RYAN TERLECKI: Well, switching gears a little bit now and we're going to talk about testosterone replacement. So one can only look at Barry Bonds from when he started with the Pittsburgh Pirates and then on to his career with the Giants and wonder if something happened. He might tell you that nothing happened. But it's clear to see that something did.

If you haven't gotten it from my past presentation, I'm a huge baseball fan. If you see my two sons walking around, you'll meet Nolan, who is named for Nolan Ryan, and Shea, of course for Shea Stadium, only because my wife didn't like the name Tiger Stadium.

So Victor Conte, now Victor was-- you can call him the mastermind-- but he was behind the BALCO scandal, so the Bay Area Lab Co-op. And he worked with a chemist from Illinois, Patrick Arnold. And essentially, they developed a protocol for treating these professional athletes.

And one of the things that you kept hearing in conversation was the cream and the clear. Well, the cream, of course, was testosterone. And you saw people like Barry Bonds breaking records. Jason Giambi, winning the MVP.

And you see it in other sports, of course. You see Lance Armstrong here. He certainly set numerous records. And later admitted to using testosterone. He's probably massaging himself for the breast tenderness that he has from the topical treatment.

A-Rod continues to set records. I think he hit his 24th grand slam last night, which is a new record. And most recently, the Biogenesis scandal, which of course took out on Jhonny Peralta from the beloved Tigers. But admittedly, there were much more players from the evil Yankees team on that roster of players. So if any Yankees fans, be advised.

So we talk about PEDs, right, performance enhancing drugs. That's bad if you're a professional athlete. But what about the average Joe? We're trying to enhance his performance.

We use the term "testosterone replacement." And I will stick to that terminology through the majority of this presentation. But it's probably more aptly referred to as testosterone therapy. Replacement replies something was lost and that we had a baseline and it's somehow down from that. But we don't know that for the majority of patients coming into your practice.

So there's been a surge. So testosterone was first used clinically in 1937, two years after its Nobel Prize-winning discovery. Now, it's nearly a $2 billion annual market, where the raw drug costs only 1% of the total. And that's a higher return on your investment than most street drugs.

In terms of prevalence, historically it's been underdisagnosed. But that may be changing with all the direct to consumer marketing. You can't turn on the TV, the radio, or open a newspaper without seeing an advertisement for some testosterone product.

People are living longer. The mean lifespan in Imperial Rome was only 20 years. So we've certainly come a long way. And so that may tend to enhance the prevalence of this condition. The Massachusetts Male Aging Study estimated that 481,000 new cases of late onset hypogonadism in the US occur per year in men between the ages 40 and 69.

So who's at increased risk for low testosterone? Well, certainly men with medical conditions such as type 2 diabetes. You may see a higher incidence among men with erectile dysfunction if they're obese or overweight, those with a history of HIV and/or AIDS, and those with COPD. Certainly men who come in with medications for chronic pain, narcotics especially, and certainly Tramadol patients, you'll see this, men with end-stage renal failure. And men over 45 years of age are going to have a higher instance than those younger.

But does it really matter? Well, it looks like it does-- a 2006 study that showed that low testosterone is associated with increased mortality.

And it has complex biological effects when we speak of testosterone. Because it's not just one hormone, one receptor. You have direct activation of the androgen receptor, but you also have two bioactive metabolites in DHT and estradiol. So you have to sort that out.

So over 80% of circulating estradiol in men is from aromatization of testosterone. Thus, as your testosterone goes down, your estradiol goes down. So previously, symptoms of hypogonadism had been solely attributed androgen deficiency. But the estradiol deficiency may be relevant. Consider things such as bone loss.

So Finkelstein, et al., just recently, here in the *New England Journal of Medicine*, did a study. They took 400 men between the ages of 20 and 50 and they got monthly GNRH analogues to suppress testosterone for 16 weeks. And then they randomly assigned patients to a placebo gel or to testosterone gel at different concentrations, between 1.25 and 10 grams per day, with half also receiving an aromatase inhibitor.

Muscle size and strength, well, those are androgen dependent. Fat mass, well, that was estrogen independent. So as your estradiol levels went down, your amount of fat increased. Sexual function, however, was both androgen and estrogen responsive. So it's more complex that what we probably think.

An adequate amount of testosterone is essential for the erectile cascade. When a critically low level of testosterone is reached for an individual, the erectile response is blunted or fails altogether. PDE5 failures in hypogonadal men can be rescued by testosterone replacement therapy. That has been shown in the literature.

Improved arterial dilation has been shown by Doppler with testosterone replacement therapy. However, if you look at the packages and you consider the indications for testosterone replacement, testosterone replacement is indicated for low testosterone. It is not considered a treatment for ED.

So we talk about different types of types of hypogonadism. The majority of what you're going to be treating in practice is going to be late onset. But primary hypogonadism, most cases of this have failure of testosterone production and failure of spermatogenesis. Congenital cause is typically associated with undescended testicles, which of course increases the cancer risk. And congenital causes are associated with changes you can see phenotypically.

Secondary causes, this is an underappreciated feature of critical illness and chronic disease. And it's actually one of the few treatable causes of male infertility. I think Dr. Howards will talk more about that tomorrow.

Secondary hypogonadism, however, is not a final diagnosis. You have to consider things like hypopituitarism, hyperprolactinemia, and/or a parasellar tumor. If you see things in a child such as micropenis, scrotal hypoplasia, then you start to think that you need to send them to a pediatric endocrinologist. Pituitary tumors associated with high levels of prolactin and hypogonadal patients are not necessarily prolactinomas.

Other causes of low T include injury or disease, such as radiation, chemotherapy-induced injury, infection, testicular tumors, cancer, medications or diseases affecting the hypothalamus or pituitary, genetic conditions. Varicocele maybe, there is some low level evidence on that. And then, of course, idiopathic causes. Always be mindful of patients that are on medications such as Risperdal. Check their prolactin levels.

Late onset hypogonadism, it's frequent, but not omnipresent in older men. The classic symptoms do blend with other comorbidities because they're relatively nonspecific. Treatment may help their sense of well being, may help metabolism, bone density, erythropoiesis, and body composition. At this point in time, transdermal substitution is preferred by most providers. But you do want to follow their PSA and hematocrit.

So a diagnosis, as I mentioned, it's oftentimes a clinical syndrome of nonspecific symptoms, with signs, as well as biochemical evidence. The presentation certainly depends on the age of onset and whether if it's pre- or post-pubertal. Symptoms in older men, as I mentioned. You can also use the Androgen Deficiency in the Aging Male Questionnaire, which you can download online.

So there are sexual symptoms of low testosterone. And they may include diminished libido, ED, change in their orgasm experience, delayed or absent orgasm, and a reduction in ejaculate volume.

There are nonsexual symptoms. They may have a depressed mood. You may see a decrease in muscle mass and/or strength. You may see decreased energy overall, along with fatigue, decreased vitality, and motivation.

In terms of signs, well, you may find decreased bone density, maybe osteopenia, maybe osteoporosis. They may report hair loss or changes in their body composition. And when these men come in, they say I'm not giving weight all over. It's just right here the central portion of my abdomen. They may report breast enlargement. And when you do their blood work, you may find anemia.

In terms of diagnosis, well, measurement of total testosterone is a good predictor, except in borderline cases, where you may be looking at free or bioavailable testosterone. You also want to assess their hemoglobin and hematocrit, PSA, LH, and prolactin.

Now in younger men, below the age of 40, they do have the circadian rhythm, where you want to check the testosterone levels in the early morning. But as men get older than that, they tend to lose that. And typically, you're not going to see much variation before 2:00 o'clock in the afternoon.

Reference ranges do very by lab and by age cutoffs. And if you look at your lab core reports, for example, you're going to see an arbitrary cutoff from 69 to 70 as to lower limit of normal testosterone. Insurance companies don't necessarily preclude you from using the cutoff of 300 if the guy is in his 70s. But providers might be less likely to refer you these patients if their lab report reports and it's got an "N", for normal, next to the lab result.

So many insurance companies and the FDA is a total less than 300. But many also do recognize a low free testosterone as an indication to support treatment. Bioavailable, while it might be most relevant in the eyes of academics, is still not recognized as supporting supplementation.

If the prolactin level is more than twice the upper limit of normal, the testosterone is less than 150, or men have LH and FSH below the normal range, you want to consider a pituitary MRI. You can also use a CT protocol, depending on where you're located. If the men have small, firm testes on exam, you might want to consider a karyotype for undiagnosed Klinefelter's.

In terms of the association with diabetes, low testosterone is an independent risk factor for the subsequent development of type 2 diabetes and the metabolic syndrome. One third of patients with type 2 diabetes already have hypogonadism. Low testosterone is associated with insulin resistance. Overweight men are twice as likely to be hypogonadal. Short-term studies have shown that testosterone replacement therapy improves insulin resistance, glycemic control, and visceral adiposity. And that actually-- I'll discuss this in a minute-- may be relevant to the prostate.

So in terms of the metabolic syndrome, it's complex, increasing your risk for cardiovascular disease and diabetes. Insulin resistance is a key factor. And hypogonadism is seen frequently in association with metabolic syndrome. These men have increased leptin, obesity, and insulin, that improves with testosterone replacement, which reduces abdominal fat and improves the action of insulin.

In terms of the association with cardiovascular disease, low testosterone is associated with the presence and degree of atherosclerosis. It's also associated with other risk factors such as visceral obesity and insulin resistance, as we've already mentioned, but also hypertension and dyslipedmia. It improves exercise-induced ischemia in men with chronic stable angina. It improves exercise capacity in men with moderate chronic heart failure.

What about the brain? Well, testosterone and its metabolites positively modulate visual, spatial, verbal, and working memory. And extremes of testosterone, both and low, may be associated with worse cognitive function. In hypogonadal men, testosterone placement improves cognitive function, mood, and libido. At usual dosages, it does not increase aggression. But it's unknown if it can prevent dementia. Studies are ongoing in this respect.

Musculoskeletal health-- low testosterone is associated with lower mass and strength, lower bone mineral density, and a higher risk for fractures and mortality. Replacement in men with low or low normal levels does improve their muscle mass and their grip strength and improves development of stem cells into a myogenic lineage.

SARMs, again, are being actively studying now. And these are androgen receptor modulators that increase muscle mass. These may be the future.

So in terms of treatment options, well, one of the things we talk about is just replacement therapy. People have asked me questions about varicocele repair. And this is somewhat controversial. There is some data, however, showing a rise in total testosterone. But there's no good data addressing the clinical condition of hypogonadism.

So in terms of injectables, most of us use IM injections when we treat patients. But it also works when it's given subcutaneously. The max concentration is reached at 72 hours. And the estradiol levels may become excessive in some man.

The usual starting doses are 200 milligrams every two weeks or 100 milligrams weekly. It is cost efficient. But they do get roller coaster results because the testosterone surges after the first 72 hours. And then they stay up there for a little bit and then it falls fairly rapidly. There's a 12-week injection of testosterone undecanoate, but it's available outside this country.

Oral agents are rarely used. The alkylated preparations have adverse effects on the liver and lipid profile. Oral undecanoate is used in other countries, not here. It's free of liver toxicity. But it does cause supraphysiologic DHT levels.

So pellets, probably more and more of us are using Testopel. It was marketed nationally in '08. But pellets were approved by the FDA going back to 1972.

It's an office procedure. The typical dose is usually between 10 and 12 pellets into the adipose of the buttock. And it's done under local anesthesia and typically dosed between three and six months.

What about Clomiphene? Well, this is for men wishing to maintain fertility and may be chosen if the testosterone to estradiol ratio is greater than 10. You can use either 25 or 50 milligrams PO. And the dosing interval varies. Most commonly, it's given every other day. But you can give 25 daily or it can even be done three times a week. And it blocks central feedback of estrogen.

Aromatase inhibitors, these are used pretty rarely actually. But they can be used in patients looking to also improve spermatogenesis. Chronic use does risk a decrease in bone mineral density. And it may be chosen preferentially if that ratio that I mentioned between testosterone and estradiol is less than 10. And the dose is typically 50 to 100 milligrams of testolactone twice daily or 1 milligram of anastrozole daily.

What about hCG? Well, this can be used in men looking to also address fertility if the oral medications, such clomiphene, are inadequate. The dose is typically 1,500 to 2,000 units Sub-Q, to three times per week. And this will maintain testicular volume. Some patients will come back on topical testosterone therapy and complain about the reduction in testicular volume, although I find that that's not the majority of patients.

So transdermal, this is what we're using most commonly. Patches are one form of supplementation. But they do cause more skin irritation than the gels. The gels do risk a potential transference issue. Most data is available on Androgel and Testim. Fortesta and Axiron, however, are alternatives.

So what about pharmacokinetics? Testosterone gel results in a maximum total serum concentration three hours after administration. And there's no suppression of LH, cortisol, or SHBG. SHBG is sometimes seem on your lab reports now as sex steroid-binding hormone, same thing.

Patients come in a lot of times asking me about compounded testosterone, if I can get them a higher concentration in a gel and if I'm willing to write for this? You can consider this if the patient's allergic to an inactive ingredient, but you should use caution. Only 2% of compound pharmacies are accredited and the formulations are not reviewed by the FDA. And they're at higher risk for contamination, problems with product stability, and inconsistent potency.

So what are the benefits of testosterone replacement? Well, as we mentioned, increased strength and lean muscle mass; decreased fat; improved bone density; decreased total cholesterol and LDL, but you can also have a small decrease in your good cholesterol; improved libido, sexual performance; increased energy; and improved sense of well-being.

Adverse effects-- well, it's contraindicated right now with active prostate cancer or male breast cancer, which is rare, but does exist. Fluid retention is rare. But it's more in the frail and then the chronically ill patients. Liver toxicity is not an issue with modern agents. I don't even follow liver panels anymore.

Sleep apnea, studies have shown both positive and negative effects. But if you have a patient with untreated sleep apnea, they need to be referred. Gynecomastia is rare. If you do see this, you can decrease the dose. Prostate enlargement-- and we can talk about this in a moment-- and ethrocytosis, which is seen in up to 40% of patients.

So what about prostate issues? So this came up the other day in conversation with a number of people here. Many patients, when they come to your office, have the misconception that testosterone causes cancer. Untreated prostate cancer, if it's diagnosed, however, is still a contraindication to treatment. But some people out there are bold enough to treat these patients and more publications are coming forward.

You may consider treatment in men with a history of prostate cancer if they have no evidence of disease, quote, "after a prudent interval" based on Grade D evidence. It's contraindicated in men with severe bladder outlet obstruction.

So the growth may be multi-factorial. Now, granted the patients you're seeing aren't typically Klinefelter's patients. But there was a study on 121 Klinefelter's patients on testosterone replacement. And they found that visceral obesity was associated with prostate volume and growth during replacement, independent from the androgen levels. So it may be more than just the testosterone replacement itself.

What about cancer? Well, Dr. Freedland's group looked at the placebo arm of the REDUCE trial. The baseline testosterone and DHT levels were unrelated to cancer detection or grade. So in a secondary analysis of just the men with low baseline testosterone, those with the lowest baseline testosterone in that low T group had the lowest prostate cancer risk.

But this was felt to support the saturation model that Dr. Morgentaler publishes a lot about. It seems to suggest that high testosterone does not predispose to prostate cancer. And low testosterone, as a global condition, just meeting the definition, is not protective. So Dr. Morgentaler has cited uncontrolled studies and anecdotal evidence that testosterone replacement does not necessarily cause increased PSA in men with untreated prostate cancer.

So the androgen hypothesis-- well, nearly all of us, coming through residency, are familiar with this, thinking that if you give testosterone to a patient, you're throwing fuel on the fire of prostate cancer. So Dr. Huggins won the Nobel Prize. And he and Dr. Hodges, in 1941, reported that castration caused prostate cancer regression in men with metastatic disease and testosterone caused cancer progression. This was based on acid phosphatase levels in only two men treated with testosterone injections for no more than 18 days, one of whom was already castrated.

So what about the saturation model? Well, some data exist to suggest that men who are at castrate levels will demonstrate prostate cancer progression if given testosterone. But this is not seen if the men are hormonally intact. Consider that most of you, if you have a patient on active surveillance who has normal testosterone, you're not going to try to make him hypogonadal.

The prostate needs androgens for growth. But it can only use so much. The saturation point is estimated as approximately 250. But certainly more research is needed.

What about the impact upon fertility? Well, post-pubertal testosterone supplementation will suppress spermatogenesis. Azoospermia is seen in 92% of men on intramuscular injections for several months. It does appear to be reversible after nine months of cessation. Despite this, up to 25% of urologists, on an AUA survey, were using testosterone to treat men for infertility. So don't do that.

So in conclusion, a level of interest on the part of the provider is important for diagnosis. Treatment of low levels improves quality and quantity of life for properly selected patients. And surveillance is necessary. Thank you.

[APPLAUSE]