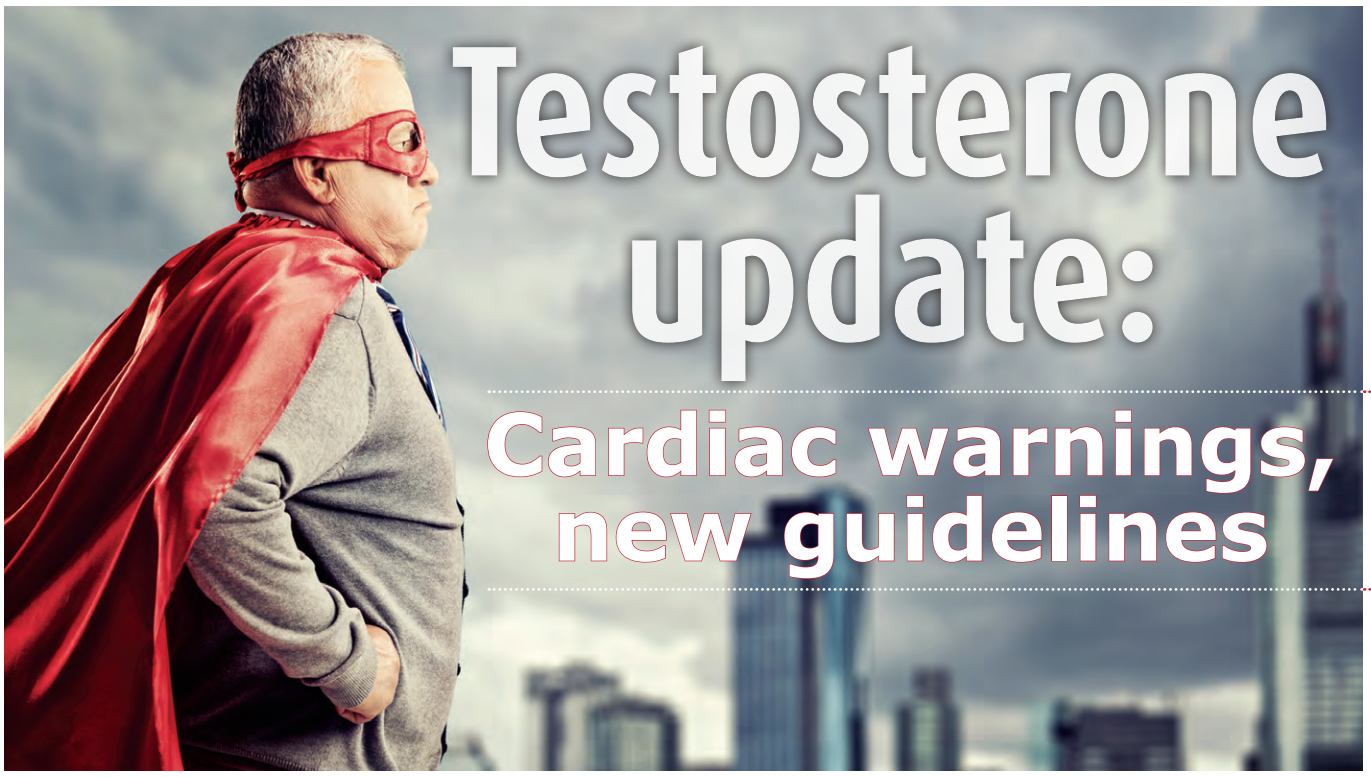


Testosterone update:

Cardiac warnings, new guidelines

Canadian group aims to give physicians clarity amid the controversy

BY JOE McALLISTER

Dr. Millar

Gomes

Recent events have given aging males and their physicians much to consider when it comes to testosterone replacement therapy (TRT)—including warnings from regulatory agencies over cardiac risks, and Canadian guidelines aimed at sorting out the confusion.

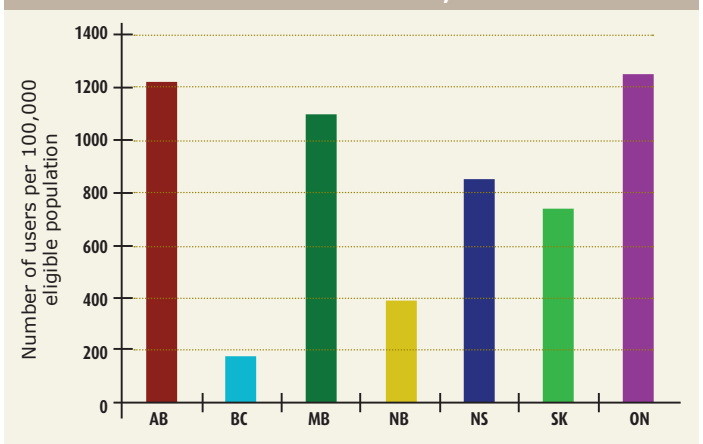
In 2014, both the U.S. Food and Drug Administration (FDA) and Health Canada launched reviews of the cardiovascular safety of TRT in the wake of studies suggesting an increased risk. In July of that year, Health Canada recommended doctors assess patients for cardiovascular risk before starting them on TRT and closely monitor them while on it. In March 2015, the FDA mandated that testosterone product labels mention stroke and myocardial infarction risk.

Meanwhile, TRT prescribing rates have continued to climb. An Ontario study, for example, showed rates among men age 66 or older increased 310% from 1997 to 2012, despite the introduction of a restricted reimbursement policy in 2006 (*PLOS ONE*, July 2014), and a U.S. study of men 40 years or older with commercial health insurance showed the rate of TRT use increased 359% from 2001 to 2011 (*JAMA Internal Medicine*, Aug. 12, 2013).

Amid those developments, the non-profit Canadian Men's Health Foundation convened a guideline panel headed by Dr. Alvaro Morales, a urologist and professor emeritus at Queen's University in Kingston, Ont., to address the diagnosis of testosterone deficiency and appropriate use of TRT (*Canadian Medical Association Journal*, Dec. 8, 2015). Dr. S. Larry Goldenberg, a professor in the urologic sciences department at the University of British Columbia, had launched the foundation in June 2014 with funding from the B.C. government, Sun Life Financial and private donors.

"These guidelines try and tackle some of the more controversial issues in the field, and the field is far from a perfect science," commented Dr. Adam Millar, an endocrinologist specializing in andrology at Mount Sinai Hospital in Toronto, who was not involved in the guidelines. Dr. Millar said he is happy doctors now have Canadian recommendations with tougher diagnostic criteria. "Patients, more than ever, are enquiring about low testosterone. Some of this is because of what they are seeing in advertising, some from Internet sites, some from online chat groups. So, physicians are testing for it more and patients are asking for it more. I think those are two big factors that are contributing to the increase in prescribing over the last few years."

Rates of publicly funded testosterone use across Canada, 2012



Ontario Drug Policy Research Network

Diagnosis

While diagnosis has often been done partially or wholly through questionnaires about aging men's overall health, the new guidelines state "questionnaires cannot be relied upon in the absence of confirmatory history, physical findings and laboratory test results." They recommend documenting total testosterone levels with a blood test taken between 7 a.m. and 11 a.m., avoiding confusion about normal daily hormonal fluctuations.

More controversial are recommendations that TRT is appropriate in patients who have "successfully treated prostate cancer" (although the patient should be referred to a specialist for monitoring) and in men "who have cardiovascular disease or are at risk of cardiovascular disease."

"This remains a highly controversial issue," said Dr. Millar about cardiovascular risk with TRT. "There are some trials that suggest harm, some trials that have a neutral result and one paper suggests a benefit."

He said patients should be referred to a specialist if there is any question of diagnosis, not just among cardiac patients but all patients. "I think men should not be considered for TRT until they have the criteria outlined in the guidelines, which include low testosterone findings on at least one occasion and symptoms consistent with it."

"Certainly the literature is still lacking regarding cardiovascular risks and testosterone replacement therapy, however the guidelines allude to this," wrote Edmonton urologist Dr. Derek Bochinski when asked to comment on the document. "The response to date has been positive," he continued. "I have had the opportunity to discuss these guidelines with some of my family medicine colleagues and I sense relief that we finally have multidisciplinary guidelines with a Canadian flare to them."

Prescribing

Tara Gomes, co-author of the Ontario study of increasing TRT prescribing rates, doesn't think the guidelines will affect that trend. "Any policy or guidelines might have a transient impact, but there seems to be strong desire for these drugs, so that trend keeps rising no matter what you put in place," said Gomes, a scientist with the Li Ka Shing Knowledge Institute of St. Michael's Hospital and the Institute for Clinical Evaluative Sciences in Toronto.

She and Dr. Millar agreed there are no set standards for testosterone levels in the aging males who are most often prescribed TRT for what is being called late-onset hypogonadism. The guidelines say TRT should attempt to reach the mid-normal range for healthy young men (14 to 17.5 nmol/l), but healthy aging men have quite different levels.

"Testosterone generally declines in the range of 1% to 3% a year," said Dr. Millar. "Many aging men (with low testosterone) don't develop symptoms classically associated with hypogonadism. We don't really have age-specific testosterone cutoff levels. We use one general cutoff for all age groups. We don't have a good answer if thresholds should change with age."

If Dr. Millar has difficulty defining proper testosterone levels in aging men, particularly those over 65, there is reason to suspect many of the prescriptions being written are not for primary hypogonadism, which is usually found and diagnosed earlier in life. They are for symptoms of hypogonadism—low libido, fatigue, loss of body mass.

"In the study we published in 2014 where we looked at users of testosterone over the age of 65, we found about two-thirds of those initial prescriptions were written by a GP," ▶

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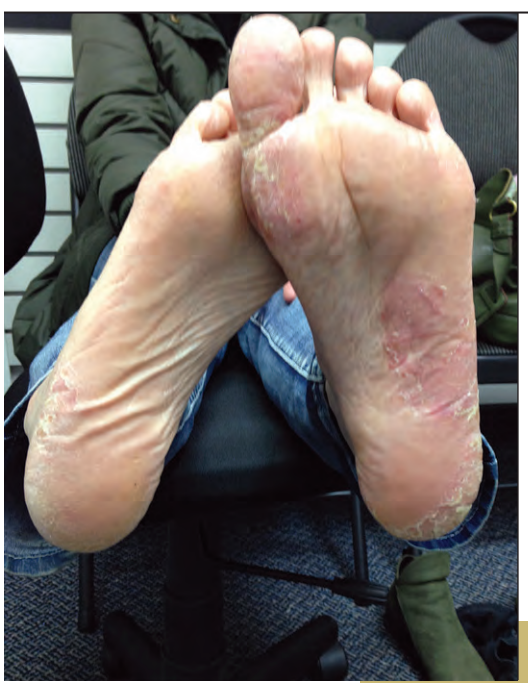
Case Report

‘Athlete’s foot’ fails to respond

BY DR. ROBERT DICKSON



This woman was initially diagnosed with athlete’s foot, but the rash also affected her hands.

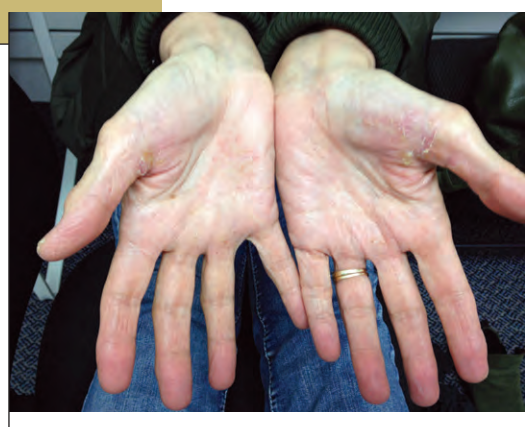
A pleasant 53-year-old fair-skinned female who had been in my practice years ago came to my clinic on New Year’s Eve with an annoying persistent rash on her feet and hands. She had seen another physician a few weeks ago who concentrated on the more spectacular foot rash and was certain she had athlete’s foot. The physician prescribed two courses of topical antifungal cream, which had no effect. No scrapings had been done to confirm the diagnosis.

The patient complained of dry, itchy, thickened skin, which seemed in her recollection to recur every winter. She was in good health, had no other medical complaints, was allergic only to cefaclor and was not in the habit of frequenting gyms or other places where she might have picked up athlete’s foot. I was immediately reluctant to accept the previous diagnosis, for several reasons. Hand involvement would be unlikely. The rash was bilateral, almost symmetrically located, and had not responded to antifungal therapy. The most important aspect of the situation, as usual, was history. I remembered the woman having had eczema almost constantly in years past. At the current visit, examination revealed mild typical eczema in her antecubital fossae and popliteal areas.

The diagnosis was apparent: variant eczema of the hands and feet characterized by lichenified, dry, itchy, thickened skin on the soles and palms. This recurred yearly in low humidity and with other aggravating factors such as cold, handwashing and occlusive footwear.

I treated the patient with high-potency topical steroids to be applied after soaking (to soften the skin and make it more permeable), especially at bedtime when other factors would not interfere with effectiveness. I recommended using mild soap and washing hands less frequently, along with other useful lifestyle changes such as wearing cotton-lined gloves to wash dishes. Application of moisturizing creams or ointments after soaking is useful but messy.

I think she will slowly get better, but I expect regression only to her “usual” eczema in the spring—and a recurrence next winter.



Courtesy of Dr. Robert Dickson

Dr. Robert Dickson is a family physician in Hamilton. This report is based on a real case from Dr. Dickson’s files.

Want to contribute a case? Please contact andrew.skelly@medicalpost.rogers.com.

Testosterone from • page 10

said Gomes. “(This) suggests they are not seeing a specialist, and perhaps increases the likelihood they are being treated for age-related testosterone deficiency rather than some of the more clinically diagnosed reasons for hypogonadism.”

However, Dr. Bochinski said he thinks GPs are appropriately testing for testosterone levels: “For the most part I think family physicians are screening the patients appropriately. . . . The guidelines now provide them with a framework to manage the patients’ followup.”

Availability and ease of use also affect the number of TRT prescriptions and the formulations used. “In Ontario, we are really seeing a surge in topical testosterone use and it is the most commonly prescribed formulation. But we don’t see that in the rest of Canada,” Gomes said. “Most of the provinces have strong restrictions or don’t list non-injectables on their public drug formularies.

“I wonder, with the topical formulations, if there is a perception among patients that these formulations are less of a drug. It seems to me that taking a pill seems like you are taking a medication, while rubbing a cream on your body may seem less invasive and less like a medical treatment.” **MP**