Erectile dysfunction and low testosterone: cause or an effect?

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BARKIN J. Erectile dysfunction and low testosterone: cause or an effect? The Canadian Journal of Urology. 2010;17(Supplement 1):2-11.

Studies have repeatedly confirmed that about 52% of men between the ages of 40 and 70 years have some degree of erectile dysfunction (ED). Other studies have shown that as a man ages, his testosterone level will naturally decrease. Over the last number of years, we have also seen that ED may be one of the earliest signs and markers of endothelial dysfunction. There appears to be an overlap between ED, metabolic syndrome, and symptomatic late onset hypogonadism (SLOH).

It is very important for the primary care physician to identify patients who are suffering from ED and/or hypogonadism, and to also identify any other existing comorbidities.
This article discusses the suggested work up, diagnosis, and management of men who present with either ED or symptoms and signs suggestive of hypogonadism (low testosterone). It also discusses the potential relationship between these conditions and metabolic syndrome.

Key Words: erectile dysfunction, low testosterone, diagnosis, management, metabolic syndrome, hypogonadism

Background

Over the last number of years, medical advances have led to improved survival and a longer lifespan. In the United States, from 2000 to 2030, the number of people age 65 and older is projected to increase from about 35 million to about 71 million, and the number of people aged 85 and older is projected to increase from 9.3 million to 19.5 million.[1] Because of the expected increased longevity of patients today, whenever a patient undergoes a medical or surgical intervention, there must be a strong consideration and discussion about the expected quality of life after the treatment.

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The human body today appears to have a built-in obsolescence. As men and women age, they undergo hormonal changes. Women undergo menopause, which is characterized by a fairly abrupt cessation of estrogen production, such that blood levels of estrogen drop to almost zero. Men, however, experience a gradual decrease in the production of androgens (such as testosterone), starting at about age 40.[2] Their testosterone levels never drop to zero. Because there is a more gradual decrease in the levels of androgenic hormones, and because there are always some hormones present, the clinical manifestations of this hormonal change vary among men.

Late onset hypogonadism (or lower than normal levels of testosterone that is a result of aging), can also be called andropause. If the man has symptoms, this condition can be called symptomatic late onset

hypogonadism (SLOH). Morales and Lunenfeld defined late onset hypogonadism 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." They added that the condition "may result in significant alterations in the quality of life and adversely affect the function of multiple organs."[3]

Not all men experience the clinical symptoms associated with low testosterone. In one study, Wang and colleagues reported that about 20% of men over the age of 50 had some SLOH and might benefit from testosterone replacement therapy (TRT).[4]

Symptoms of hypogonadism most commonly include decreased libido and/or erectile dysfunction (ED). In 1993, a National Institute of Health consensus group defined ED as "the consistent (at least 3 month) inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[5]

The Male Massachusetts Aging Study -- a prospective, population-based study of over 1100 white men who were aged 40 to 70 years at study entry and followed for up to 10 years --reported that about 52% of men aged 40 to 70 years experience some degree of ED.[6] ED can have a significant impact not only on a man's physical health and self-esteem, but also on his quality of life and relationship with his partner.

Primary care physicians and other clinicians need to be aware of three important aspects of ED. First, comorbidities and risk factors associated with ED are very similar to those that are associated with endothelial or vascular dysfunction. Second, men with ED may also have low testosterone levels (or late onset hypogonadism), and men who have late onset hypogonadism may also have ED. Lastly, hypogonadism, ED, and metabolic syndrome appear to be closely related.

Erectile dysfunction

The vascular mechanism of ED

The endothelium (blood vessel lining) responds to stimuli so that the blood vessel either opens (vasodilation) or closes (vasoconstriction). Testosterone may activate the enzyme that produces nitric oxide. Production of nitric oxide increases the production of cyclic guanosine monophosphate (cGMP), which causes vasodilatation. Phosphodiesterase-type 5 (PDE-5) enzymes break down cGMP, and PDE-5 inhibitors block the breakdown of PDE-5.[7]

Risk factors for ED

The most common risk factors for endothelial dysfunction are hypercholesterolemia, hypertension, increasing age, diabetes, tobacco use, and hereditary predisposition.[8]

Recent studies have suggested that erectile dysfunction may be one of the most common manifestations of endothelial dysfunction. Several studied have identified risk factors for ED that are similar to the risk factors for endothelial dysfunction.

The Male Massachusetts Aging Study identified multiple risk factors for ED: diabetes, heart disease, hypertension, low high-density lipoprotein (HDL) levels, depression, high levels of anger, and smoking (in patients who also had heart disease or hypertension).[6]

In a study published in 2003, Safarinejad and colleagues report that tobacco use was associated with a 2.4-fold increased risk of ED. Coronary artery disease (CAD) and peripheral vascular disease (PVD)--both signs of endothelial dysfunction--were also strongly associated with ED: CAD was linked with a 1.61-fold increased risk and PVD was linked with a 2.44-fold increased risk. Other factors linked with ED--other than the male sex and increasing age--included diabetes (3.72-fold increased risk), hypercholesterolemia (1.71), hypertension (1.69), and use of therapeutic and recreational drugs (3.71).[8]

A study by Kaiser and colleagues suggests that vascular ED may be an early marker for endothelial dysfunction. The researchers compared 30 men who had a mean age of 46, Doppler- proven ED, and no clinical evidence of cardiovascular disease (CVD) with 27 age-matched controls. They found that the men with ED had significantly lower brachial artery flow-mediated vasodilation, which suggests that men with ED have a peripheral vascular abnormality associated with the nitric oxide pathway.[9]

Similarly, a study by Montorsi and colleagues suggests that vascular ED may be an early marker for CVD. The researchers looked at 300 men with angiography-confirmed CAD. They found that 147 men (49%) had coexisting ED, and in 67% of these men, the ED had preceded symptoms of CAD.[10]

Diabetes is a risk factor for both ED and endothelial dysfunction. A study by Gazzaruso and colleagues suggests that in men with diabetes, ED might be a marker for silent CAD. They compared 133 diabetic men who had silent CAD seen on angiography versus 127 diabetic men with no evidence of myocardial ischemia. One third of the patients with silent CAD had ED, whereas only 5% of those without silent CAD had ED.[11]

Several other studies also suggest that there is a strong relationship between endothelial dysfunction, PVD, coronary ischemia, and ED. The clinical implication is that it is very important for the family care practitioner to ask patients about possible ED as part of history-taking during a physical examination. If the family care practitioner detects ED, especially in a younger man, he or she should consider referring the patient for a cardiac work up to detect possible cardiac disease.

Patient management

History

When taking the history of a patient with ED, it is very important for clinicians to obtain answers to the following questions. How old was the patient when he first experienced ED? Was the onset of ED acute or gradual? What physical, physiologic, metabolic, iatrogenic, or psychological factors may have contributed to ED? For example, was the man feeling guilty because he was having an extramarital affair? Does the man experience ED only with his wife, only at home, and not when he is on holiday? The clinician also needs to determine if the patient has risk factors for the development of ED such as diabetes, neurologic disorders, tobacco use, excessive alcohol intake, obesity, lack of exercise, or the use of recreational or pharmaceutical drugs. It is also important to ask the patient about lower urinary tract symptoms (LUTS) that may be a sign of benign prostatic hyperplasia (BPH). Symptoms of frequency, urgency, nocturia, hesitancy, and dribbling are the most common complaints associated with bladder dysfunction or an enlarged prostate. Men with moderate to severe LUTS have an increased risk of developing ED.[12] Treating LUTS can sometimes correct the ED and similarly, treating ED can sometimes improve LUTS.

Physical examination

The physician needs to examine the patient's penis to confirm that there are no abnormal curvatures, plaques, or evidence of trauma, and that the foreskin is not too tight.

Sometimes men will complain about the size of their penis. It is difficult to estimate the erect size of the penis from its size in the flaccid state. However, by stretching the penis, the clinician can estimate the full size based on the length of the corpora cavernosa. In a very obese man with a very deep supra-pubic fat pad, sometimes the penis will retract and appear to be much smaller than it actually is. The clinician should also examine the meatus to ensure sure that it is open and that there is no obstruction to the urinary outflow that may contribute to inflammation of the prostate. Inflammation of the prostate could also cause painful ejaculation which may suppress the desire for sex.

It is important to examine the man's testicles to make sure that there are no abnormal masses. The size, quality, and consistency of the testicles will also help the examiner determine if the patient has any congenital abnormalities. A small, soft testicle may not be producing testosterone efficiently.

Finally, it is very important to examine the prostate by performing a digital rectal examination (DRE). Often one can detect prostate abnormalities such as a significantly enlarged prostate, a disparity in the feel of the two sides of the prostate, or even a discrete, hard, suspicious nodule suggestive of prostate cancer. An enlarged prostate can contribute to LUTS, which can also increase the risk of developing ED.

Laboratory tests

It is important to order laboratory tests that can help identify potential causes of ED. The following basic screening tests can help determine whether the patient has normal hypothalamic-pituitary axis function: thyroid stimulating hormone (TSH), random blood glucose, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Some clinicians suggest doing the latter three tests only if the testosterone level is abnormal. For patients who are about to receive TRT, the following additional laboratory tests should be done: cholesterol, lipid profile, liver enzymes, hemoglobin, and prostate-specific antigen (PSA).

Treatment

First-line treatment for ED includes treating modifiable risk factors (such as hypertension), counseling about making lifestyle changes (such as exercising more, losing weight, and not smoking), and treating the condition with one of the oral phosphodiesterase type-5 (PDE-5) inhibitors, which currently include sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra).[13] The three PDE-5 inhibitors have similar pharmacokinetic profiles and adverse effects, Table 1.

It is important not to create false expectations in patients. I advise patients to take the drug at least 1 hour before anticipated sexual intercourse. PDE-5 inhibitors are most effective when taken on an empty stomach. They can be taken with food and a moderate amount of alcohol, although this will delay drug absorption.

Clinicians need to inform patients about drug differences -- for example, tadalafil is a longer-acting drug than sildenafil or vardenafil. Patients also need

TABLE 1. **Pharmacokinetics and adverse effects of PDE-5 inhibitors**

	Sildenafil	**Tadalafil**	**Vardenafil**
t1/2	4 hrs	17.5 hrs	4-5 hrs
Tmax	1 hr	2 hrs	1 hr
Bioavail	41%	unknown	15%
Food	high fat meal delays onset by 60 min	no effect	no effect but high fat meal delays onset by 60 min
Alcohol	no effect	no effect	no effect
Elimin	feces (80%) urine (13%)	feces (61%) urine (36%)	feces (91%-95%) urine (2%-6%)
Metab	CYP3A4	CYP3A4	CYP3A4
Most frequent adverse effects (seen in 4% or more patients in clinical trials)	headache, flushing dyspepsia, nasal congestion, respiratory tract infection	headache, dyspepsia, back pain, myalgia nasal congestion, flushing	headache, flushing, rhinitis

to know that although the drugs act in a similar way, individuals may have different side effects from each drug. Therefore, if a patient experiences a certain side effect from one of the drugs, he should not be afraid to try one of the other choices. A patient will generally be offered one or two drugs and instructed how to start taking the drug and how to increase the dosage. It is important to encourage a patient to try a drug at least 6 times before he switches to another drug.

None of the PDE-5 inhibitors always works the first time or works every time for every patient. When prescribing these drugs, it is important to provide patients with information about the drugs and how they are used, and to encourage realistic expectations about onset of response, reliability, and performance.

PDE-5 inhibitors are contraindicated in patients who are taking nitrates such as nitroglycerin in pill, spray, or patch form. Administering vardenafil along with non-uroselective alpha blockers (terazosin or doxazosin) may lead to hypotension in some patients. PDE-5 inhibitors can safely be taken with drugs for diabetes, high cholesterol, and low testosterone.[14-16]

If PDE-5 inhibitors alone are not effective in overcoming ED, some men who also have low testosterone levels may benefit from simultaneous TRT.

If this is not effective, men may be offered second-line treatment, such as a noninvasive external vacuum erection device (VED). More invasive alternatives include use of a prostaglandin E1 drug (alprostadil) with vasodilatory properties, and which is available in a type that can be injected into the side of the penis (Caverject) and a type that is inserted into the urethra (Medicated Urethral Suppository for Erection [MUSE]). Another option is injection of a triple therapy of phentolamine, prostaglandin and papaverine. Implantation of a malleable or inflatable penile prosthesis is generally the last alternative.

Recent studies of PDE-5 inhibitors

Sildenafil

A study by Goldstein in 1998 showed that 85% of men who had taken sildenafil for ED were able to achieve an erection hard enough for satisfactory sexual intercourse.[17]

Tadalafil

Until recently, PDE-5 inhibitors were prescribed as needed. About 2 years ago, Health Canada's Health Protection Branch (HPB) approved the use of tadalafil at a dosage of 5 mg/day. Porst and colleagues reported that in a study of men who still had ED after taking 20 mg tadalafil as needed for up to 2 years, after switching to 5 mg daily tadalafil, 40% of the men were salvaged and had less ED.[18] The 5 mg/day dosage did not lead to any serious drug related adverse events. The most common adverse events were dyspepsia, headache, and back pain, each of which occurred in about 5% of the men-- a lower rate than seen in a previous study of tadalafil at a dosage of 20 mg on demand. Peak plasma levels of tadalafil are lower with the lower drug dosage, which might explain the lower incidence of adverse events with the 5 mg daily dosage. After 3 to 5 days

of this daily dose, the drug level is maintained within an effective therapeutic range, meaning that the man is now capable of having intercourse at any time.

In another study by Porst et al, tadalafil was given to men who did not have ED but had LUTS secondary to BPH.[19] The study, which compared escalating dosages of tadalafil versus placebo, found a dramatic improvement in the patients' LUTS with all dosages of tadalafil. Urine flow rate Qmax (peak urinary flow rate) and post-void urine residual, as calculated from patient self-reports of voiding, did not change significantly, but the symptoms of frequency and urgency decreased. One of the cornerstones of managing patients with BPH and LUTS is the use of alpha blockers to reduce smooth muscle tone at the bladder neck and prostate capsule which can lead to improved urine flow rates and decreased frequency and urgency symptoms. For a more detailed discussion, see the article on BPH by Toguri and Barkin in this supplement.[20]

Vardenafil

Management of patients with prostate cancer has become more aggressive over the last few years, mainly because most men are now diagnosed at an early stage of the disease when a potential cure is possible. ED is one of the most common adverse effects following radical prostatectomy. To try to minimize this adverse effect, patients may be given PDE-5 inhibitors before and after surgery.

A recent study by Montorsi found two surprising results in patients who had undergone radical prostatectomy and received vardenafil. First, a dosage of 20 mg of vardenafil as needed appeared to be more effective than a dosage of 10 mg/day. In addition, even if patients delayed starting to take vardenafil for many months after undergoing radical prostatectomy, more than 50% responded to this ED treatment.[21]

Late onset hypogonadism

Testosterone is the male sex hormone that, after stimulating the proper development of secondary sexual characteristics in the prepubertal male, most commonly contributes to the libido in the post-pubertal man. Testosterone, as will be discussed later, has an impact at all stages of a man's life.

Total testosterone includes free testosterone (1% to 2% of the total), testosterone bound to albumin (about 35%), and testosterone bound to sex hormone binding globulin (SHBG; about 65%). Free testosterone and testosterone bound to albumin make up bioavailable testosterone, which is available to tissues.[7]

Phosphodiesterase enzymes hydrolyze both cGMP and cyclic adenosine monophosphate (cAMP). cGMP contributes to smooth muscle relaxation in the corpora cavernosa of the penis, which allows increased blood flow to the penis and an increased ability to attain and maintain an erection. Testosterone may activate the nitric oxide synthase (NOS) enzyme that produces nitric oxide. Low testosterone levels mean that production of nitric oxide is decreased, which will prevent the erection cascade that is activated by cAMP. Castrated rats have a decrease in NOS-containing fibers and a decreased erectile response. If the rats receive exogenous testosterone, these conditions are reversed.[22]

The Massachusetts Male Aging Study found that in men aged 40 to 70 years, 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 SHBG increased by 1.3% per year.[6]

Patient management

History

Overall symptoms of late onset hypogonadism include diminished energy (as well as vitality and sense of well-being), increased fatigue, depression, reduced muscle mass and strength, reduced bone density, anemia, and decreased cognitive ability. Sexual symptoms of late-onset hypogonadism include ED, decreased libido, difficulty achieving orgasm, diminished orgasm intensity, decreased fluid production with orgasm, decreased penile sensation, and decreased body hair. The patient may appear frail.[4]

Conditions that are associated with late onset hypogonadism include HIV-associated weight loss, end-stage renal disease, moderate to severe chronic obstructive lung disease, obesity, and even diabetes.[23]

To assess risk of late onset hypogonadism, John Morley, MD, at Saint Louis University School of Medicine in Saint Louis, Missouri, developed the Androgen Deficiency in Aging Men (ADAM) questionnaire, which consists of 10 questions, Figure 1.[23] Positive answers to two specific questions or to three other questions suggest that the patient has late onset hypogonadism.

Physical examination

The physical examination entails looking for the signs of hypogonadism such as smaller size and abnormal consistency of the patient's testicles, less body hair, central obesity, as well as muscle wasting and other signs of frailty. It is important to perform a DRE to help rule out prostate cancer, before treating a patient with TRT.

St. Louis University ADAM questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Note: A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

Figure 1. The androgen deficiency in aging men (ADAM) questionnaire to detect late onset hypoganidism.[23]

Laboratory tests

Testosterone is secreted in a diurnal pattern with a peak secretion in the morning, and often men with low levels of testosterone report that they no longer have morning erections. Late onset hypogonadism is diagnosed based on testosterone levels that are determined in two blood samples drawn before 11 a.m. on different days. Although there are inter-laboratory differences, the commonly accepted lower limit of the normal range for total testosterone is 300 ng/dL.[24]

When a patient has the potential diagnosis of late onset hypogonadism, in addition to measuring testosterone, the following blood tests may be done: FSH, LH, prolactin, glucose, and TSH. High LH and low testosterone levels suggest that the patient has primary testicular failure with an intact cerebral feedback mechanism.

If the patient has confirmed low testosterone levels and clinical signs of hypogonadism, the performance of the other confirmatory hormonal tests is not necessary. Treatment for low testosterone is the same regardless of its cause. In addition, prior to prescribing TRT, it is important to determine the patient's PSA level, to help to identify prostate cancer. The patient's hemoglobin level should also be determined, because TRT can sometimes increase the hemoglobin to a polycythemic level. TRT should be curtailed or stopped when the patient's hematocrit is equal to or greater than 52% to 54%.[24]

Treatment

Earlier forms of oral TRT were methylated testosterones, which were metabolized in the liver, potentially leading to liver toxicity and cardiovascular events. All of the TRTs presently available in Canada, listed in Table 2, are esterified and metabolized in the lymphatic system, where they are converted to estrogen and dihydrotestosterone. Therefore, since they are metabolized outside the liver, they do not cause liver toxicity and are much safer than the older forms.

Testosterone therapies are delivered by intramuscular injection or oral ingestion or a transdermal route (patch or gel). Oral testosterone has to be taken several times a day with fatty foods, to maintain target blood levels. Injectable testosterone can cause a peak in the testosterone blood level within 24 hours of injection. Intramuscular injection dosages can be titrated so that they can be given every 3 to 4 weeks. The major disadvantage of the patch form of testosterone is that many users develop moderate to severe skin reactions. The gel form of testosterone is applied once a day and care must be taken so it is not inadvertently transferred to the skin of women and

TABLE 2. **Testosterone replacement therapies for hypogonadism that are available in Canada**

Delivery mode	**Product**
Intramuscular	Testosterone enanthate (Delatestryl) Testosterone cypionate (Depo-testosterone) Testosterone undecanoate (Nebido)*
Oral	Testosterone undecanoate (Andriol)
Transdermal	Skin patch: - Testosterone transdermal system (Androderm) Gel: - Testosterone gel (AndroGel, Testim)

*Currently available in Europe; expected to be available in Canada later in 2010

children. In the future, because of new developments, men with low testosterone may be treated with intranasal TRT, a long-acting intramuscular testosterone therapy, or possibly a sublingual testosterone.

The treatment goal for most men receiving TRT for SLOH is to attain target of the "normal" blood levels of testosterone. In these men, TRT can result in improved sexual satisfaction, increased libido, increased muscle mass and strength, stabilized or increased bone mass, decreased body fat, improved skin appearance, improved mood and feeling of wellbeing, decreased hot flashes, preserved pubic hair, and increased production of red blood cells.[25-27] The men who do not benefit from this therapy may have a condition other than SLOH, or they may have androgen receptors that are refractory to testosterone.

The biggest concern for the family care practitioner when he or she is prescribing TRT is the impact on the prostate. A study by Morgantaler and colleagues showed that patients who received exogenous testosterone in appropriate amounts to achieve target blood levels of testosterone did not have an increased risk of developing prostate cancer.[28] Prostate cancer today is the number one diagnosed noncutaneous cancer in North American men. It is important to do a DRE and determine a patient's PSA level prior to commencing TRT, in order to ensure that the man has no underlying prostate cancer.

Primary care physicians need to carefully and regularly monitor patients who are receiving TRT, in order to detect any undesirable changes in PSA levels, DRE findings, liver-function tests, or hemoglobin levels. If a patient's PSA level increases by more than 20% within 6 months, TRT should be stopped. If the patient's PSA level subsequently returns to the baseline level within 3 months, then a repeat challenge with TRT would be appropriate. If the PSA level rises again, then a prostate biopsy should be performed, since the rising PSA level may indicate an underlying cancer.

Possible prostate cancer suggested by a rise in PSA levels or an abnormal DRE needs to be confirmed by a biopsy. If the biopsy detects cancer, then the patient can be treated effectively because of the likelihood that the cancer has been detected very early in its development.

The treatment goal of TRT is to have the patient's testosterone level in the upper end of the normal range. As long as the patient is within the normal (eugonadal) range, then a benign prostate does not grow significantly, and PSA levels should remain normal.[29] Studies have suggested that among men diagnosed with prostate cancer, those with low-normal or below normal testosterone levels had more aggressive cancers.[30] This suggests that a normal testosterone level may actually protect a man from prostate cancer.

The most notable human models for hypogonadism are the unfortunate men who, years ago, were diagnosed with metastatic prostate cancer and underwent surgical castration, which resulted in abrupt, complete hypogonadism. The commonest signs and symptoms after surgical removal of the testicles were hot flashes, osteoporosis, decreased muscle strength and muscle mass, decreased energy levels, emotional disturbances, ED, decreased libido, depression, decreased feelings of well-being, and very poor quality of life. These are the same signs and symptoms seen in SLOH, although they do not occur as abruptly in that condition.

Some clinicians have questioned whether it is advisable to offer TRT to men who have undergone primary treatment for prostate cancer. My approach is that if a man has undergone surgery that resulted in negative margins and if he has had a PSA of zero for 2 years, then he can be offered hormonal replacement in small amounts with very careful follow up.[31]

Metabolic syndrome

Over the last few years, researchers have identified a combination of risk factors that comprise metabolic syndrome. It is important to identify patients who have metabolic syndrome, because this syndrome is associated with a 2-fold increased risk of cardiovascular events and a 5-fold increased risk of being diagnosed with type 2 diabetes.[32] According to a statement issued in 2005 by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI), a patient has metabolic syndrome if they meet 3 of 5 criteria, Table 3.[32]

A study by Laughlin and colleagues found that testosterone levels in men with metabolic syndrome were 22% lower than in men without this syndrome.[33] Testosterone insufficiency in older men was associated with a 1.33-fold increased risk of death over a 20 year period, independent of multiple risk factors. In addition, testosterone levels were lower in men with diabetes than in men without diabetes. Another study showed that testosterone levels are lower in men with a high body mass index (BMI) than in men with a lower BMI.[34] Low testosterone levels are also associated with increased depression, and impaired cognitive functions.[35] Testosterone is also important for bone health. A study of men with minimal trauma hip fractures found that these men had significantly lower testosterone levels compared to men without hip fractures.[36]

TABLE 3. **Metabolic syndrome: AHA/NHLBI criteria. Clinical identification (three or more present)**

Risk factor	Defining level
Abdominal obesity	
Male waist	> 102 cm
Female wait	> 88 cm
Triglycerides	> 1.7 mmol/L
HDL-C	
Men	< 1.0 mmol/L
Women	< 1.3 mmol/L
Blood pressure	> 130/> 85 mm Hg c
Fasting glucose	> 5.6 mmol/L

AHA = American Heart Association; NHLBI = National Heart, Lung, and Blood Institute

Men with lower than normal testosterone levels may also have ED and metabolic syndrome. It is important to identify these three criteria.

Clinical implications

If a patient has ED, but a good libido and no other signs of hypogonadism, first-line treatment for his ED consists of modifying lifestyle factors (improving the diet, exercising more, and stopping smoking), followed by PDE-5 inhibitor therapy.

If a patient has signs or symptoms of hypogonadism as well as ED, a TRT can safely be prescribed with a PDE-5 inhibitor, and these can be beneficial. Symptoms of metabolic syndrome, such as hypertension or high cholesterol, would in turn, would require other specific medications.

ED, late onset hypogonadism, or both

The patient's symptoms will determine the appropriate workup, Table 4.

If the patient's primary symptoms are those of ED, and the patient's history and physical examination do not reveal any symptoms or signs of hypogonadism, then the physician's next steps are:

1) Have the following blood tests done: complete blood count (CBC), blood urea nitrogen (BUN), electrolytes, creatinine, FSH, LH, testosterone (free, total, bioavailable), prolactin, blood glucose, C-reactive protein (CRP), and lipid profile.
2) Treat the patient with a PDE-5 inhibitor.

On the other hand, if the patient has symptoms and signs of hypogonadism, after the history and complete physical examination, the physician's next steps are:

1) Have the same blood tests done as for a patient with ED only, as well as blood tests for PSA and liver function.
2) Treat the patient with TRT for 3 months.
3) If patient feels better, continue giving the patient the same dosage of testosterone. Repeat the blood tests including PSA, and perform a DRE--at 6 months and then annually. Expect about a 30% response with TRT if the problem is ED alone.
4) If the patient does not respond, check the blood test results to see if there is a biochemical response. If there is no biochemical response, or if the patient's drug compliance is questionable, then the physician can change the type of testosterone.
5) If the patient does not respond, but his blood levels of testosterone are satisfactory, then the patient could have another problem such as depression.

If the patient presents with both late onset hypogonadism and ED, then simultaneous administration of TRT and a PDE-5 inhibitor is safe and effective.

TABLE 4. **Erectile dysfunction versus late onset hypogonadism**

Erectile dysfunction	Late onset hypogonadism
Ages 40+	Ages 40+
Inadequate erections	Erections may be normal
Sexual desire normal	Sexual desire decreased
Often identifiable risk factors	Often no ED risk factors
Usually gradual onset	Gradual onset
Little response to hormone supplements	Often good response to hormone supplements
Normal testosterone	Erections not usually major focus
Sexual concerns	
May be hesitant to try intercourse	

Conclusion

Increasing age is the most common risk factor for both ED and late onset hypogonadism. Both conditions, however, are potential markers for other significant comorbidities. It is important for primary care practitioners to ask patients about symptoms of ED and late onset hypogonadism. Primary care practitioners also need to understand that metabolic syndrome is much more common in men with low testosterone levels, and metabolic syndrome itself predisposes men to ED and CVD, and more importantly, it carries a higher risk of death. It is no longer acceptable to trivialize either ED or late onset hypogonadism. Clinicians need to take a good patient history and perform a patient work up to be able to diagnose ED and/or late onset hypogonadism. If both conditions are present, the clinician needs to offer sequential or simultaneous treatment depending on the major symptom.

Even today, more than a decade after the release of the first PDE-5 inhibitor, men are still embarrassed to discuss ED. Now that we have identified ED as a significant marker of potential vascular disease, it is critical for the primary care physician to initiate a discussion about ED with their male patients.

The appropriate, successful treatment for ED will not only result in tremendous patient satisfaction, but more importantly, the diagnosis could potentially be a life-saving one.

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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