Erectile dysfunction and hypogonadism (low testosterone)

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Erectile dysfunction (ED) is one of the earliest signs and markers of present or potential future endothelial dysfunction. One of the causes of ED can be low testosterone levels or hypogonadism. This article describes ways to identify and diagnose patients with ED or hypogonadism, and it offers a plan for treatment of these conditions. The mainstay first-line medical therapies for ED are phosphodiesterase-5 (PDE-5) inhibitors. For patients with symptomatic hypogonadism, testosterone replacement therapy is both safe and effective.

Key Words: erectile dysfunction, hypogonadism

Background

Erectile dysfunction (ED) has been defined by a consensus panel at the National Institutes of Health (NIH)[1] as "the inability to obtain or maintain the erection for satisfactory sexual performance." The prevalence of ED is fairly similar in different areas of the world. An estimated 52% of men aged 40 to 70 years have some degree of ED, and the prevalence increases with age.[2] One of the causes of ED can be low testosterone levels or hypogonadism.

Late onset hypogonadism was defined by Morales and Lunenfeld as "a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens," which could significantly alter a patient's quality of life and adversely affect multiple organs.[3] If a man manifests symptoms ascribed to hypogonadism, the condition can be called "symptomatic late-onset hypogonadism (SLOH)." In the past, late-onset hypogonadism was also called andropause, male menopause, or testosterone deficiency syndrome.

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Erectile dysfunction

The Massachusetts Male Aging Study -- a prospective, 10 year study that followed over 1100 men aged 40 to 70 years at study entry -- found that ED was more prevalent in patients with diabetes, heart disease,

hypertension, low high-density lipoprotein (HDL) levels, hypogonadism, smoking (in men with heart disease or hypertension), high levels of anger and dominance, and depression.[2] Complete ED was prevalent in 44% of men with treated heart disease, 25% of men with treated hypertension, and 17% of men with treated diabetes. This study suggested that there was a relationship between hypogonadism and ED, and it demonstrated common vascular comorbidities that were prevalent in the men with ED.

Nitric oxide, the main vasodilator produced by the endothelial cells that line blood vessels is released in response to pharmacological stimuli such as bradykinin and acetylcholine or physiological stimuli such as increased shear stress in blood vessel walls. In healthy endothelium, low levels of nitric oxide are continuously released to keep blood vessels dilated. Nitric oxide has three other effects. It exerts an antithrombotic effect by inhibiting platelet aggregation. It exerts an anti-inflammatory effect by preventing the adhesion of white blood cells (leukocytes) to the endothelium. Lastly, it exerts an anti-atherosclerotic effect by reducing the oxidation of low-density lipoprotein (LDL) cholesterol, the proliferation of smooth muscle cells, and decreasing the expression of adhesion molecules that would attract cholesterol.

Endothelial dysfunction, erectile dysfunction and cardiovascular disease

Endothelial dysfunction, where there is a reduced dilation response of blood vessels (which can be due to decreased production of nitric oxide by endothelial cells), is one of the most common causes of ED. Risk factors for endothelial dysfunction and ED are similar.

Risk factors associated with endothelial dysfunction include hypercholesterolemia, hypertension, increasing age, male gender, diabetes mellitus, tobacco use, hereditary predisposition, and hyperhomocysteinemia. Risk factors associated with ED include diabetes mellitus (3.72-fold increased risk), drug intake (3.71), peripheral vascular disease (2.44), tobacco use (2.41), hypercholesterolemia (1.71), hypertension (1.69), and coronary artery disease (CAD, 1.61), while the risk from increasing age and hereditary predisposition are unknown.[4]

Since there is such a large overlap of the risk factors associated with endothelial dysfunction and ED, it is important for physicians to ask questions concerning the symptoms and signs of endothelial dysfunction when men present with ED, and vice versa.

A recent study of 133 men with type 2 diabetes suggests that ED may be a marker for vascular disease.[5] The study found a strong, independent association between ED and silent CAD. One-third of patients with silent CAD had ED, whereas only 5% of patients without silent CAD had ED. The study concluded that ED could be a potential predictor of silent CAD.

Another study compared 30 men with a mean age of 46 years who had Doppler-proven ED and no clinical evidence of cardiovascular disease versus 27 age-matched healthy men (controls).[6] There was a significantly increased risk of vascular disease in the men with ED, again suggesting that ED can be a signal of vascular disease. Compared with the healthy controls, men with ED exhibited significantly lower brachial artery flow-mediated, endothelium dependent and independent vasodilatation, suggesting the presence of a peripheral vascular abnormality in the nitric oxide pathway.

Another study concluded that ED may be an early marker for cardiovascular disease, surfacing long before the discovery of CAD.[7] In this study of 300 men with angiographically-documented CAD, 147 men (49%) had ED. Among the 147 men with coexisting ED and CAD, the onset of ED preceded CAD symptoms in 97 patients (66%).

Diagnosing and managing erectile dysfunction

The first step in diagnosing ED is to obtain a complete patient history and perform a physical examination. Information from the patient history should identify the time of onset of ED as well as any precipitating factors such as illness, accident, surgery, or trauma. The physician also needs to obtain answers to the following questions. Was the onset of ED gradual or fairly abrupt? Does the patient have any associated diabetic, neurologic, or other medical conditions that would predispose him to having ED? Is the ED situational or global? Is the ED associated with premature ejaculation or is premature ejaculation the primary patient symptom? (Some patients do not realize the difference between the two conditions). Does the patient have difficulty obtaining or maintaining an erection? Does the patient smoke or drink alcohol? Does the patient take recreational or medical drugs? What are his dietary habits? Does he exercise? The physical examination should confirm that the patient has normal secondary sex characteristics with a normal penis and testicles.

Management of ED should be initiated by the primary care physician (PCP). After diagnosing ED, the first management step is to counsel the patient about modifying reversible causes such as smoking,

excessive alcohol intake, drug abuse, lack of exercise, and obesity.[8] Once patients have been diagnosed with ED and have received advice about making lifestyle changes and modifying their risk factors, most men will request a "quick fix" using medical treatment.

PDE-5 inhibitors

The mainstays of first-line medical treatments for ED are the phosphodiesterase-type 5 (PDE-5) inhibitors and counseling.[8] If these first-line treatments are unsuccessful, the patient may be referred to a specialist and be offered second-line treatments (such as vacuum devices, injectable agents, or intraurethral therapy) and, failing those, third-line treatments (such as a penile implant).[8]

The mechanism of action of PDE-5 inhibitors is based on the normal biochemical pathway for an erection. In the normal erectile response, nitric oxide produced upon arousal increases the production of cyclic guanosine monophosphate (cGMP), which causes vasodilation and an erection.[9] PDE-5 enzymes then cause the breakdown (metabolism) of cGMP.

In ED, men are given a PDE-5 inhibitor to prevent the breakdown of cGMP and increase nitric oxide and cGMP concentrations, which leads to a stronger, longer-lasting erection.[9]

It was previously believed that hypogonadism, or low levels of serum testosterone, only impact a patient's libido. We now know that testosterone is a precursor of nitric oxide and affects the ability to obtain an erection and the quality of an erection.

Low testosterone levels contribute to the development of ED by increasing smooth muscle apoptosis, reducing erectile tissue relaxation, and reducing nitric oxide production.[10,11]

Sildenafil (Viagra) was the first PDE-5 inhibitor approved in Canada. This was followed by the approval of tadalafil (Cialis) and then vardenafil (Levitra). Originally, all three drugs were prescribed to be taken as needed 45 minutes before the anticipated sexual activity. In clinical trials of all three of these drugs, it was reported that, on average, 32% of men responded within 16 minutes of taking the drug. In clinical practice, physicians should advise patients to take the PDE-5 inhibitor at least one hour before a planned sexual encounter and to remind patients that some sexual stimulation (foreplay) is needed for the drug to take effect. This is because arousal is required to cause the initial release of nitric oxide, which is then potentiated under the influence of the PDE-5 inhibitor.

Each drug has a different half life, which affects the "window of opportunity" where the drug has its maximum efficacy. The absorption of the drugs may also depend on whether they are taken with or without food or alcohol. Different PDE-5 inhibitors also have different other pharmacokinetic properties and adverse effects.[12] Only a few head-to-head trials have compared the characteristics of different PDE-5 inhibitors or patient preferences for these drugs. Typically, in clinical practice, a patient will be offered prescriptions for two or three different PDE-5 inhibitors and given instructions about how to achieve an optimal response. The patient will be told attempt to achieve successful intercourse after taking one of the PDE-5 inhibitors, on four to six occasions. The patient is instructed to repeat this with the second or third PDE-5 inhibitor, if needed. The patient will thus determine which preparation works best for him and his sexual lifestyle.

PDE-5 inhibitors are contraindicated for men who are taking nitrates of any type. An unpredictable number of men taking a nitrate and a PDE-5 inhibitor could sustain a significant bout of hypotension that may precipitate a stroke or myocardial infarction.[13-15]

In 2009, a lower-dose (5 mg), daily form of tadalafil was approved in Canada. The rationale for developing this product was that the patient would always be ready for a sexual encounter, be more compliant, and have greater satisfaction. The lower dose would result in a steady, sustained blood level of the drug without peaks and valleys, thereby reducing the incidence of the potential side effects of headache, flushing, and backache.

There have been some recent trails subsequent to the original registration trials for the PDE-5 inhibitors. One trial that compared daily vardenafil versus on-demand vardenafil for the treatment of ED following radical prostatectomy found no difference in the recovery of erectile function.[16] Another trial of ED treatment looked at "erection hardness scale" outcomes and reported that 82% of men using sildenafil had an erection that was firm enough to achieve satisfactory sexual activity.[17]

Another study compared treatment with sildenafil versus placebo in men who had "mild ED," that is, they had an International Index of Erectile Function (IIEF) score of 22 to 25 out of 25.[18] In this 8-week, double blind study, 176 men were randomized to either placebo or flexible dosing with 25 mg, 50 mg, or 100 mg of sildenafil. In all outcomes – IIEF scores, Erectile Dysfunction Inventory of Sexual Satisfaction (EDITS) scores, Quality of Erection Questionnaire (QEQ) scores, and Erection Hardness Score (EHS) – men who received sildenafil had significantly improved scores compared to men who received placebo. These men with mild ED did not have any significant differences

in comorbidities, baseline demographic characteristics, or medication use compared to patients in other trials who had more severe ED. This suggests that even mild ED is a risk factor for diseases associated with ED.[19]

These studies highlight the importance of assessing patients for potential ED as part of their routine clinical evaluation, because ED can be an indicator of other potential comorbidities such as cardiovascular disease, high cholesterol, or diabetes. Physicians may consider referring men with even mild ED for a cardiac evaluation to rule out underlying cardiovascular disease.

Hypogonadism

In addition to providing information about ED, the Massachusetts Male Aging Study also provided information about changes in testosterone that occur with aging. The key findings were that free testosterone declined by 2.8% per year, total testosterone declined by 1.6% per year, albumin-bound testosterone declined by 2.5% per year, and testosterone bound by sex hormone binding globulin (SHBG) increased by 1.3% per year.[2]

A healthy man produces about 5 mg to 7 mg testosterone each day. Only 1% to 2% of testosterone is free or "bioavailable" to tissues, however, and the rest is bound to plasma proteins. Around 35% is bound to albumin and around 65% is bound to SHBG.[2]

In women, menopause, occurs around age 50 and has a fairly abrupt onset with the complete cessation of reproductive hormone production. All women undergo menopause, and it is manifested clinically. In men, testosterone deficiency syndrome can begin around age 40, and it occurs as a gradual decrease in testosterone production, where blood levels of testosterone drop but never fall to zero. Not all men have a decrease in testosterone, and not all men are affected in the same way by a decrease in testosterone. In some men, testosterone levels may drop from the upper end to the middle or lower end of the normal range, which can still result in noticeable symptoms.[20]

Testosterone is vital for normal functioning throughout a man's life. Signs and symptoms of testosterone deficiency include diminished levels of energy, sense of vitality, or sense of well-being, or increased fatigue, as well as depression, reduced muscle mass and strength, reduced bone density, anemia, frailty, and sexual symptoms such as diminished libido, ED, difficulty achieving orgasm, diminished intensity of the experience of orgasm, and diminished penile sensation.[3]

Testosterone deficiency is a common comorbidity in many medical conditions including diabetes, metabolic syndrome, depression, and obesity. Testosterone production and metabolism are affected by tumors or other disease in the sellar region, HIV-associated weight loss, end-stage renal disease and maintenance hemodialysis, moderate to severe chronic obstructive lung disease, radiation to the sellar region, and certain medications.[21] It is important for physicians to look for low testosterone in patients who have these comorbidities or are receiving these treatments.

The Androgen Deficiency in Aging Men (ADAM) questionnaire, developed by John Morley, MD, at the Saint Louis University School of Medicine, in Missouri, is a useful, validated questionnaire, when investigating whether a patient may have biochemical hypogonadism.[20] If the patients' history and clinical assessment (including the ADAM questionnaire) suggest potential hypogonadism, the subsequent recommended diagnostic evaluation includes laboratory tests to determine total testosterone and other markers.[21]

Studies have shown that men with diabetes have lower total testosterone levels that also correlate with increased SHBG levels.[22-24]

Loughlin and colleagues examined the relationship between low testosterone, metabolic syndrome, and mortality in a prospective study of 794 men aged 50 to 90 years.[25] They reported that close to one-third of the men (29%) had low testosterone (< 8.7 nmol/L). Men with low testosterone had a 1.33-fold greater risk of death (confidence interval [CI] 1.10-1.62). Testosterone levels were inversely related to interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) levels. Men who had metabolic syndrome had a 3.05-fold increased risk of low testosterone (CI 1.88-4.95).

In men, metabolic syndrome is strongly associated with low testosterone levels and significant health risks. Total and bioavailable testosterone are inversely associated with body mass index (BMI).[24]

Testosterone replacement therapy

Many studies have confirmed the association between hypogonadism and other morbidities such as depression, osteoporosis, decreased muscle strength, and lipid abnormalities. Testosterone replacement therapy is expected to benefit patients by affecting these comorbidities.

Potential benefits of testosterone replacement therapy include increases in overall health and survival,[25] strength,[26] sexual desire,[27] energy,[28] emotional well-being,[28-30] cognition,[29] bone mineral density,[31] glycemic control,[32] cardiovascular health,[33-35] and erectile function,[36,37] improvement in some metabolic

syndrome symptoms,[32] and reduction in body fat.[38]

Many types of testosterone therapy are available in Canada, including pills (testosterone undecenoate [Andriol]), gels (AndroGel, Testim), patches (Androderm), and injections (testosterone cypionate [Depo-testosterone], testosterone enanthate [Delatestryl], each with its benefits and potential side effects.

When choosing which testosterone replacement therapy to prescribe, the physician should adopt the ASTEP approach, which stands for "availability, safety, tolerability, efficacy and preference." Typically, a patient taking testosterone replacement therapy properly will perceive a benefit after 3 months.

Regular patient follow up is very important after initiation and continued testosterone replacement therapy. This therapy is associated with a wide range of potential side effects including activation site effects (irritation, redness, and rash), acne, enlarged prostate, change in mood, depression, sleep disturbances, breast enlargement, hair loss, baldness, headache, increased serum prostate-specific antigen (PSA) levels, increased red blood cell (RBC) count, prolonged or painful erections, aggression or aggressive behavior, breast pain, weight gain, and dizziness.[39-42] Other potential side effects include fluid retention, worsening of sleep apnea, and polycythemia.[3]

To date, no study has shown that replacing testosterone in a hypogonadal male and elevating testosterone levels to the eugonadal range increases the risk of aggravating benign prostatic hyperplasia (BPH) or lower urinary tract symptoms (LUTS), or increases the risk of developing prostate cancer. However, if the patient has underlying prostate cancer, testosterone replacement therapy may unmask the prostate cancer earlier. The physician may detect a small rise in PSA secondary to the testosterone-stimulated clinically significant prostate cancer. If the cancer is identified at an early stage, the patient has the best chance of obtaining a cure.

Morales et al summarized the relationship between testosterone and the prostate, as follows. In hypogonadal men who receive testosterone replacement therapy, prostate volume increases, but only to the size expected for eugonadal men. Recent placebo-controlled studies have reported that there were no significant differences in prostate volume, PSA, and LUTS in the men receiving testosterone replacement therapy versus men receiving placebo. Testosterone promotes the growth of an established prostate cancer, but it has not been shown to promote the development of prostate cancer.[43]

Hoffman and colleagues showed that among men who were diagnosed with prostate cancer, those with lower testosterone levels had a greater risk of developing a more aggressive form of prostate cancer, as demonstrated by their higher Gleason scores (8-10).[44]

The addition of testosterone replacement therapy may provide a more controlled and favorable response in hypogonadal men who are not responding to oral hypoglycemic agents,[23] PDE-5 inhibitors,[45] or antidepressants.[46,47]

Conclusion

ED is related to low testosterone levels. Testosterone is essential for a normal erection because of its impact on nitric oxide production. Some men with low testosterone levels can have normal erections, and some men with normal testosterone have poor erections. Therefore, it is important to assess a patient for both conditions. Simultaneous therapy with testosterone replacement therapy and PDE-5 inhibitors is safe and appropriate in the right situations. If a man has symptomatic hypogonadism, testosterone replacement therapy is both safe and very effective in improving his physiologic, psychologic, and physical life. □

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on Androgel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined.

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