symptoms will progress into feeling depressed, sleep disturbance, and lack of concentration. At its lowest level, symptoms such as hot flushes and erectile dysfunction will occur.[1] But this theory is not the same with patients we found in our Andrology clinic, since sign and symptoms of LOH in certain level of total testosterone varies between individuals. To diagnose LOH clinically, one tool that is routinely used in daily practice is the Saint Louis University Androgen Deficiency in the Aging Male (ADAM) questionnaire. This questionnaire includes 10 questions. The test considered positive if answers are "Yes" to question 1, 7 or any 3 other questions. Question number 1 is "Do you have a decrease in libido – (sex drive)?" while question number 7 is "Are your erection less strong?".[12] These 2 questions are theoretically very related to LOH, as mentioned in the theory before. But one note should be carefully considered in deciding based on the results of this questionnaire. A study by Bernie, et al.[13]) in 2014 showed that even though ADAM's questionnaire has a high sensitivity (83,3-97%), it has quite low specificity (19,7-36,6%). It means that there is a high possibility of false positives in identifying patients with LOH. So it is important for clinicians to always check and evaluate testosterone levels in patients with positive ADAM's questionnaire before initiating treatment in patients with LOH. We also found that BMI in this patient can be categorized into underweight. Study by Gurayah et al. found that the incidence of hypogonadism was higher in obese and underweight men compared with men with normal BMI.[14] This underweight condition may also be related to the low testosterone level in this case.

As mentioned, testosterone levels should be routinely checked in patients suspected of LOH based on ADAM's questionnaire. At first, testosterone level is measured using immunoassays method as it is fast, cheap, and reliable. Now the gold standard in evaluating testosterone is by mass spectrometry method.[15] Low testosterone levels should be diagnosed based on two examinations of blood samples taken at different times and under the same conditions. It should be noted that the blood samples should be taken before 10.00 AM, as it is related to the circadian rhythm of testosterone level in plasma.[4] Next question is how low is low enough to be given TRT in patients with LOH. A study by Park, et al.[16] combined several cutoff values for total and free testosterone taken from other studies. ISSAM in 2015 stated that the cutoff value of total testosterone is <350ng/dL (12 nmol/L) and free testosterone is <65 pg/mL. the

cutoff values of total testosterone and free testosterone stated by the Endocrine Society in 2018 are <300ng/dL and <5ng/dL respectively. Several Andrology and Sexual society also stated a different cutoff value. ISSM and Nieschlag textbook(1) cutoff values for total testosterone are the same with ISSAM (<350 ng/dL pr 12 nmol/L) and AUA cutoff values for total testosterone is same with Endocrine Society (<300 ng/dL). EAU cutoff value for total testosterone is slightly higher, 12,1 nmol/L.[4] Winters and Huhtaniemi in his book "Male Hypogonadism: Basic, Clinical and Therapeutic Principles" stated that TRT should be initiated if the repeat morning total testosterone level <350 ng/dL and/or the serum free of bioavailable testosterone are below the normal laboratory reference.[9] In Indonesia or Asia, there is still no specific cutoff values of low total testosterone. One study assessing the level and total free testosterone when the signs and symptoms of andropause appeared. Study by Pangkahila, W. in 2016 found that the level of total and free testosterone in Indonesia when symptoms of LOH appeared is still in normal range and higher compared to Caucasian population. The mean total testosterone level in patients with LOH that was diagnosed clinically in this study is 475.73 $\pm$ 133,32 ng/dL and mean free testosterone level is 10.44 $\pm$ 2.90 pg/dL. This higher level of total and free testosterone in this population may be caused by higher susceptibility compared to Caucasian.[17] So, the conclusion about how low is low enough to be given TRT is based on physician's perception. The question at which testosterone levels substitutions initiated has been determined by the physician's perception of hypogonadism than by the patients complain. Various cut off values and guideline has been stated above, but at the end the physician's perception of hypogonadism is the main reason and consideration about giving TRT.[1]

Testosterone replacement therapy are first discovered in 1940s with testosterone implants as the agent. Up until now, several route of administration of TRT has been found, such as intramuscular (IM) injections, oral, transdermal, trans buccal and intranasal. There are several reported effects of TRT given. Reported benefits are increasing positive mood, sexual desire, muscle strength, lean body mass, bone mineral density, hemoglobin levels and decreasing body fat and fat mass. However, it should be noted that TRT also has a negative impact. Reported TRT risks known are increase PSA, acne or oily skin, testicular atrophy, gynecomastia, polycythemia, and sleep apnea.[5] The only two absolute contraindication or TRT are carcinoma prostate and carcinoma mammae. Relative contraindications are PSA level >4 ng/mL or > 3ng/mL in patients with high risk (African or family history of prostate cancer), hematocrit >50%, lower urinary tract symptoms (LUTS) caused by Benign Prostate Hyperplasia (BPH), uncontrolled or severe congestive heart failure.(1,15) Before given TRT, several things need to be settled. The most important thing is that we should understand the pharmacokinetics of the testosterone given to our patients.[1] TRT cannot be given in patients who still want to preserve his fertility function. Hemoglobin and hematocrit should be checked, and patients should be well informed about the risk of polycythemia. PSA level should be measured in patients aged 40 and above, if possible, should be followed by digital rectal examination. If PSA level >4 ng/mL and nodule/irregularity was found in DRE, a proper and holistic follow up by urologist is needed. Complete blood count, lipid profile and liver function test are recommended to be checked.[15,18] After given TRT several psychic and sexual parameters should be evaluated, such as mood, libido, erections, sexual activity, body weight and proportion, muscle mass and strength, sebum production, etc. Laboratory parameters that can be evaluated are serum testosterone, gonadotropins, estradiol, liver enzyme, lipid levels, HbA1c, etc. Ejaculate volume, prostate size and PSA can also be evaluated in patients given TRT. The most important factor in evaluating TRT are as follows. First, it is important to know the pharmacokinetics of testosterone given. Second serum testosterone level should be measured directly before TRT is given to adjust the dosage and duration of TRT. If gynecomastia was found, estradiol level should be checked, lowering the dosage or change the route of administration. Liver function test should be measured every year even though the TRT given is not hepatotoxic. PSA level should measure every 3-6 months and every year thereafter; >4 ng/mL or increase >0,4 ng/mL compared to PSA level before is the alert for the evaluation of TRT and prostate problem.[1]

4. Conclusion

Clinician should understand the physiologic hormonal changes in elderly. Total and free testosterone is decreased in this population. There are several specific symptoms related to hypogonadism, most importantly are decreased sexual desire, erectile dysfunction, and decreased frequency of morning erections. After diagnosing LOH clinically by using the ADAM questionnaire, it is important to evaluate the total or free testosterone level in plasma. Several consensuses

stating different cut-off values. But in the end, at which testosterone levels substitution is initiated has been determined by the physician's perception of hypogonadism than by the patient's complaint. Various cut-off values and guidelines have been stated above, but the physician's perception of hypogonadism is the main reason and consideration for giving TRT. Choosing a different route of TRT administration is needed; pharmacokinetics needs to be understood. Evaluating TRT given is important to maximize the treatment's outcome. Somatic and laboratory parameters should be periodically evaluated.

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Authors' Contributions

Both authors have contributed to the final manuscript. The contributions are collected the data, drafted the manuscript, constructed the main conceptual idea and critical revision of the article. Both authors discussed the results and contributed to the final manuscript.

Conflict of Interest

Both authors stated that there is no conflict of interest.

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