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CME MOC

Cleveland Clinic Journal of Medicine

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Prostate cancer screening: Two views

A hand-foot rash after chemotherapy

Diarrhea in a transplant recipient

SGLT-2 inhibitors help glucose and the heart and kidney

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Cleveland Clinic at 100, the *Journal* at 90

Cleveland Clinic 100 YEARS EST. 1921

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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 1950 Richmond Rd., TR404, Lyndhurst, OH 44124.

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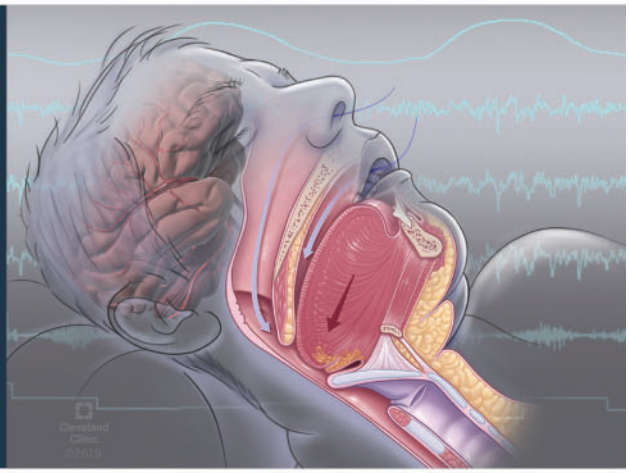
Obstructive Sleep Apnea:

A Cleveland Clinic State-of-the-Art Review

CME-Certified Online Series



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Obstructive Sleep Apnea Basics

Want to know the symptoms, risk factors and prevalence of OSA? **Jessica Vensel Rundo, MD, MS**, discusses screening tools that can be used to assess for OSA risk.

Beyond Heart Health: Consequences of Obstructive Sleep Apnea

Ever wondered about the relationship between OSA and metabolic disease, and OSA and cognitive impairment? **Harneet K. Walia, MD**, presents OSA's impact on one's quality of life.

Treatment of Obstructive Sleep Apnea: Alternatives to PAP Therapy

Want to know alternatives to PAP therapy? **Tina Waters, MD**, highlights conservative option, surgical interventions, oral appliance therapy, and nasal expiratory positive airway pressure therapy.

Sleep Apnea and the Heart

Are you able to identify the physiology of sleep-heart interactions? **Reena Mehra, MD, MS**, describes the association of OSA and cardiovascular health.

Positive Airway Pressure: Making an Impact on Sleep Apnea

Do you know the newest clinical trials and large observational studies related to PAP therapy for OSA? **Colleen G. Lance, MD**, discusses advanced PAP therapies, as well as the problem achieving PAP adherence.

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The Clinic and the *Journal:* Respecting the past and welcoming the future

This year is the 100th anniversary of the founding of Cleveland Clinic. While CCJM is most emphatically not an "in-house" journal, a centennial does warrant some self-backslapping and, as with all anniversaries, it is an opportunity to reflect on where we have come from and where we are going.

The concept of the multidisciplinary Clinic was born from experiences shared by Cleveland physicians at field hospitals in World War I. Three surgeons (Drs. Frank Bunts, George Crile, and William Lower) and one internist (Dr. John Phillips) established a group practice in 1921, a hospital in 1924, and shortly thereafter a dedicated research facility. The last I find most striking—that a group of clinicians, even while struggling to launch and gather acceptance for their novel practice in the community, would feel strongly enough about the need to advance and contribute knowledge that they would embark on such an effort. The Mayo brothers, who established their clinic in 1889, also recognized the value of linking medical practice with clinical investigation—bench to bedside.

In the current issue, we present two historical perspectives written by former editors of the *Journal*. Dr. John Clough, historian of all things Cleveland Clinic, is also the former chairman of rheumatology at the Clinic and a lupus investigator. John briefly summarizes the growth of the Clinic, reflecting on his own 50-plus years here in research, clinical practice, and administration. I succeeded John as editor in chief of the *Journal* in 2005.

Dr. James Taylor was editor in chief before John, in 1982–1992, and he is known nationally for his writing and experience in allergic patch testing. He reflects on the history of the *Journal* up to the present, noting challenges medical publications face. Thinking about these challenges segues naturally into reflections on the future.

Medical publications face rising costs, and print publications are especially challenged. Historically, costs have been offset by advertisements and, for some journals, by subscription fees. For CCJM, the Clinic has underwritten much of the cost, a vivid (and costly) demonstration of the institutional leadership's commitment, especially that of Dr. Tom Mihaljevic (President and CEO) and Dr. Jamie Stoller (Chairman of the Education Institute) to postgraduate medical education with the goal of improving medical care. As pressures increase on journals to go digital, and as "in the moment" social media seemingly dominate the lives of an entire generation, we have maintained our belief in the value of the printed format for the information that we present—although we additionally post all of our material online free of charge. And we continue to provide free CME credit for articles appearing in the *Journal*.

But it is our authors, our editorial staff, and our peer reviewers who make CCJM what it is. I wish to update you on some upcoming changes. Kristi Thomsen, who has been our Executive Editor since she took the reins from Phil Canuto in 2014, is

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doi:10.3949/ccjm.88b.01021

Cleveland Clinic

Neuro Pathways Podcast

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CONTINUED FROM PAGE 6

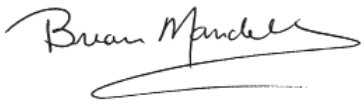
retiring. We thought Phil was irreplaceable, but Kristi has ably managed the flow of manuscripts and has helped us deal with key transitions in our online publishing. Kristi will indeed be missed. And the major in-house regret is that there will be no in-person retirement party.

Taking on the role and tasks of Executive Editor will be Mary Cusick. Mary has been with the Clinic since 2008 in several editorial and publication roles and with *CCJM* since 2015. She has overseen special projects and most recently has been our linchpin in the collation and editing of content on our COVID-19 Curbside Consult online postings. She also gets no party, just a list of manuscripts that I am late in reviewing.

Lastly, this month we are excited to introduce the first issue of the United Kingdom edition of *CCJM*. Intended to showcase the educational component of our presence at Cleveland Clinic London, *CCJM-UK* will include material from *CCJM* as well as some additional material targeting our international readers.

Professor Olaf Wendler, MD, PhD, will serve as Chief Editor of *CCJM-UK*. Dr. Wendler is the new Chair of the Heart, Vascular, and Thoracic Institute at Cleveland Clinic London. He is a Fellow of the Royal College of Surgeons and Professor of Cardiac Surgery at King's College London. I plan to take advantage of his unique expertise in complex valvular heart disease, so you can look forward to hearing from him in the future.

We at *CCJM* join you all in hoping for a peaceful and safer 2021.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

COMMENTARY

John D. Clough, MD

John D. Clough, MD, is a rheumatologist. He practiced with Cleveland Clinic's Department of Rheumatic and Immunologic Diseases from 1971 until his retirement in 2008, serving as chair from 1979 to 1991. Over the years, he has served Cleveland Clinic in several other capacities, including Chairman of the Division of Health Affairs from 1991 to 2004, Editor in Chief of the *Cleveland Clinic Journal of Medicine* from 1997 to 2005, and publisher of the Cleveland Clinic Press. He currently volunteers in the Cleveland Clinic Archives Department.

Cleveland Clinic 100 YEARS EST. 1921

Cleveland Clinic—A century of progress

When Cleveland Clinic's founders-to-be (Drs. Frank E. Bunts, George W. Crile, William E. Lower, and John Phillips) returned home to Cleveland in 1919 after serving in World War I, the first 3 resumed their practices in the Osborn Building, near Playhouse Square in downtown Cleveland. They had already determined that they would form a group practice with some of their close colleagues, including Phillips, which would operate out of a new, specially designed building that would also support research and eventually education as well as clinical practice.

They leased a parcel of land at the corner of Euclid Avenue and East 93rd Street, formed a company with the help of Bunts's son-in-law, attorney Edward C. Daoust, to design and construct the building, and opened the new group practice in February 1921 with a professional staff of 15 members. A new hospital was added in 1924, a new research building was finished in 1928, and new outpatient facilities were opened in 1931 after a disastrous fire in 1929 killed Phillips and 123 others who happened to be in the original Clinic building. The Clinic survived that setback and thrived, growing exponentially into the 21st century.

It is somewhat sobering to realize that, as we approach the 100th anniversary of the founding of the Cleveland Clinic, I have been associated with the organization in one form or another for more than half of its history (55 years). Although I never met the founders (they were all gone by some 25 years before I got here), I did know Crile's son George Jr., called Barney, and other members of the Crile family.

So I have observed the Clinic's transformation from a relatively small regional organization into the massive international entity we are familiar with today. About 10 years before I arrived on the scene, the Clinic had significantly reformed its governance by establishing an elected physician board of governors, allowing the professional staff a greater voice in the direction of the organization, including decisions about growth. This cemented physician control of the Clinic and set it on a course of continued growth. (All of this is recounted in the several editions of the Clinic's history *To Act as a Unit*).[1,2]

In July 1965, when my wife Mary and I moved to Cleveland from Washington, DC, to begin our internships at Cleveland Clinic (she in pediatrics, I in internal medicine and rheumatology), the institution was very different from what it is now. It included 2 outpatient buildings, a small research building, and a single 484-bed hospital with a small 4-bed intensive care unit, 3 of which had to be pushed into the hallway if one of the occupants needed to be resuscitated. Believe it or not, there was also a small emergency room, marked by a small sign identifying it as the "Ambulance Entrance" on East 90th Street. There were 127 "full staff" physicians and surgeons, mostly specialists, all of whom knew each other, as did the small and compact house staff. The culture was characterized by cooperation and collegiality. The physicians—staff and house staff—interacted both professionally and socially. Interns and department heads would mingle in the hospital cafeteria with little sense of hierarchy.

In 1965, when my wife and I began our internships, the institution was very different from what it is now

Although the Clinic had a prestigious cardiovascular research program headed by Irvine Page, discoverer of angiotensin and serotonin, who had arrived at the Clinic mid-career in 1945, it did not yet have a medical school. Yet, despite this apparent drawback, the few posi-

doi:10.3949/ccjm.88a.20185

tions in the medical, surgical, mental health, and pediatric training programs offered at the Clinic were highly sought after, because the Clinic was a hotbed of clinical and research activity with a strong emphasis on education.

Pioneered by F. Mason Sones, the use of coronary cineangiography to diagnose coronary artery occlusion was just gathering steam at that time. This led eventually to the establishment of coronary bypass graft surgery as the treatment of choice for prevention of heart attacks in patients with severe occlusions. From the point of view of the house staff, a majority of the medical admissions during the week were to the Sones-Shirey-Sheldon service.

Other, less well-known but innovative initiatives abounded. On the medical side, endocrinology pioneered a program called "diabetic recheck." On a regularly recurring basis, patients with diabetes returning for follow-up were treated to a meal (usually breakfast), a group educational event with opportunity for questions, and a physician appointment. This sounds like the "medical home" idea of recent times, but it was in full flower at the Clinic in the 1960s. The result was that the hospital had few medical emergencies due to diabetic acidosis, unlike the situation I had come from.

Cleveland Clinic has grown from a relatively small hospital with emphasis on medical research and education to a world-wide organization

Bruce Stewart and his colleagues in urology, nephrology, and immunopathology developed an aggressive approach to kidney allotransplantation, which was greatly aided by the development of tissue typing in the immunopathology laboratory of Bill Braun and later by the use of immunosuppressive drugs.

Barney Crile created a furor among cancer surgeons by advocating limited excision of malignant breast tumors in selected patients. For this inexcusable transgression, he was expelled from the Academy of Medicine of Cleveland and roundly castigated around the country. Eventually, he was shown to be correct.

And there was much more going on—the use of methotrexate by Art Scherbel and his colleagues to treat severe rheumatoid arthritis, the discovery by Virginia Donaldson and Dick Evans that absence of a C1-esterase inhibitor caused hereditary angioneurotic edema, and the exploration of guided radiation to treat brain tumors by Joe Hahn are just a few examples.

With all this activity, the reputation of Cleveland Clinic was spreading, the demand for services was increasing, and the organization was growing at an exponential rate. In the middle of the 1990s, several circumstances transformed the Clinic from a large, though regional, entity with a good reputation to a huge international organization. The rise of for-profit healthcare prodded the Clinic to link up with other Cleveland metropolitan hospitals. Changes in the health insurance industry spurred the growth of outpatient centers throughout the region. The Clinic's growing reputation in cardiology led to a national and international reputation. And longstanding relationships spurred growth in international medicine.

Today, Cleveland Clinic has grown from a relatively small hospital with emphasis on medical research and education to a world-wide organization with 18 hospitals (6,026 beds), more than 220 outpatient locations, more than 4,500 physicians also serving patients in southeast Florida, Nevada, Toronto, Abu Dhabi, and London, as well as a medical school in Cleveland in partnership with Case Western Reserve University.

Clearly things have changed a lot since 1965. The days of all the doctors having lunch together in the hospital cafeteria are over. Curbside consultations on the Skyway still happen, but when we are dealing with many institutes and departments, some of which contain more than 100 physicians, the opportunities for spontaneous interaction between doctors in different departments are much more limited. The use of electronic media to aid communication has helped this, but the quality of communication, even with video, is different from that of face-to-face. This is an issue that Clinic administration continues to face. Nonetheless, our ability to care for our patients is infinitely better today than it was 100 or 55 years ago, and no one in their right mind would want to return to those "good old days."

DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contribution, could be perceived as a potential conflict of interest.

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COMMENTARY

James S. Taylor, MD, FAAD
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Cleveland Clinic Journal of Medicine: Evolution and a look ahead

Cleveland Clinic has been publishing a scientific journal for 90 of its first 100 years, contributing to and chronicling our 3 founding missions of better care of the sick, investigation of their problems, and further education of those who serve.[1] The evolution of the *Cleveland Clinic Journal of Medicine* (*CCJM*), the flagship publication of the Clinic, also reflects the stark realities and changes in scientific publication and graduate medical education over the past 4 decades.

Forty years ago, when I was editor in chief of *CCJM*, I wrote a history of its first 50 years,[1] which was updated to the first 80 years by the current editor in chief[2] in 2011! Initially published as the *Cleveland Clinic Bulletin* in 1931, the *Journal* became the *Cleveland Clinic Quarterly* in 1932 and *CCJM* in 1987.[3]

Republication of articles by Clinic authors from other journals ceased in 1934.[1] The core of the *Journal* then became original investigation research articles plus a mix of subject reviews, case reports, editorials, specialty-specific features, letters to the editor, and book reviews. Since 1995 our bread and butter has been timely clinical and bench-to-bedside reviews and practical teaching articles with a focus on continuing medical education, supplanting articles of original investigation research.[4] Free *AMA PRA Category 1 Credit*™ for continuing medical education and maintenance of certification remains a key offering of *CCJM*. Cleveland Clinic is currently the largest provider of continuing medical education in the United States, in the number of offerings and participants, with *CCJM* accounting for 27% of that number (S. Kawczak, e-mail November 2, 2020).

doi:10.3949/ccjm.88a.20187

The *Journal* has evolved in other ways. In 1983, we expanded our circulation from 16,000 to 40,000.[5] In 1987, morphing from the *Quarterly* to *CCJM*—originally published 10 times a year and now monthly—we further expanded our circulation to 100,000.[3] In that year, we began accepting advertising and changed the targeted readership focus to general and subspecialty internal medicine, which now includes hospitalists, cardiologists, endocrinologists, pulmonologists, and infectious disease specialists. Currently, print copies of *CCJM* are received by more than 128,000 readers, and a monthly electronic table of contents alert and a weekly electronic newsletter go out to more than 160,000. In addition to clinical reviews and editorials, regularly appearing departments now include Symptoms to Diagnosis, 1-Minute Consult, Smart Testing, The Clinical Picture, and Medical Grand Rounds.

Cleveland Clinic is 100 years old and has had a medical journal for 90 of those years

CCJM authors are a mix of local, national, and international; nearly half are Cleveland Clinic staff. The *CCJM* mission statement mandates authors "to identify new findings that are changing the practice of medicine and to advise readers how to apply them in daily patient care. Authors are chosen for their experience, acquired through caring for patients, teaching other physicians, and researching clinical questions" (P. Studer, e-mail September 25, 2020). All articles (except for Medical Grand Rounds) are peer-reviewed by Clinic and external reviewers, with a list of reviewers published annually.

CCJM and its predecessors have published new findings, innovations, and procedure reviews by authorities at the Clinic,[2,6] including symposia and specialty issues in cardiology,

neurology, pediatrics, and dermatology. The *Journal* currently publishes specialty supplements in cardiology, diabetes, infectious disease, and pulmonary medicine. While claims of attribution may be precarious, the *Quarterly* published the first use of topical nitrogen mustard in mycosis fungoides (cutaneous T-cell lymphoma) (1959; confirmed in a 1983 commentary[6]), a now-established therapy, and the first 3 cases of acute beryllium pneumonitis as a new occupational disease in the United States (1943; confirmed in a 1983 commentary[7]). The publication on acute beryllium pneumonitis began a quarter-century collaboration of the Clinic with the beryllium industry in Cleveland. Additionally, a major cultural landmark in Cleveland was highlighted in the *Quarterly* in a detailed, illustrated medical tour through the Cleveland Museum of Art.[8]

Scientific journal editors face a range of issues including disclosure of conflict of interest by authors and reviewers, anonymity of review, timely solicitation and handling of articles with deference to reviewers and authors, and the writing of rejection letters. Additionally, potential misconduct may occur such as dual publication, dual submission,[9] and plagiarism, whether intentional or not, and *CCJM* and many other journals now use duplication-detection software.

CCJM has evolved while maintaining its scientific excellence, integrity, and editorial independence

The behind-the-scenes editorial and publishing team is the driving engine critical to any journal's smooth operation and survival, no less at *CCJM*.[1,4] The *Journal* has been most fortunate to identify and attract an impressive group of talented and collaborative editors, each with their own unique skills, which significantly improves the final product. They have been gratefully acknowledged with praise in the past,[1,4,10] and the current cadre is listed on the *Journal* masthead.

Advertising income is a major lifeblood of controlled circulation journals and has been a cornerstone of *CCJM*'s expanded circulation and frequency since 1987, when *CCJM* first hired an advertising executive.[3,4] Syndicated surveys that assess and analyze physician readership are important in ad sales, and those currently performed by Kantar Media show *CCJM* always ranking high.

Open-access and online publishing are current hot issues in medical research and publishing. *CCJM* is an open-access journal requiring only registration, with content (text, images, figures, and data) accessible online without financial or technical barriers to readers. Online publishing has evolved in parallel to open-access, with advantages including availability of supplementary material with increased author and reader interaction. The latter comes with links to references, video, and other resources and novel metrics that can assess an article's immediate impact.[11,12]

COVID-19 has had an enormous impact on open access internationally and on the multitude of pandemic-related articles (> 79,000 in PubMed in the past year), with journals posting more accepted articles on line ahead of print. Authors are also posting more research articles to preprint servers for timely feedback *before* submission to a journal for formal peer review.[13] *CCJM* has a new practical online series, COVID-19 Curbside Consults, with key clinical, imaging, testing, treatment, and health system practices, authored by clinicians facing the pandemic daily.

A 2019 National Library of Medicine search identified 167 journals that had once been published by hospitals and academic medical centers, but most of them had changed names or ceased publication, and only 6 were currently indexed in MEDLINE. *CCJM* is 1 of only 2 of the 6 surviving journals that are published monthly (M. Simonson, e-mail August 10, 2019).

In the current environment of electronic and information overload, *CCJM* is well suited to navigate future challenges. The *Journal*'s major strengths include that it is both owned and published by Cleveland Clinic, and has successfully evolved over the past 90 years while maintaining its scientific excellence, integrity, and editorial independence. We recount the history of *CCJM* with pride and believe it to be well positioned for success in its next century.

DISCLOSURES

Dr. Taylor has disclosed owning stock in AstraZeneca, Cigna, Johnson and Johnson, Kao Brands, Merck, and Opko Health.

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CME MOC

2021

JANUARY

SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
January 23–24
LIVE STREAM

FEBRUARY

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LIVE STREAM

BASIC AND CLINICAL IMMUNOLOGY FOR THE BUSY CLINICIAN
February 5
LIVE STREAM

MARCH

MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
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LIVE STREAM

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LIVE STREAM

CONTROVERSIES IN ENDOMETRIOSIS, ADENOMYOSIS, AND FIBROIDS
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Cleveland, OH

COMPREHENSIVE LIFELONG EXPEDITIOUS CARE OF AORTIC DISEASE
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Cleveland, OH

INTENSIVE REVIEW FOR THE GI BOARDS
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GENETICS EDUCATION SYMPOSIUM – GENETICS AND GENOMICS: APPLICATIONS FOR THE PREVENTION, DETECTION, AND TREATMENT OF CANCER
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Cleveland, OH

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COMMENTARY

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Prostate cancer screening and the role of PSA: A UK perspective

PROSTATE CANCER is the most common solid-organ cancer and the second-leading cause of cancer death in Western men.[1] Nearly 50,000 men are diagnosed with prostate cancer each year in the United Kingdom, and more than 11,000 die of it.[2] Prostate cancer is therefore a significant killer of men. And it is usually a silent killer, asymptomatic in its curable stages. Hence, to save lives from prostate cancer, we must diagnose it early, before symptoms appear.

See related editorial, page 17

We advocate PSA screening for all middle-aged men, especially if they have risk factors

Fortunately, the serum biomarker prostate-specific antigen (PSA) has become widely used over the last 40 years.[3] True, it is an imperfect test. PSA is prostate-specific, not cancer-specific. Conditions such as benign prostatic hyperplasia, prostatitis, recent instrumentation of the urinary tract, urinary tract infection, and even ejaculation can cause a rise. But temporal trends in PSA can provide better accuracy than single readings in determining risk of prostate cancer, and can signal the need for subsequent investigation.

RATIONALE FOR SCREENING

We believe that PSA screening should be offered to all middle-aged men, especially if they have prostate cancer risk factors:

- Age > 50
- Black ethnicity
- A first-degree relative with prostate cancer.

The European Randomised Study of Screening for Prostate Cancer (ERSPC)

This multinational European trial randomized 182,160 men to undergo screening for prostate cancer (intervention) or not (control).[3] Screened men had PSA tests every 2 to 4 years and a prostate biopsy if their PSA concentration was greater than 3 ng/mL. At 16 years of follow-up,[3] 20% fewer men had died of prostate cancer in the intervention group than in the control group. The number needed to be screened to diagnose 1 case of prostate cancer was 18 in this latest follow-up of the study, a significant lowering compared with the prior study report.

The study investigators concluded[3] correctly that PSA screening significantly reduces prostate cancer mortality, with a larger absolute benefit with longer follow-up. Hence, my view is that for men with a long life expectancy (ie, most middle-aged men), screening for prostate cancer with PSA is warranted.

The PLCO study provides no useful information over the ERSPC

The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO),[4] which included a prostate-screening arm, found more cancers in screened men but no survival advantage.

However, the PLCO study was smaller than the ERSPC and was heavily contaminated, as 44% of men in the control group (assigned to no-screening) had PSA tests anyway, so really it was a study of screening vs less screening. Further, the assigned interventions and subsequent investigations were not well adhered to: some men allocated to having their PSA checked did not get tested, 44% of men allocated to no-PSA testing got tested anyway, and only about a third of patients with a PSA level higher than 4 ng/mL had a prostate biopsy.[4] All in all, this study does not really provide any useful information over ERSPC.

doi:10.3949/ccjm.88a.20164

Active surveillance is now preferred in most men with low-risk prostate cancer

Plenty of evidence from several studies shows that low-risk prostate cancers (PSA < 10 ng/mL, Gleason grade 6, and unilateral cancer) usually grow slowly and are safe to monitor, with active treatment advised if surveillance tests show progression.

The world's largest comparative-effectiveness randomized study of PSA-screened interventions (ProtecT) showed no survival benefit from surgery or radiation therapy compared with active surveillance at a median of 10 years.[5]

Prostate biopsy is no longer always the next step for men with elevated PSA

In my opinion, multiparametric magnetic resonance imaging (MRI) should be the next step in the investigation of men who have an elevated PSA. This allows men with a normal scan to be monitored, since MRI will detect most clinically significant prostate cancers (negative predictive value 80%–90%).[6] Men with suspicious findings on MRI can proceed to prostate biopsy.

While this has become widespread practice in the United Kingdom, in the United States many insurance companies will not reimburse for prebiopsy MRI, and thus, alternatives such as blood-based biomarkers are often used. There are no head-to-head studies comparing prebiopsy biomarkers and MRI; however, MRI can be used to guide the locations of any subsequent biopsy (see below), whereas biomarkers cannot. I prefer to use MRI.

Prostate biopsy is more accurate and has fewer side effects than ever before

Many prostate cancer experts have replaced transrectal prostate biopsy with MRI-targeted transperineal template biopsy, performed as an outpatient procedure with the patient under general anesthetic. As well as enhancing the prostate cancer detection rate, this technique also reduces the risk of biopsy-related infections and thus decreases antibiotic resistance. Further, fusing the prebiopsy MRI images onto the biopsy platform improves the accuracy of targeting suspicious lesions on MRI; these "fusion" biopsies improve detection of clinically significant cancer while decreasing detection of indolent disease.[7]

Again, although this technique is gaining in popularity in the United Kingdom, it is significantly more expensive than prostate biopsy under local anesthesia, and thus has had limited uptake so far in the United States.

PSA level before age 50 accurately predicts future risk of prostate cancer

Several studies have shown that the PSA level before age 50 is a stronger predictor of prostate cancer risk than race or family history.[8] This information could be used to guide the frequency of future PSA testing: "smart" screening.[9] A 45-year-old man with a PSA level less than 1 ng/mL would be advised that his next PSA test should be done in 5 years' time, whereas a man of the same age and race with the same family history with a PSA of 1.5 ng/mL would be advised to have it rechecked in a year.

Further, incorporating novel biomarker panels such as the 4K score, PSA derivatives like PSA density, and polygenic risk scores can improve the accuracy of prostate cancer screening and give more confidence in determining which men to investigate further, which to monitor and at what frequency, and which to safely discharge.

Patients with low-risk prostate cancer do not generally need treatment

KEY POINTS

- Prostate cancer is a significant killer of men.
- Prostate cancer is asymptomatic during its curable stages.
- PSA screening saves lives.
- Patients with low-risk prostate cancer do not generally need treatment, whereas those with intermediate- and high-risk cancers usually benefit from curative therapy.
- Not all men with a raised PSA need a prostate biopsy, thanks to MRI scanning.
- Prostate biopsy is now more accurate, safer, and more comfortable for patients when informed by an MRI.
- PSA levels before age 50 accurately predict future risk of developing prostate cancer.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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EDITORIAL

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Prostate cancer: To screen or not to screen? The question is complicated

Whether to screen for prostate cancer remains controversial due to the complexity of balancing the harms and benefits. Prostate cancer is the most common cancer in men and the second-leading cause of male cancer deaths. An estimated 192,000 men received the diagnosis during 2020, and 33,000 died from the disease. In contrast, lung cancer was diagnosed in about 116,000 men, and more than 72,000 died of it.[1]

See related article, page 14

The problem of prostate cancer overdiagnosis can be appreciated from autopsy studies. A review of 19 studies of autopsy-detected prostate cancer reported that in men age 70 to 79 who died of unrelated causes, 36% of US White men and 51% of US Black men were found to have malignant tumors in their prostate.[2] Similarly, the Prostate Cancer Prevention Trial reported that biopsies reveal prostate cancer in 15% of men who had normal findings on digital rectal examination, normal prostate-specific antigen (PSA) levels, and no symptoms of the disease.[3] Clearly, most cases of prostate cancer are not deadly, and yet tens of thousands of American men die of it each year.

Decisions about screening are difficult mainly due to the adverse effects of treatment, which include urinary incontinence and erectile dysfunction. Men undergoing radiation therapy are also at risk for rectal bleeding from radiation proctitis and for secondary (radiation-induced) cancers. Men who are treated and then develop a rising PSA without evidence of metastatic disease may then be treated with hormonal therapy, which, in that setting, has known side effects and harms but no proven benefit. In other words, a screening test can lead to a cascade of treatment decisions and consequences. Balancing harms and benefits depends, in part, on the individual man's priorities and values; hence, shared decision-making is widely advocated.

doi:10.3949/ccjm.88a.20192

In this issue of *Cleveland Clinic Journal of Medicine* (page 14) Sooriakumaran presents the argument in favor of screening based on the most recent data available and current practices for prostate cancer screening, diagnosis, and treatment. Several key facts deserve to be highlighted.

Decisions about screening are difficult mainly due to the side effects of treatment

First, there is strong evidence of a disease-specific mortality benefit from screening. The European Randomized Study of Screening for Prostate Cancer reported that with 16 years of follow-up, there was roughly a 20% reduction in the risk of death from prostate cancer (hazard ratio 0.80, $P < .001$).[4] Based on the study results, 570 men would need to be invited to undergo screening in order to prevent 1 death from prostate cancer. Similarly, 1 death was prevented for every 18 cases diagnosed.

Second, decision-making has become more sophisticated and individualized about whom and when to biopsy, how to perform the biopsy, and, if cancer is diagnosed, which cancers need active treatment. These changes have mitigated the cascade from elevated PSA to biopsy to surgery or radiation therapy. The trend is toward reducing the burden of overdiagnosis by being more selective regard-

ing who gets biopsied and who gets treated.

It's also worth noting that worrisome changes in prostate cancer epidemiology have occurred since the use of PSA screening tests became less common after the US Preventive Services Task Force recommended against screening.[5] With less screening, the diagnosis of clinically localized disease has declined while the incidence of locally advanced and metastatic disease has increased.[6] For instance, between 2010 and 2016, the incidence of metastatic prostate cancer in men over age 75 increased 5% per year on average.[7] The implication of the rising number of men with metastatic disease at diagnosis, given that metastatic prostate cancer is incurable, is that prostate cancer mortality may start to increase after decades of decline. Thus, while the problem of overdiagnosis has been reduced, the cost of that progress is likely to be more prostate cancer deaths.

The best path forward is not more screening or less screening, but rather to continue to develop better screening tests and algorithms for deciding who stands to benefit from early diagnosis and treatment. In the meantime, shared decision-making remains appropriate. Prostate cancer screening reduces prostate cancer deaths, but at a cost. Different men will weigh the harms and benefits differently.

DISCLOSURES

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COMMENTARY

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COVID-19 diagnostic testing and the psychology of precautions fatigue

A 65-YEAR-OLD MAN is hospitalized with mild dyspnea and myalgias. After an initial nasopharyngeal swab is negative for SARS-CoV-2, the hospital staff requests that special respiratory precautions be discontinued without a second test. They cite a low observed yield of repeated testing and the burden of precautions on workflow.

Hospital policies regarding the necessity of a confirmatory second negative test are based on the chances of an initial false negative in a population with an estimated probability of disease. However, staff perception of residual disease risk is based on the chances of a patient's having COVID-19 despite having tested negative. Psychological fatigue arises from incessant gowning, gloving, and masking among patients extremely unlikely to have COVID-19. This fatigue leads to a reduced vigilance that degrades the value of precautions across all patients in isolation.

PRECAUTIONS FATIGUE IS ANALOGOUS TO ALARM FATIGUE

The COVID-19 crisis is an opportunity to reframe clinical decision-making. Despite decades of teaching clinical reasoning, promulgating practice guidelines, and advocating shared decision-making to allocate scarce resources, excessive testing and monitoring persist. One consequence is alarm fatigue,[1] caused by false-positive (clinically insignificant) notifications of status changes—when alarms persistently sound with little purpose, people stop paying attention.

A generation ago, analogous concerns generated surgeons' desire for human immunodeficiency virus screening to enable selective implementation of special precautions rather than universally applied intensive measures. The large number of COVID-19 patients and hospitalized "patients under investigation" (PUIs) for whom special respiratory precautions are ordered is creating a previously unseen degree of "precautions fatigue." The current practice environment represents an opportunity for experiential cognizance of well-intentioned efforts at error avoidance that become diluted through overly broad application.

With the increased incidence of disease in the community, more readily available testing, recognition of nosocomial transmission, and fewer admissions for diseases other than COVID-19, the proportion of hospitalized patients being evaluated for COVID-19 is markedly higher than it was earlier in the pandemic. When testing was scarce, costly, and time-consuming, patients were tested only if they had multiple COVID-19 symptoms and a known exposure or relevant travel history. With increasing incidence, populations being tested have broadened, escalating the number of patients considered at risk and creating anxiety among healthcare workers through both the presence of true disease and the ubiquitous respiratory precautions signs on isolation rooms.[2]

The COVID-19 crisis is an opportunity to reframe clinical decision-making

CONSEQUENCES OF PRECAUTIONS FATIGUE

Unless incremental increases in testing are specifically targeted at high-prevalence groups, higher testing rates generally result in both a lower proportion of positive test results (lower diagnostic yield due to reduced average pretest probability) and less-severe disease, on average, among those who test positive.[3] Since hospital-

doi:10.3949/ccjm.88a.20086

ized PUIs affect behavior of hospital staff and deplete personal protective equipment, it is important to understand their effect on the psychology of inpatient healthcare workers and on disease transmission.

Precautions fatigue has become evident in hospitals, reducing the average effectiveness of precautions the same way that alarm fatigue desensitizes staff, reducing the average clinical benefit of each alarm triggered.[1] Precautions fatigue results in guideline-discordant reuse of personal protective equipment, reduced attention to facial protection (given barriers to its access), less-vigorous encouragement of patient mask-donning, and dramatic reductions in direct patient contact.

Early in the pandemic, a substantial proportion of hospitalized PUIs were eventually diagnosed with COVID-19, for several reasons. Testing had a relatively high yield because protocols restricted testing to high-risk populations, as understanding of the clinical spectrum of disease was poor and testing capability and availability were limited. Testing had higher sensitivity due to policies (inadvertently) restricting testing to patients with greater viral shedding and substantial nasal secretions.[4] Also, there was a time lag between sending the sample and getting the result, so that for PUIs, initial results of nasopharyngeal swabs were not available for 2 to 3 days, leaving them at a higher instantaneous probability of disease, ie, probably at one point in time.

False-omission rates are more dependent on prevalence than false-negative rates

More recently, when the clinical presentation suggests the disease, most hospitalized PUIs have received negative results on their first test before being admitted, which reduces the probability of disease to the false-negative rate. The exceptions are those with a positive first test (who would be admitted to a COVID-19 unit and would no longer be considered under investigation) and those with a pretest probability sufficiently low for liberation from PUI status after a single negative test.

FALSE-NEGATIVE RATES VS FALSE-OMISSION RATES

Diagnostic tests have known or imperfectly estimated sensitivities and specificities, which depend on the tests themselves and factors such as sample quality, body habitus, and timing of sampling relative to the natural history of disease. Although the sensitivity of polymerase chain reaction testing of a nasopharyngeal swab for SARS-CoV-2 has not been established, many hospitals have been using an estimate of 70%, based on early studies.[5]

As a test characteristic, sensitivity does not generally depend on disease prevalence in the population tested. However, if less-symptomatic populations and asymptomatic preprocedure inpatients are tested, lower levels of viral shedding and lower volume of nasal secretions among those tested may decrease the sensitivity, as studies of influenza have demonstrated.[4] Therefore, while we assume the sensitivity is 70%, a lower value would increase both the false-negative rate and the false-omission rate (ie, 1 minus the negative predictive value).

A relatively low positive predictive value and high false-discovery rate (1 minus the positive predictive value) have been implicated in the poor response times associated with alarm fatigue.[1] However, reductions over time in attentiveness to precautions among staff caring for COVID-19 PUIs is due to the aggregate of both true and perceived lower prevalence of disease, considering all those tested as the denominator. The true prevalence of disease is decreased due to increased testing rates and the fact that most PUIs have had a negative test result. The latter leads to a probability of disease given as:

$$P(\text{negative test} \mid \text{COVID} +)$$

ie, the probability that a diseased patient would test negative, which is equal to the false-negative rate times the true prevalence within the tested population. However, staff perceptions of residual disease prevalence will be based on the false-omission rate, given as:

$$P(\text{COVID} + \mid \text{negative test})$$

ie, the probability that a patient who tests negative has COVID, rather than the false-negative rate.

Two relevant considerations arise from the distinction between precautions policies among those with a first negative test, which are often based on the false-negative rate. First, the false-omission rate varies much more with prevalence than the false-negative rate. For example, assuming the sensitivity is 70% and the prevalence is 10%, the false-negative rate and false-omission rate are nearly identi-

cal at 0.03 and 0.0326, respectively. However, if the prevalence is 50%, the false-negative rate and false-omission rate diverge to 0.15 and 0.233, respectively, creating clinically significant relative and absolute differences.

Moreover, let us assume the specificity is 99%. Based on Fagan's nomogram and a calculated negative likelihood ratio of 0.30, the post-test probability of disease at prevalence rates of 10% and 50% would be 0.03 and 0.23, nearly indistinguishable from the false-omission rates.

Second, precautions-laden inpatient units reduce the perceived COVID-19 prevalence among isolation precautions hospital rooms, caused by true diminishing marginal returns to incremental increases in testing that occur as a result of surveillance bias. There is a substantial literature on the psychology of false positives,[6] but little empirical evidence regarding cognitive processes surrounding false negatives. Despite this, previous literature shows that everyday human cognitive judgments follow the statistical principles of perception and reveal a close correspondence between implicit human probabilistic models and empiric statistical models.[7] Cognitive heuristics are operationalized based on predictive values and their complements, such that, in the same way that false-discovery rates drive alarm fatigue, false-omission rates are likely the principal psychological driver of precautions fatigue. The commonality of empiric statistics and psychologic processes is a rationale for using decrements in the false-omission rate as a quantitative measure of the contribution of incremental testing to diagnostic yield.

RETURN TO THE CASE SCENARIO

Since false-omission rates are more dependent on prevalence than false-negative rates, they should be considered in COVID-19 liberation pathways. Practically, this means that, in addition to the well-recognized adverse effects of precautions,[8] decisions about liberating patients from COVID-19 precautions should consider the reduced clinical benefit of isolation if precautions fatigue causes noncompliance as an unintended consequence. Medical literature suggests that contact precautions are used more often than evidence warrants, which creates more harm than benefit.[8] A learning healthcare system should use the COVID-19 experience to incorporate the real impact of precautions fatigue into decision algorithms and clinical pathways.

Protection of hospital staff and limiting nosocomial transmission of COVID-19 are critical. However, overuse of special precautions in patients unlikely to have true disease can lead to precautions fatigue that diminishes vigilance among staff, thereby vitiating the value of isolation. Hospital leadership should assertively select patients for testing and re-testing, considering that precautions fatigue markedly reduces the average effectiveness of precautions for all isolation rooms.

DISCLOSURES

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A patient with breast cancer and a rash on her hands and feet

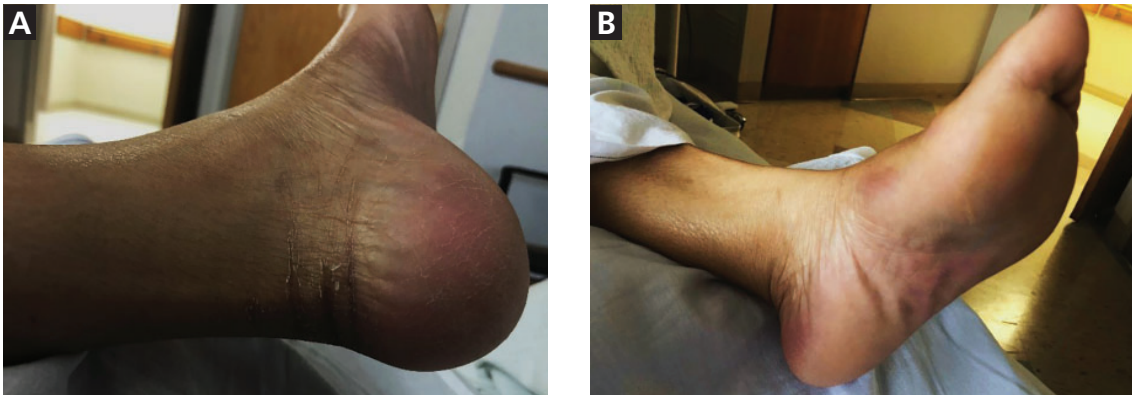

Figure 1. Erythema and skin desquamation on the heel (A), and patchy erythema over the plantar and lateral foot (B).

Treatment strategy: chemotherapy interruption, longer intervals between treatments, and dose reduction

A 56-year-old woman with invasive triple receptor-positive ductal carcinoma of the breast presented with persistent vomiting, diarrhea, and abdominal pain. She had completed her third cycle of docetaxel, carboplatin, trastuzumab, and pertuzumab chemotherapy 3 days earlier.

She was afebrile, her pulse rate was 126 beats per minute, and her blood pressure was 121/66 mm Hg. Her abdomen was diffusely tender without rebound or guarding.

Laboratory testing revealed a white blood cell count of 4.3×10^9/L (reference range 4.0–11.0 × 10^9/L) and normal serum electrolyte levels.

She was admitted for chemotherapy-related intractable vomiting and diarrhea and was started on intravenous fluids and symptomatic management.

On hospital day 4, she reported burning pain in her left foot. Examination revealed erythema over the plantar surface of the left foot, with pain worsened by palpation and ambulation. She remained afebrile and was started on cefazolin for empiric treatment of cellulitis in the setting of an immunosuppressed state.

Over the next 2 days, the pain progressed to include both hands and feet. Examination showed erythema involving the plantar, lateral, and calcaneal regions of both feet with mild skin desquamation (**Figure 1**). Also noted were erythema of the palmar surface of the hands and onychomelanosis (**Figure 2**). Antibiotics were stopped. The oncology service deemed these symptoms as hand-foot syndrome secondary to docetaxel treatment. The patient's gastrointestinal symptoms improved, and 2 days after the antibiotics were stopped, she was discharged with emollients for her hands and feet.

HAND-FOOT SYNDROME

Hand-foot syndrome is a cutaneous adverse effect of cytotoxic chemotherapy. It can present as palmar-plantar dysesthesia manifested as tingling and burning pain followed by an erythematous rash, dry skin, desquamation, or

doi:10.3949/ccjm.88a.20020

ulceration of the palms of the hands and soles of the feet 2 to 12 days after chemotherapy.[1]

Pathophysiologic mechanisms include rapidly dividing skin cells, gravitational forces, anatomic abundance, and dilation of blood vessels in these areas, as well as increased drug concentration in the eccrine glands of the palms and soles.[1,2]

Chemotherapy agents associated with hand-foot syndrome include 5-fluorouracil, liposomal doxorubicin, docetaxel, and capecitabine.[1] Docetaxel in particular has been reported to cause the syndrome when used as a single chemotherapeutic agent.[3,4]

The risk of developing hand-foot syndrome appears to depend on peak drug concentration and total cumulative dose. Therefore, a major treatment strategy is to interrupt the chemotherapy, lengthen the interval between treatments, and reduce the dose. Other options include cold compresses, leg elevation, topical or systemic steroids, creams, and pyridoxine.[1,2]

Clinicians should keep in mind that hand-foot syndrome can mimic other common conditions such as erythromelalgia, chemotherapy-induced Raynaud phenomenon, erythema multiforme, infection (cellulitis, erysipelas), and other drug reactions.[5]

Although the syndrome is self-limiting, it can have a significant negative impact on quality of life due to pain and limitation in daily activities.[2] Because it is directly related to dose or duration of drug administration and can recur with subsequent exposure, chemotherapy dose modifications may be needed.[2]

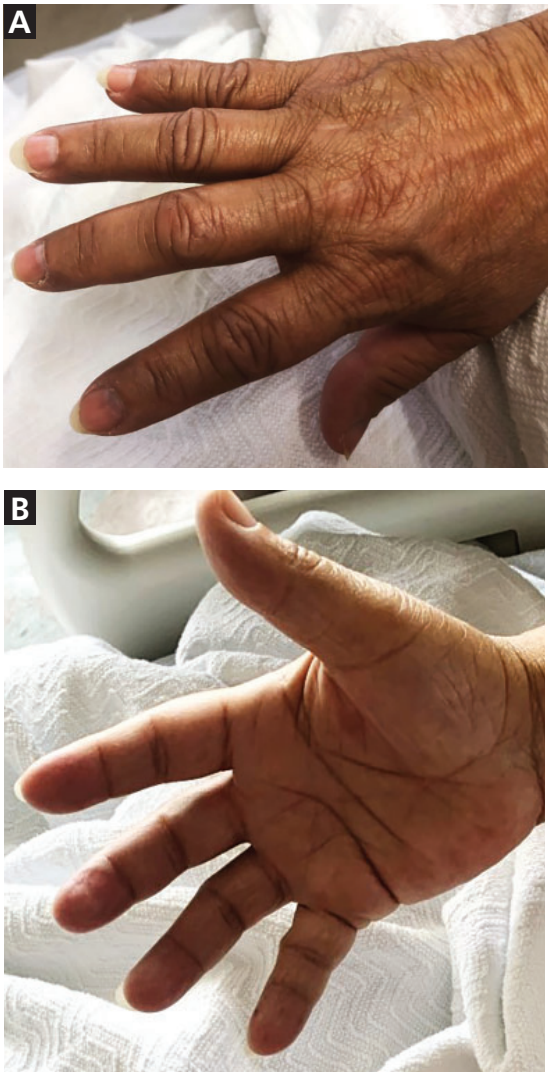

Figure 2. Note the violaceous nailbed of the second digit (onychomelanosis) (A), with patchy erythema prominent over the hypothenar eminence (B).

TAKE-HOME POINTS

In patients on chemotherapy, clinicians need to be aware of hand-foot syndrome in the differential diagnosis of extremity pain and erythema, its implications for quality of life, and available treatment options. Hand-foot syndrome is self-limiting and can be managed supportively together with chemotherapy interruption, interval lengthening, and dose reduction.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Cryptosporidiosis in an immunosuppressed patient with persistent diarrhea

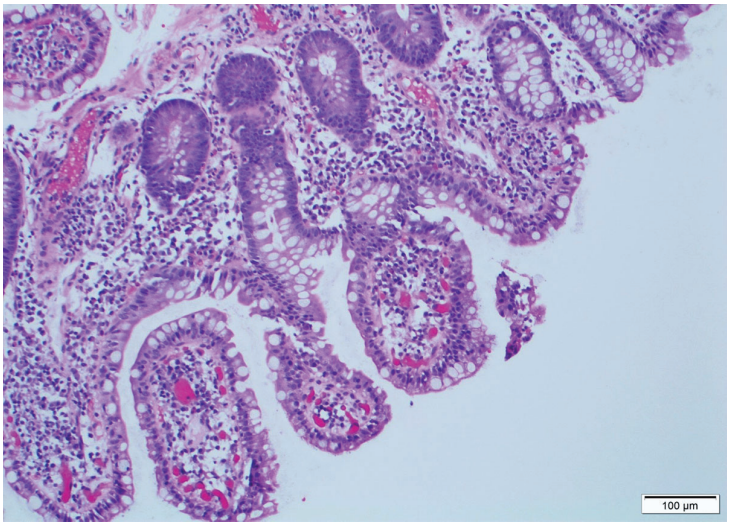

Figure 1. Hematoxylin and eosin stain of terminal ileum biopsy (scale bar 100 µm) revealed marked increased lymphoplasmacytic infiltrate in the lamina propria, with villous blunting.

A 29-year-old woman receiving immunosuppressants for bilateral lung transplant performed 14 years earlier because of a surfactant protein C deficiency presented with a 1-month history of worsening watery diarrhea, nausea, vomiting, abdominal cramping, and subjective fevers. She said she had no hematochezia, hematemesis, suspicious food intake, recent contact with sick people, or family history of inflammatory bowel disease.

Her medications included tacrolimus, mycophenolate, and low-dose prednisone with no recent dosage adjustments. Her most recent tacrolimus level, measured 3 months earlier, was 8.8 ng/mL (reference range 10–20 ng/mL), and her average absolute lymphocyte count was 4.78×10^9/L (reference range 1.18–3.74×10^9/L). The physical examination was unremarkable except for mild generalized abdominal tenderness and signs of dehydration.

doi:10.3949/ccjm.88a.20016

INVESTIGATING THE CAUSE

The patient was admitted for intravenous fluid administration and diarrhea workup. The differential diagnosis included a broad array of typical and opportunistic gastrointestinal infections, especially those with a higher incidence in immunosuppressed hosts, including parasites (eg, *Giardia*, *Cryptosporidium*), bacteria (eg, *Clostridioides difficile*, *Campylobacter*), and viruses (eg, cytomegalovirus). Noninfectious causes including medication toxicity, immunologic reactions, inflammatory bowel disease, and malignancy also were considered.

Results of the complete blood cell count were normal. Her aminotransferase levels were mildly elevated, with an alanine aminotransferase of 60 U/L (reference range 6–55 U/L) and aspartate aminotransferase of 41 U/L (reference range 5–34 U/L); alkaline phosphatase and total bilirubin levels were normal. Her tacrolimus level was 16.2 ng/mL. A quantitative cytomegalovirus DNA test was negative.

Stool tests for fecal leukocytes, ova and parasites, *C difficile* toxin (using a polymerase chain reaction test), Shiga toxins, *Giardia* antigen, and pancreatic fecal elastase were normal. The fecal calprotectin level was 189 µg/g (reference range 0–120 µg/g).

Further workup

Abdominal computed tomography with contrast enhancement showed no acute intra-abdominal abnormalities.

The patient underwent upper endoscopy and colonoscopy, with normal findings. Multiple biopsies were taken, including some of the terminal ileum. Results showed nonspecific villous blunting (**Figure 1**) and many mucosal apical basophilic circular-shaped organisms with epicellular invasion and marked increased lymphoplasmacytic infiltrate in the lamina propria (**Figure 2**). All of these are consistent with cryptosporidiosis.

Stool sample immunofluorescent assays for *Cryptosporidium* oocyst antigens later confirmed the diagnosis of cryptosporidiosis.

CRYPTOSPORIDIOSIS

Cryptosporidium parvum and *Cryptosporidium hominis* are unicellular parasites that usually cause self-limited diarrhea in immunocompetent hosts; however, they can cause life-threatening diarrhea in immunocompromised patients, especially those with impaired cell-mediated immunity or interferon-gamma production.[1]

The pathophysiology of diarrhea remains unclear. Theories suggest a combination of malabsorption and secretory diarrhea secondary to mucosal attachment, villous architecture distortion, epicellular invasion, inflammatory response, and cellular apoptosis.[1–2] *Cryptosporidia* can also involve the biliary system by spreading through the intestinal lumen.

Direct immunofluorescence and polymerase chain reaction testing are the most sensitive and specific diagnostic tests for cryptosporidiosis.[3] Although routine stool examination for ova and parasites remains the simplest and most widely available test, its sensitivity is limited by low levels of oocyst shedding and variable microscopic expertise.

In general, microscopy of tissue biopsies from the gastrointestinal tract is limited by the patchy distribution of infection; however, it was the key to the diagnosis in our patient.

Therapy in immunocompromised patients, other than those with human immunodeficiency virus infection, involves reducing the dose of immunosuppressive therapy and initiating dual antibiotics.[4]

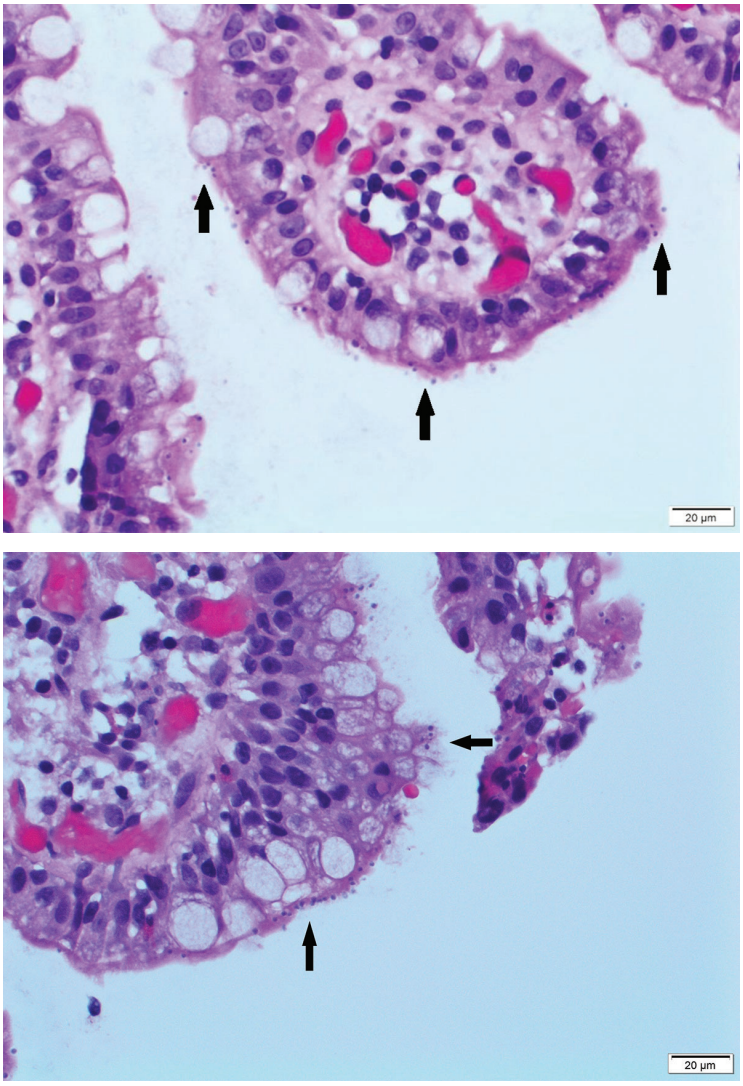

Figure 2. Hematoxylin and eosin stain of terminal ileum biopsy (scale bar 20 µm) revealed many mucosal, apical, basophilic, circular-shaped organisms, with epicellular invasion (black arrows).

We treated our patient with 14 days of nitazoxanide 500 mg twice daily and azithromycin 500 mg daily and reduced her mycophenolate dose, and her symptoms resolved. ■

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Perioperative management of pregnant women undergoing nonobstetric surgery

ABSTRACT

Nonobstetric surgery during pregnancy should be avoided if possible, but when surgery is required, an obstetrician should be part of the perioperative team. In general, preoperative assessment is similar regardless of whether a woman is pregnant, but cardiovascular, pulmonary, hematologic, and renal changes of pregnancy can increase surgical risk and must be taken into account. Special management considerations include pregnancy-associated laboratory changes, timing of surgery, anesthesia choice, intubation precautions, patient positioning, preoperative blood typing, intraoperative fetal monitoring, and venous thromboembolism prophylaxis.

KEY POINTS

Surgery increases the risk of complications in pregnancy, including preterm delivery.

Surgery that cannot wait until after delivery should be conducted during the second trimester, if possible.

During surgery, pregnant women should be placed in the left lateral tilt position at 30° to avoid vena cava compression.

Neuroaxial anesthesia is preferred if possible.

Low-molecular-weight heparin in prophylactic doses is recommended perioperatively to prevent venous thromboembolism.

doi:10.3949/ccjm.88a.18111

Important physiologic changes take place during pregnancy that optimize maternal and fetal outcomes but increase risk during surgery. Accommodating normal changes and identifying and managing risk factors should guide perioperative planning.

This article reviews physiologic changes in pregnancy, implications for perioperative management of nonobstetric surgery, and practical notes for clinical management.

NONOBSTETRIC SURGERY IN PREGNANCY IS RARE AND RISKY

From 0.2% to 2.0% of pregnant women undergo nonobstetric surgery.[1,2] In order of frequency, the most common procedures are appendectomy, cholecystectomy, adnexal surgery (for torsion or masses), trauma repair, small-bowel obstruction surgery, and breast surgery.[2–4]

The American College of Surgeons National Surgical Quality Improvement Program reported a postoperative complication rate of 5.8% in pregnancy. Complications included reoperation within 30 days (3.6%), infections (2%), wound problems (1.4%), respiratory complications (2%), thromboembolic complications (0.5%), transfusion requirements (0.2%), and death (0.25%).[4]

A study of 5,591 pregnant women in Taiwan[5] found that the rates of the following postoperative complications were higher than among nonpregnant women:

- Sepsis (odds ratio [OR] 1.75, 95% confidence interval [CI] 1.47–2.07)
- Pneumonia (OR 1.47, 95% CI 1.01–2.13)

TABLE 1

Benign cardiovascular findings in pregnancy

Physical examination
Increased intensity of arterial pulses
Cephalic and lateral displacement of the point of maximum impulse
Prominent splitting of the second heart sound
Systolic murmur in the pulmonary and tricuspid areas
Enhancement of preexisting murmurs
Systolic-diastolic murmur heard over 1 or both breasts ("mammary souffle")[10]
Electrocardiogram
Left axis deviation
Left atrial dilatation
Q-wave and T-wave inversion in III
Q wave in aVF
T-wave inversion in V_1, V_2, and V_3

Preterm delivery is a common and feared complication of surgery

- Urinary tract infection (OR 1.29, 95% CI 1.08–1.54)
- Death (OR 3.94, 95% CI 2.62–5.92).

One of the most common and feared complications from the obstetric perspective is preterm delivery. In a series of 86 pregnant women who underwent nonobstetric surgery in 1992 through 2014, the rate was 41% despite low rates of intraoperative and immediate postoperative complications.[6]

CARDIOVASCULAR CONSIDERATIONS

Pregnancy affects the cardiovascular system in several ways that are important to understand. The leading cause of pregnancy-related death in the United States is cardiovascular disease, with 17.2 deaths per 100,000 live births in 2015.[7] Pregnancy can unmask underlying congenital cardiac disease or an undiagnosed cardiomyopathy.[8]

Increased blood flow, vasodilation

In pregnancy, cardiac output increases by 40% due to an increase in plasma volume (which also leads to dilutional anemia), the basal heart rate increases by 10%, and vasodilation leads to a 10- to 20-mm Hg reduction in systemic blood pressure.[9] These changes lead to an increased hypotensive response to both general and spinal anesthesia.[2]

Cardiovascular examination reveals multiple signs of increased blood flow (**Table 1**).[10]

Note. A persistent third heart sound (gallop) or any diastolic murmur is abnormal and warrants immediate assessment.[2]

Special cardiovascular assessment not usually needed

American Heart Association and American College of Cardiology 2014 guidelines for preoperative cardiac evaluation for noncardiac surgery advise the same approach for pregnant and nonpregnant patients.[11] Obstetric patients rarely need cardiovascular diagnostic studies.

Several electrocardiographic changes (**Table 1**) can be attributed to heart elevation by the enlarged uterus and to increased blood volume.[12]

Echocardiography can be safely used in pregnancy.[13] Its indications are to assess underlying congenital heart disease, heart valve disorders, a new nonphysiologic murmur, or a third or fourth heart sound.[14]

Note. For pregnant women with heart disease, the CARPREG (Cardiac Disease in Pregnancy) II index is useful for preoperative evaluation (**Table 2**).[8]

RESPIRATORY CONSIDERATIONS

The growing uterus pushes up on the diaphragm, restricting the lungs and reducing functional residual capacity by about 20% when the patient is upright and 50% to 70% when recumbent.[15,16] Minute volume and tidal volume increase during pregnancy by about 35%, predisposing patients to respiratory alkalosis.[17] Thus, one would expect faster induction with inhalation anesthesia.[2]

Despite the expected pulmonary changes associated with pregnancy, tachypnea should be regarded as unusual and warrants formal assessment. If the patient suddenly begins breathing rapidly, evaluate for pulmonary embolism.[17]

TABLE 2

Cardiac Disease in Pregnancy (CARPREG) II risk index

Predictor	Points
History of cardiac events or arrhythmia	3
Baseline New York Heart Association class III/IV or cyanosis	3
Mechanical heart valve	3
Decreased ventricular function	2
History of mitral or aortic valve dysfunction	2
Pulmonary hypertension	2
Coronary artery disease	2
Aortic disease	2
Late pregnancy assessment	1
No previous intervention for existing cardiac problem	1

Score	Incidence of adverse cardiac events
0 or 1	5%
2	10%
3	15%
4	22%
> 4	41%

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Pulmonary preoperative assessment and optimization

Attempts to place an endotracheal tube fail in about 1 in 300 cases in pregnancy, a rate about 10 times higher than in the general population.[18,19]

Anesthesiologists should consider reduced functional residual capacity, possible increased airway edema, and reduced oxygen delivery secondary to the physiologic anemia of pregnancy as risk factors for hypoxemic respiratory failure.[2]

No formal guidelines have been published for preoperative pulmonary assessment in pregnancy. The most important purpose of assessment is to identify risks of a difficult airway and aspiration. The American Society of Anesthesiologists updated its general practice guidelines for managing difficult airways in 2003,[20] and Mhyre et al[21] proposed an algorithm in 2011 specifically for difficult intubations in obstetrics.

The 4-class Mallampati classification is used to assess the airway. Class 3 (ie, with the patient sticking out her tongue, the soft and hard palate and base of the uvula are visible but not the tonsils, or only the hard palate is visible) indicates increased likelihood that mask ventilation and endotracheal intubation will be difficult. For patients in this class, all airway protective measures should be taken.[21,22]

For patients who must be supine and in anticipation of periods of apnea (eg, before endotracheal intubation), supplemental oxygen should be used, and lung expansion maneuvers are strongly recommended to prevent atelectasis.[17,23]

In anticipation of a "difficult" airway, consider smaller endotracheal tubes and fiberoptic intubation.[2]

RENAL CONSIDERATIONS

Anatomic changes of a pregnant uterus cause some degree of urinary stasis and dilation of

Pregnancy can unmask underlying congenital cardiac disease or undiagnosed cardiomyopathy

TABLE 3

Changes in laboratory values in pregnancy

Laboratory test	Change in pregnancy	Implication
Serum creatinine and blood urea nitrogen	Decrease due to increased glomerular filtration	Nonpregnancy normal values may indicate developing renal failure
Urine protein	Hyperfiltration leads to proteinuria	Small increases are normal, but > 300 mg/24 hours may indicate preeclampsia
Alkaline phosphatase	Increases due to placental production	
Bilirubin and aminotransferases	Decrease	Nonpregnancy normal values of aminotransferases may indicate HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome
Thyroid-stimulating hormone	Decreases early, gradually normalizes	Free triiodothyronine and free thyroxine levels are stable and are better indicators of thyroid function than total values
Corticotropin and cortisol	Increase	Serum or salivary cortisol is not a reliable indicator of pathology

If the onset of tachypnea is sudden, evaluate for pulmonary embolism

the pyelocaliceal system, increasing the propensity to develop urinary tract infections.[2,24]

In addition, a 50% higher glomerular filtration rate and other pregnancy-associated changes may cause specific laboratory values to either increase or decrease, so it is important to be aware of the "pregnancy normal" (**Table 3**).[24–26] Increased plasma volume dilutes serum levels of albumin by an average of 1 mg/dL. This may cause serum calcium levels to decrease, although ionized calcium stays in the normal range.[26]

HEMATOLOGIC CONSIDERATIONS

In pregnancy, the red blood cell mass volume increases, but the plasma volume increases more, leading to dilutional anemia.[27] At the same time, pregnancy is associated with a 6- to 10-fold higher risk of deep vein thrombosis than in age-matched women.[28] This procoagulant state is attributed to increased production of clotting factors I, II, V, VII, VIII, X, and XII and a reduction of factors of the fibrinolytic system.[29]

Therefore, perioperative management should include prophylaxis against deep vein thrombosis[30] with low-molecular-weight heparin (LMWH) in prophylactic doses.[31,32]

Some obstetricians routinely switch anticoagulation from LMWH to unfractionated heparin after gestational week 37 in anticipation of labor or emergency cesarean delivery. However, the safety profile of LMWH is superior to that of unfractionated heparin in pregnancy, with lower risks of bleeding, heparin-induced thrombocytopenia, and heparin-associated osteoporosis.[33] In addition, several factors enhance the bioavailability of LMWH: it does not cross the placenta, it is less deactivated by tissue proteins owing to its smaller molecular size,[34,35] and its half-life and volume of distribution increase in pregnancy.[36]

Consider Rh blood type

If surgery entails risk of uterine trauma and maternal-fetal hemorrhage, the mother's blood group should be identified preoperatively.

If the mother is Rh-negative and the fetus is Rh-positive, the mother should be given anti-D immune globulin to minimize or prevent maternal-fetal isoimmunization.[37] In general, the American College of Obstetricians and Gynecologists[38] recommends giving prophylactic anti-D immune globulin to unsensitized Rh D-negative women at 28 weeks of gestation. After birth, in the case of Rh D-positive neonates, all confirmed unsensitized Rh D-negative women should receive anti-D

immune globulin within 72 hours of delivery (evidence level A).[38]

Anemia

The Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis consensus for management of anemia in pregnancy recommends administration of intravenous iron in patients with severe iron deficiency anemia (hemoglobin < 8 g/dL) or newly diagnosed iron deficiency anemia beyond 34 weeks of gestational age.[39] If the patient requires red blood cell transfusion, this should ideally not be influenced by arbitrary hemoglobin levels. In nonbleeding patients, red blood cell transfusion of a single unit can be considered when hemoglobin levels are less than 6 g/dL.

GASTROINTESTINAL CONSIDERATIONS

Gastroesophageal reflux is common in pregnant women owing to the growing uterus occupying more abdominal space, as well as progesterone contributing to slowing of gastric emptying time and reduced inferior esophageal sphincter tone.

Perioperative use of prokinetics, antacid medications, and reflux prevention strategies (eg, elevating the head of the bed at least 15°, fasting 8 hours) are recommended.[40] However, one should avoid enteral particulate antacids (ie, colloid suspensions containing aluminum or magnesium hydroxide), which increase the risk of pneumonitis if aspirated.[41]

Pregnant women should be considered to have full gastric content before surgery. If intubation is needed, a rapid sequence intubation protocol is indicated.[2]

Pregnancy causes several changes in liver function (**Table 3**).[40]

ENDOCRINE CONSIDERATIONS

Hormonal changes during pregnancy are critical to maternal and fetal homeostasis.[40] Changes occur in multiple systems, including the thyroid, and in glucose and adrenal metabolism.[42]

Human chorionic gonadotropin is structurally similar to thyroid-stimulating hormone (TSH), resulting in TSH suppression during the first trimester. Human chorionic gonadotropin peaks at the end of the first trimester, and TSH tends to normalize by the end of pregnancy. Free triiodothyronine and free thyroxine levels tend to remain stable throughout pregnancy, and their measurement is preferred to total hormone levels, given the dilutional decrease of circulating albumin and increase in thyroid-binding globulin.[42,43]

Pancreatic islet cells tend to hypertrophy, resulting in higher serum insulin levels that contribute to hypoglycemic episodes in early pregnancy. However, placental growth and increased secretion of placental lactogen increase insulin resistance, which may contribute to gestational diabetes in genetically predisposed patients.[40]

The pituitary tends to enlarge by about one-third during pregnancy, although this almost never leads to symptoms of optic chiasm compression. Prolactin levels increase progressively throughout pregnancy, enabling milk production.[42]

The placenta also produces corticotropin-releasing hormone, which increases the production of corticotropin and cortisol. It may be difficult to distinguish whether increased serum or salivary cortisol indicates a normal or pathologic state.[44]

GENERAL PERIOPERATIVE CONSIDERATIONS

Timing of surgery

Elective surgery should be postponed until after delivery, but urgent procedures necessary to save a patient's life should be pursued regardless of pregnancy stage.[45]

Although patients can be reassured that anesthetic gases do not appear to be teratogenic, surgery during the first trimester may affect the rest of the pregnancy.[23] The third trimester poses the highest risk for both mother and fetus; at that time, surgery becomes more technically difficult, and the fetus's higher perfusion needs increase the risk of fetal hypoxia.

If there is a choice, the second trimester is the best time to undergo necessary surgery.

Include an obstetrician on the team

The American College of Obstetricians and Gynecologists and the American Society of Anesthesiologists recommend involving an obstetric specialist to help assess and manage pregnant women requiring any surgical or in-

Risk of failed endotracheal intubation is about 10 times higher in pregnancy

vasive procedure. An obstetric care provider with cesarean delivery privileges and a pediatric or neonatologist team should be available during the procedure.

Minimally invasive is best

Particularly for patients needing abdominal surgery, a laparoscopic approach is preferred to reduce risk of fetal complications.[46,47]

Avoid supine positioning

During the second and third trimesters of pregnancy, the uterus compresses the inferior vena cava when the patient lies flat, reducing venous return by about 30%, with a consequent decrease in cardiac output and placental perfusion. For these reasons, patients should lie on their side during surgery.[48] In a study using magnetic resonance imaging,[49] the maximum aortocaval decompression was achieved with a left-lateral tilt position of 30°.

The anesthesiologist should place the patient in a 30° left lateral decubitus position and maintain normovolemia, oxygen saturation greater than 95%, and normal arterial pressure of carbon dioxide.[45,50]

Preoperative diagnostic tests

A persistent third heart sound (gallop) or any diastolic murmur is abnormal

The most commonly required tests include hematocrit and preoperative blood type and antibody screen. Otherwise, routine preoperative testing is not justified for most patients with no active systemic comorbidity.[23,51] The need for other studies is based on risk factors and predisposing conditions.[2,12,52]

Fetal monitoring

Viable fetuses older than 23 weeks gestational age (or > 22 weeks in some centers) should have continuous monitoring and simultaneous contraction activity monitoring throughout any surgical procedure.

ANESTHESIA CONSIDERATIONS

Identifying risk factors for complications associated with induction of anesthesia is paramount. In addition to a physical assessment, clinicians should ask about personal and family history of bleeding disorders, coagulopathy, and complications related to anesthesia (eg, malignant hyperthermia).[23]

Risk of anesthetic morbidity and mortality in pregnancy are most associated with airway edema, restrictive lung physiology, and aspiration.[53] Other risk factors are eclampsia or preeclampsia, postpartum shock, pulmonary embolism, obesity, uncontrolled arterial hypertension, and emergency surgery.[54,55]

Increasing use of regional anesthesia instead of general anesthesia[56] during delivery has led to reduced mortality. Hawkins et al[57] found a 59% reduction (from 2.9 to 1.2 deaths per million patients) in anesthesia-related maternal mortality in the years 1991 to 2002 compared with 1979 to 1990. The relative risk of death during general anesthesia decreased from 6.7 before 1996 to 1.7 after that year. The improvements were associated with reduction in general anesthesia, as regional anesthesia rates increased during that time.

Neuraxial anesthesia preferred

Neuraxial anesthesia is preferred if possible. However, specific changes in the central nervous system affect neuraxial anesthesia during pregnancy. Epidural vein engorgement and reduced epidural-space volume increase the spread of epidurally injected local anesthetics and also the risk of a bloody spinal tap.[2]

Anticoagulation considerations for neuraxial anesthesia are similar in pregnant and nonpregnant patients. Before performing a neuraxial procedure, it is recommended to wait at least 12 hours (for prophylactic dosages) and 24 hours (for full anticoagulation dosages) after administering the last dose of LMWH, and 6 hours after an unfractionated heparin infusion.[31]

Aspirin use

Surgery may proceed for patients treated with low-dose aspirin. The Collaborative Low-Dose Aspirin Study in Pregnancy[58] did not find increased bleeding risk in patients taking aspirin with spinal anesthesia, although they did find a nonsignificant increase in the need for allogeneic blood transfusion. A randomized comparison of aspirin against placebo found no association of low-dose aspirin during pregnancy with epidural anesthesia complications.[59]

TAKE-HOME POINTS

The perioperative assessment of the pregnant patient undergoing surgery is similar to that of the nonpregnant patient; however, the physi-

ologic changes of pregnancy must be taken into consideration.

Diagnostic and therapeutic decisions should not neglect the mother and not withhold needed care for her with the purpose of protecting the fetus.

It is preferred to wait until the postpartum period for any elective surgery. However, if surgery is necessary, it can best be done during the second trimester. Emergency surgery should be pursued regardless of the gestational age. The preferred approach for abdominal surgery is by laparoscopy.

The preferred anesthetic approach is neuroaxial anesthesia if possible.

Close communication among the internist, obstetric-gynecology specialist, and anesthesiologist is paramount to optimize the resources and clinical outcomes of the surgical obstetric patient.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Prescribing testosterone and DHEA: The role of androgens in women

ABSTRACT

In women, the androgens testosterone and dehydroepiandrosterone (DHEA) play important physiologic roles in reproductive tissues, mood, cognition, the breast, bone, muscle, vasculature, and other systems. This article reviews the effects of androgens in women, as well as the indications and best-practice recommendations for the use of androgen therapy.

KEY POINTS

Currently, the only evidenced-based indication for testosterone therapy in women is for treating hypoactive sexual desire disorder in postmenopausal women. Several randomized controlled trials have established the short-term safety and efficacy of prescribed testosterone in women when doses approximate physiologic levels.

When treatment is offered, transdermal preparations are preferred, and testosterone levels should be checked before and during treatment to ensure physiologic dosing. Decisions to continue treatment are based on clinical response; hormone levels do not correlate with symptom burden, and testing is intended only to ensure safe delivery of treatment.

Clinicians should avoid diagnosing female androgen deficiency on the basis of hormonal testing, as the syndrome is not well defined, and interpreting androgen levels and their physiologic effects is complex.

doi:10.3949/ccjm.88a.20030

Estrogens are the principal sex hormones responsible for female reproductive maturation and sexual characteristics. However, androgens are also important for female sexual health and well-being.[1] The physiologic effects of androgens are in part due to their role as precursors for estrogen synthesis, but these hormones also have independent effects on female reproductive tissues, mood, cognition, breasts, bones, muscles, vasculature, and other systems.[1]

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Here we will discuss the physiologic roles of androgens as well as the indications and best-practice recommendations for androgen therapy in women.

ANDROGEN SYNTHESIS, PRODUCTION, AND MEASUREMENT IN WOMEN

The biologically active androgens in women are dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and dihydrotestosterone.

In women, roughly 25% of androgen production occurs in the adrenal glands, 25% occurs in the ovaries, and the rest occurs peripherally.[2] DHEA-S, DHEA, and androstenedione are the main prohormones that are peripherally converted to the active androgens testosterone and dihydrotestosterone. DHEA-S is almost exclusively produced in the adrenal glands, whereas DHEA, androstenedione, and testosterone are produced in the adrenal glands and ovaries and by peripheral conversion. In target tissues, circulating testosterone is converted to dihydrotestosterone by 5-alpha-reductase and aromatized to estradiol.

TABLE 1

Conditions that affect circulating levels of sex hormone-binding globulin (SHBG)

Decrease SHBG (increase free [active] testosterone)
Obesity
Exogenous androgen therapy
Insulin
Glucocorticoids
Increase SHBG (decrease free [active] testosterone)
Pregnancy
Exogenous estrogen therapy
Liver cirrhosis
Hyperthyroidism

Androgen levels decline with age throughout a woman's life, starting in her mid-30s.[3] Menopause is not associated with a rapid decline in androgen production; the postmenopausal ovary is hormonally active and accounts for 40% to 50% of postmenopausal testosterone production.[4,5] Consequently, women who have undergone bilateral oophorectomy have a marked decrease in circulating testosterone levels, though serum concentrations of DHEA and androstenedione remain stable due to adrenal compensation.[4] Ten years after the onset of menopause, circulating testosterone and androstenedione levels are half of perimenopausal levels.[6]

The effects of sex steroids on the cardiovascular system are not fully understood

In circulation, active testosterone is free or bound to albumin. Testing of total testosterone levels also measures inactive testosterone, which is bound to sex hormone-binding globulin (SHBG), a liver-synthesized protein with a high affinity for sex steroids. Conditions that increase or decrease SHBG inversely affect circulating levels of free (active) testosterone (**Table 1**).

Peripheral conversion of precursor hormones to active testosterone is tissue-specific and depends on membrane and cellular receptor expression as well as activity of converting enzymes.[1] Measured serum testosterone concentrations do not correlate with peripheral tissue androgen production or tissue receptor sensitivity. Therefore, androgen effects on body tissues are complex, and there is no absolute testosterone level that defines "androgen deficiency." Low serum testosterone levels in women should be interpreted with caution.

Liquid or gas chromatography and tandem mass spectrometry assays are reliable and accurate laboratory methods for measuring total testosterone and give reproducible results. In contrast, direct radioimmunoassays for measuring testosterone are considerably less accurate.[7] Salivary assays are neither sensitive nor specific and are not recommended for clinical use.[2] Serum DHEA-S is the most reliable measure of adrenal androgen production.[1]

ANDROGEN EFFECTS IN WOMEN

Cardiometabolic

The effects of sex steroids on the cardiovascular system are not fully understood. Similar to the vascular benefits of estrogen during the premenopausal years (promoting vasodilation, limiting atherosclerotic plaque progression, reducing inflammation),[8,9] testosterone acts directly on the vasculature in a concentration-dependent fashion, and indirectly after being converted to estradiol. At physiologic levels, testosterone enhances nitric oxide production and influences both potassium and calcium ion channels, leading to vasorelaxation.[8] Low testosterone levels have been associated with unfavorable cardiovascular outcomes.[8] However, testosterone promotes vasoconstriction at supraphysiologic levels.[8]

A prospective study of over 2,800 postmenopausal women showed that a higher testosterone-to-estrogen ratio correlated with a higher risk of heart failure and coronary heart disease, whereas higher levels of estrogen seemed to have a protective effect.[10]

The effects of exogenous testosterone on the cardiovascular system have been investigated in prospective, randomized controlled trials, though these trials have typically been of limited duration (less than 2 years). Most of them showed no increase in adverse cardiovascular events with testosterone therapy as long as testosterone levels remained within normal physiologic ranges,[8,9,11] but most of them excluded women at high risk of cardiovascular disease.[7]

Meta-analyses have shown that, compared with placebo, oral testosterone is associated with an increase in low-density lipoprotein cholesterol and decreases in high-density lipoprotein cholesterol and triglycerides,[12–14] though transdermal testosterone therapy has neutral effects on the lipid profile.[12] Testosterone therapy (oral or transdermal) does not significantly affect glycemic markers, blood pressure, body mass index, or hematocrit when serum testosterone levels remain within normal physiologic ranges.[7,12]

A nonsignificant increase in risk of venous thromboembolism has been reported; however, concurrent estrogen use may be a factor.[7]

Skin and hair

Dihydrotestosterone, converted from testosterone by 5-alpha-reductase, is the most potent androgen acting on hair follicles.[15] In the scalp, dihydrotestosterone promotes miniaturization of hair follicles and shortens the antigen phase of hair growth, leading to hair loss.[15]

Women with female pattern hair loss tend to have higher androgen-to-estrogen ratios. Activation of androgen receptors at hair follicles on the chin, cheeks, and upper lips leads to coarse hair growth or hirsutism.[16] In women with polycystic ovary syndrome, hirsutism may be related to excess ovarian testosterone production, whereas most women with idiopathic hirsutism have normal serum androgen levels, suggesting exaggerated 5-alpha-reductase activity.[16] A meta-analysis found the risk of hirsutism to be 10.7% in women on testosterone therapy compared with 6.6% with placebo ($P = .011$).[14]

Androgens stimulate the growth and secretory function of sebaceous glands, leading to increased sebum production, in turn providing a growth medium for *Cutibacterium acnes*.[15] Although most women with acne have normal serum androgen levels, a meta-analysis reported the risk of acne to be 7.0% in women on testosterone therapy vs 4.7% with placebo ($P < .001$).[14]

Cognition and mood

The brain, like many organs, is affected by ovarian hormone withdrawal. Studies have shown that both estrogen and testosterone have anti-inflammatory and neuroprotective effects on the brain.[17] There are androgen receptors throughout the central nervous system, with actions that affect sexual desire, thermoregulation, cognition, sleep, visual spatial skills, and language.[16] A review of the protective effects of sex steroids on Alzheimer disease suggests that testosterone reduces oxidative stress and accumulation of amyloid beta within the brain and accelerates nerve regeneration.[17]

Though most women going through menopause do not have major cognitive changes, some have changes that significantly affect their quality of life; this may be especially concerning to young women undergoing oophorectomy.

Only a few randomized controlled trials have evaluated the effects of testosterone treatment on cognition, and they are limited by small sample size and, in some trials, by concurrent estradiol therapy. That said, the available data do not suggest any negative effects of testosterone therapy on cognition, well-being, or mood in postmenopausal women.[13,17,18]

Davis et al[19] found that postmenopausal women taking transdermal testosterone gel 300 µg/day for 26 weeks and not taking other hormonal therapies showed significant improvement in verbal learning and memory but not well-being. Huang et al,[18] in a randomized controlled trial in hysterectomized women (with or without oophorectomy) found that intramuscular testosterone therapy at physiologic and supraphysiologic doses with concurrent transdermal estradiol did not affect cognitive function.

There is no absolute testosterone level that defines 'androgen deficiency'

Musculoskeletal

Androgen receptors are present on osteoblasts. Low endogenous androgen levels in menstruating and postmenopausal women have been associated with low bone mass and increased risk of vertebral and hip fractures.[20,21] Conversely, higher free testosterone levels in postmenopausal women have been associated with lower hip fracture risk.[22] However, lacking randomized controlled trials to assess the effect of testosterone therapy on fracture risk, the use of androgens for bone health and fracture prevention cannot be recommended.

The Testosterone Dose Response in Surgically Menopausal Women trial was a multicenter, double-blind, placebo-controlled trial

TABLE 2

Conditions that cause a low androgen state in women

Decreased ovarian androgen production
Chemotherapy
Radiation
Ovarian failure or insufficiency
Oophorectomy

Decreased adrenal androgen production
Adrenal insufficiency

Hypothalamic-pituitary axis
Malnutrition
Anorexia
Hypopituitarism

Medications
Corticosteroids
Hormonal contraceptives
Antiandrogenic agents
Oral estrogen therapy
Opioids

of testosterone in hysterectomized women with or without oophorectomy, after a 12-week run-in period of transdermal estradiol administration. Testosterone recipients demonstrated improved lean body mass and muscle performance in a dose-dependent fashion, with women on supraphysiologic doses having the most improvement compared with placebo.[23]

In contrast, other studies have found neutral effects on lean body mass, total body fat, or muscle strength when testosterone is given at physiologic doses.[7] It is difficult to draw definitive conclusions, given that the studies were typically small and were conducted in women on concomitant estrogen therapy.

The Endocrine Society recommends against diagnosing 'female androgen deficiency'

Breast and endometrium

Breast tissue has abundant levels of aromatase; thus, in theory, testosterone may have indirect proliferative effects on the breast by being converted to estrogen. However, in vitro breast cultures and in vivo primate studies demonstrate that testosterone's effects on breast tissue is antiproliferative and proapoptotic, with inhibition of estrogen receptor alpha as well as breast cancer cell growth.[24] These effects largely depend on the type and dose of androgen therapy as well as the breast cancer cell line.[25]

A recent systematic review and meta-analysis found no change in breast density after testosterone therapy.[12] In addition, short-term testosterone therapy was not associated with any of the following adverse effects: breast pain, tenderness, engorgement, masses, or breast cancer.[13]

In an open-label study of transdermal testosterone 300 µg daily, 900 surgically menopausal women, ages 20 through 70, were followed for up to 4 years.[26] Three cases of invasive breast cancer were reported in that time, consistent with population background rates of breast cancer.

Androgen therapy poses a theoretical risk of endometrial hyperplasia; however the risk is likely very low at physiologic levels because levels of endometrial aromatase expression are low. Early studies have shown no evidence of endometrial stimulation with androgen therapy in postmenopausal women.[1]

SHOULD WOMEN BE SCREENED FOR LOW ANDROGEN LEVELS?

Symptoms of "female androgen insufficiency" have been popularly described as including sexual dysfunction, chronic fatigue, dysphoric mood, and diminished sense of well-being. However, low serum androgen levels do not reliably correlate with a clinically defined syndrome. Even among oophorectomized women, a decline in serum testosterone level does not consistently correlate with clinical symptoms.[27] Lack of congruency among current laboratory assays also limits the development of biochemical criteria to diagnose androgen insufficiency in women.

For these and other reasons, the Endocrine Society recommends against diagnosing "female androgen deficiency" or using testosterone to treat low androgen states in women.[28] There is no evidence to support testosterone therapy for female well-being, mood, vasomotor symptoms, bone health, cardiovascular health, or metabolic dysfunction.[8,27,29]

It is important to remember that numerous medical conditions and medications can result in low androgen levels in women (**Table 2**).

ROLE OF ANDROGEN THERAPY IN FEMALE SEXUAL HEALTH

The only evidence-based indication for testosterone therapy in women is to treat hypoactive

sexual desire disorder after menopause.[7,28,29] Currently, no testosterone formulation for women has been approved by the US Food and Drug Administration (FDA), though vaginal DHEA (prasterone) has been approved for treatment of moderate to severe dyspareunia.

Female sexual dysfunction

Female sexual dysfunction is multifactorial, often influenced by biologic, emotional, cultural, and interpersonal factors. It can manifest as decreased sexual desire, painful intercourse, and diminished arousal or orgasmic response, or both.

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[30] merged the previous diagnoses of female hypoactive sexual desire disorder (HSDD) and female arousal disorder (FAD) into a single diagnosis of *female sexual interest/arousal disorder* (FSIAD). While HSDD and FAD have overlapping features, the Fourth International Consultation on Sexual Medicine and the International Society of the Study of Women's Sexual Health (ISSWSH) recommend against combining these diagnoses for clinical purposes.[31,32] According to the ISSWSH, HSDD can be defined by 6 or more months of any of the following[32]:

1. **Lack of motivation for sexual activity,** including
   - Absent or decreased spontaneous sexual thoughts or fantasies
   - Absent or decreased responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity.
2. **Loss of desire to initiate or participate in sexual activity,** including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders and is combined with clinically significant personal distress that includes frustration, grief, incompetence, loss, sadness, sorrow, or worry.

Randomized controlled trials in postmenopausal women who reported decreased sexual desire have demonstrated that testosterone therapy positively influences sexual function, though none have defined target serum androgen levels that correlate with sexual function.[8,27]

Four 24-week randomized controlled trials in natural and surgically menopausal women with sexual dysfunction compared transdermal testosterone patches (300 µg/day) and placebo.[33–36] The patch significantly increased sexual desire and sexually satisfying events while decreasing sexual-related distress (in 3 of 4 studies) compared with placebo. In one study,[36] sexually satisfying events increased by 2.1 episodes per month with the transdermal patch compared with 0.98 with placebo ($P < .001$).

The safety and efficacy of the patch in postmenopausal women was also evaluated in the 52-week APHRODITE study (A Phase III Research Study of Female Sexual Dysfunction in Women on Testosterone Patch Without Estrogen).[37] Two doses, 150 µg/day and 300 µg/day, were compared with placebo. Significant improvements were noted in sexual desire and sex-related distress in both treatment groups (300 µg/day, $P < .001$, and 150 µg/day, $P = .04$). Adverse events were minimal, the most common being application-site reaction, acne, breast pain, headache, and hirsutism. All metabolic markers remained stable, including liver enzymes, serum lipids, complete blood cell counts, and metabolic panels.

Female sexual dysfunction is multifactorial

Many randomized controlled trials have shown insignificant changes in levels of total or free testosterone after treatment with the 300 µg/day transdermal testosterone patch.[27]

A transdermal testosterone spray was studied in a randomized controlled trial in women with FSIAD and low serum free testosterone. The self-reported frequency of satisfactory sexual events was greater with active treatment than with placebo.[38]

A 12-week, double-blind randomized controlled trial found improved well-being ($P = .003$), mood ($P < .06$), and sexual function ($P < .001$) in women receiving testosterone cream 10 mg/day compared with placebo.[39] During the study period, serum testosterone levels stayed in the high-normal range for postmenopausal women, and no adverse events were noted.

In contrast, 2 large phase 3 randomized controlled trials investigating transdermal testosterone gel 0.22 g/day in women with sexual dysfunction showed no statistically significant differences in sexually satisfying events or sexual desire between treatment and placebo

groups.[28] Inconsistencies between studies could be due to dosing and route of administration.

Comments. There is sufficient high-quality evidence to support letting postmenopausal women with HSDD try testosterone, for a short time, after other reasons for their sexual concerns have been excluded. Evidence is lacking to support the use of testosterone for sexual dysfunction in premenopausal women.

Before starting testosterone therapy for HSDD, all women should undergo a thorough medical and psychosocial assessment and physical examination. Other contributors to symptoms should be identified and addressed before starting testosterone therapy, including medication side effects, mood disorders, relationship concerns, or the genitourinary syndrome of menopause.

Though there is evidence of benefit, currently there are no approved testosterone formulations for women in the United States. Regulated, safe delivery methods are needed.

Systemic DHEA therapy has not been shown to improve symptoms of sexual dysfunction in women who have normal adrenal function.[7]

Before starting testosterone, women should undergo a thorough medical and psychosocial assessment

GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary syndrome of menopause (GSM), formerly known as vulvovaginal atrophy, is an umbrella term describing urinary, genital, and sexual dysfunction as a result of a decline in sex hormone levels. It affects up to 70% of postmenopausal women, and without treatment, symptoms tend to progress over time.[40] Common symptoms of GSM include dyspareunia, vaginal dryness and irritation, dysuria, urinary frequency, urinary urgency, recurrent urinary tract infection, and alkaline shift in vaginal pH.[39]

Nonhormonal therapies, such as vaginal moisturizers and lubricants, do not restore the integrity of genitourinary tissues. Hormonal therapies, including vaginal estrogen and DHEA, are safe and the most effective treatments for GSM.[38,39]

Androgen and estrogen receptors are present in the vaginal mucosa, submucosa, stroma, smooth muscle (vaginal, urethral, and bladder), and vascular endothelium. In the vagina, androgens regulate vaginal mucin production in epithelial cells, improve blood flow by increasing nitric oxide, and influence neurotransmitter content and nerve density.[41] There is a positive correlation between testosterone levels and volume of urethrovaginal tissue.[39]

DHEA therapy for GSM

The only FDA-approved vaginal androgen for GSM is intravaginal DHEA 6.5 mg (prasterone), which improves cell maturation, pH, and dyspareunia compared with placebo,[42] leads to improvements in all domains of sexual function,[43] and has neutral effects on the endometrium after 12 months of therapy.[44] Most studies suggest no significant increase in serum levels of sex steroids with the use of vaginal DHEA.[45] Women who have no history of estrogen-dependent cancers should be routinely offered treatment for GSM with vaginal estrogen or DHEA.

In a 12-week 3-armed randomized controlled trial,[46] postmenopausal women with a history of breast or gynecologic cancer, received compounded vaginal DHEA 3.25 mg/day, DHEA 6.5 mg/day, or a nonhormonal moisturizer. Dyspareunia and dryness improved in all groups, with no significant differences between either dose of vaginal DHEA and plain moisturizer ($P < .005$). However, women in the DHEA 6.5-mg/day group reported a significant improvement in sexual health compared with the other groups ($P < .0001$). (DHEA is currently not approved to treat sexual dysfunction.)

In a secondary analysis in breast cancer survivors,[45] serum DHEA-S and testosterone concentrations were significantly higher in both DHEA groups than in women using plain moisturizer, though levels remained within normal postmenopausal ranges. Serum estradiol levels were increased in the DHEA 6.5-mg/day group but not the DHEA 3.25-mg/day group. The subgroup of women concurrently taking aromatase inhibitors had no difference in serum hormone levels with vaginal DHEA compared with a plain moisturizer.

Testosterone therapy for GSM

Data on the safety and efficacy of testosterone therapy for treating symptoms of GSM are scant and results are inconsistent. Several studies suggest that vaginal testosterone im-

proves symptoms.[28] However, these studies are limited by small sample sizes, supraphysiologic serum levels, inconclusive efficacy and safety, and lack of power. More research demonstrating safety and efficacy is needed before clinical use is considered.

PRESCRIBING TESTOSTERONE THERAPY

Despite studies showing potential benefits in sexual health, no testosterone formulations for women have been approved for use in the United States for this indication. Short-term low-dose transdermal formulations are the preferred method of testosterone delivery for women, based on available safety data and side effect profiles. The twice-weekly 300-µg/day patch was previously approved in Europe; however, it is no longer available due to low sales.[27] This product was never approved in the United States.

Testosterone formulations available in the United States are indicated for use in men only, and clinicians should use caution when prescribing them to women. To avoid supraphysiologic dosing, women should be prescribed a tenth of the recommend male dose—or less. However, even when only 1 month's worth of a male product is prescribed, a patient will have a year's supply of medication, which increases the risk for supraphysiologic dosing if she applies the product more than recommended, and does not return to be assessed for safe blood levels. Compounded formulations are frequently used for women; however, these products are not subject to potency and purity regulations.

Topical products should be applied to the inner thigh, buttock, abdomen, or vulva to avoid transfer to contacts. The breast and arms should be avoided. We recommend use in an area that can be shaved, in case of increase in hair growth. Adverse events are limited when serum testosterone levels remain in physiologic ranges.

Oral testosterone undergoes first-pass metabolism in the liver and tends to be associated with more side effects and adverse events than other formulations.[13,14] For this reason, the most recent consensus statement discourages the use of oral testosterone.[8]

Oral combination esterified estrogen-methyltestosterone (EEMT) has been on the market since the 1960s. It was approved by the FDA on the basis of its safety before the current safety and efficacy requirements were enacted. The manufacturers have not sought reapproval. Oral EEMT is indicated for use in postmenopausal women with moderate to severe vasomotor symptoms not improved on estrogen alone. Two doses are available (estrogen 1.25 mg plus methyltestosterone 2.5 mg, and estrogen 0.625 mg plus methyltestosterone 1.25 mg), and short-term use is recommended. A 2003 postmarketing safety surveillance study revealed very few serious adverse events in women using EEMT between 1989 and 2002.[47]

If oral therapy is chosen, cardiometabolic risks should be assessed at follow-up visits. In addition, liver function tests should be monitored periodically.

Intramuscular and pellet therapies should be avoided. These options expose users to potential for prolonged exposure and supraphysiologic dosing.[8]

Monitoring during treatment

Once a decision to start systemic testosterone has been made, the Endocrine Society and the Global consensus position statement on the use of testosterone therapy for women recommend checking baseline testosterone levels before initiating therapy.[7,8,28] Levels should then be followed 3 to 6 weeks after therapy is initiated and every 6 months thereafter to avoid toxicity and supraphysiologic dosing.[28] Serum hormone levels do not correlate with clinical response, and measuring them is intended to ensure safe delivery of treatment. In contrast, women using vaginal DHEA should not have blood hormone levels checked, as the serum concentration of sex steroids is minimally affected by this route of administration.

The only FDA-approved vaginal androgen for GSM is intravaginal DHEA

The follow-up should focus on a clinical assessment of perceived risks vs benefits. The goals are to improve sexual desire, arousal, orgasmic function, pleasure, or sexual responsiveness, with a reduction in sexual concerns and distress. The treatment should be stopped in women who do not respond to therapy after 6 months of consistent use.

When hormone levels on treatment approximate the normal physiologic levels of a premenopausal woman, there is no significant

increased risk of alopecia, clitoromegaly, or voice changes.[8,28] However, these potential concerns should be reviewed with patients. Mild increases in acne or hirsutism may be seen. The risk of vaginal bleeding was increased in the users of the 300-µg/day patch, though no increased risk of endometrial hypertrophy was observed over 12 months.[28] Any woman with postmenopausal bleeding should undergo endometrial assessment, whether or not she is using hormonal therapies.

There is no indication to perform additional breast imaging, cardiac testing, or other laboratory tests. However, patients should be seen at least annually in clinic to ensure they are up-to-date with their preventive screenings. When serum testosterone levels remain in normal physiologic ranges, studies show that neither oral nor nonoral testosterone therapy significantly affects the lipid profile, glycemic markers, blood pressure, body mass index, or hematocrit.[7,13] No current evidence links physiologic-dose testosterone therapy with adverse cardiovascular events, though most studies followed patients for less than 5 years and excluded those considered at high risk for cardiovascular disease and breast cancer.[8,9,11] A recent meta-analysis showed that testosterone therapy was not associated with more serious adverse events than placebo or a comparator.[12]

TAKE-HOME POINTS

- Androgens play an important physiologic role in women and can promote sexual health.
- Clinicians should avoid making a diagnosis of androgen deficiency in women, as the syndrome is not well defined.
- Well-designed, randomized, placebo-controlled trials are needed to establish long-term safety, efficacy, and appropriate dosing of testosterone therapy in women.
- Evidence suggests that testosterone therapy in women is associated with few adverse events when serum hormone levels remain within physiologic ranges.
- Currently, the only evidence-based indication for testosterone therapy in women is for the treatment of HSDD in postmenopausal women, but only after a thorough evaluation and consideration of other causes of the sexual concerns.
- Transdermal therapy is the preferred method of delivery.
- Serum testosterone levels should be monitored at regular intervals to avoid supraphysiologic dosing

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Trials and tribulations of testosterone therapy in women: Importance of adhering to the evidence

Sexual health is an important part of women's lives. When sexual function is impaired, it can negatively affect quality of life, self-image, and relationship satisfaction and lead to poorer health outcomes.[1,2] As many as 43.1% of women of all ages report a sexual problem, with 12% of women having or reporting a distressing sexual problem.[2] A biopsychosocial approach is ideal for evaluating, diagnosing, and treating women who have sexual dysfunction.[3]

See related article, page 35

Testosterone should not be touted for improving energy, well-being, or other outcomes not supported by data

Testosterone treatment has been found to be effective in select postmenopausal women who are diagnosed with hypoactive sexual desire disorder (HSDD), which is characterized by low sexual desire causing distress.[4] However, no US Food and Drug Administration (FDA)-approved formulation of testosterone is available for women in the United States, due to its unknown long-term safety.

This has not stopped many physicians and other medical practitioners from prescribing custom-compounded or dose-reduced male products to women.[5] Some prescribers have shared partial truths through Internet-based marketing to support "bioidentical" testosterone as a "natural" hormone, free of risk and with unfounded benefits,[6] making it difficult for women to know whom to trust and where to go regarding their sexual health concerns.

In this issue of *Cleveland Clinic Journal of Medicine*, Smith and Batur[7] provide a comprehensive review of the effects of androgens in women, as well as clinically relevant best-practice recommendations for the use of androgens in women. They discuss the different types of endogenous androgens and how they interact with various biologic systems in women. They appropriately highlight how a state of "female androgen insufficiency" has not been established in women, such as exists for men, as low serum androgen levels do not reliably correlate with symptoms such as chronic fatigue or decreased mood in women. They also discuss the difficulty of accurately measuring testosterone levels, including pointing out that salivary testing is not recommended for clinical use.

doi:10.3949/ccjm.88a.20195

LABELS MATTER: DESIRE VS AROUSAL

Nomenclature from the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* specifies the category of female sexual dysfunction called *female sexual interest and arousal disorder* (FSIAD),[8] which may be useful for psychiatry or behavioral health practitioners, but does not have support from clinical data nor practicality in the clinical settings in which practitioners manage sexual problems.

Based on the published evidence, reputable organizations such as the Fourth International Consultation on Sexual Medicine and the International Society for the Study of Women's Sexual Health have clearly stated that desire and arousal are distinct conditions. Thus, the nomenclature and diagnostic criteria for HSDD and FSIAD must remain separate when diagnosing, treating, and coding female sexual dysfunction.[9,10] In

fact, the female sexual health outcome evaluated in the studies demonstrating efficacy of testosterone in postmenopausal women was not FSIAD, but rather sexual satisfaction, sexual desire, or HSDD.

NEW PUBLICATIONS

Smith and Batur's review is timely and summarizes some important information published over the last year. For example, a 2019 systematic review and meta-analysis of randomized controlled trial data found that transdermal testosterone is effective for postmenopausal women with low sexual desire causing distress, with few short-term side effects (acne and hair growth), particularly when dosed in the normal physiologic range for premenopausal women.[5]

Further, they point out that there are not enough data to let us say that testosterone treatment is associated with improved individual well-being, cognitive health, or musculoskeletal outcomes, claims that are commonly endorsed by custom-compounding bioidentical providers.

Recently, the Global Consensus Position Statement on the Use of Testosterone Therapy for Women was published and endorsed by many respected US and international organizations such as the International Menopause Society, the Endocrine Society, the North American Menopause Society, and the International Society for the Study of Women's Sexual Health.[11] One of its evidence-based and expert-supported recommendations is that the only indication for the use of testosterone in women is for treatment of postmenopausal women who have been diagnosed with HSDD and that the dosage should approximate a normal physiologic level of testosterone for a premenopausal woman.

Importantly, the Global Consensus Position Statement recommends against compounded bioidentical testosterone therapy in view of lack of evidence of efficacy and safety, and cautioned against testosterone pellets or injections, which typically result in supraphysiologic concentrations. Those levels may lead to long-term, irreversible side effects including voice changes and clitoromegaly.

Consistent with this recommendation, the National Academies of Sciences, Engineering, and Medicine[12] recently published a review and called for custom-compounded bioidentical hormones to be listed as "difficult to compound" as a first step to improving quality control. They recommended that state medical boards of pharmacy expand and improve oversight and standardization of these products due to clinical concerns regarding the safety and effectiveness of custom-compounded bioidentical hormones.

With more and more FDA-approved bioidentical hormone products available, healthcare practitioners have access to a wealth of safe and effective treatments for their female patients. Hopefully, with growing clarity regarding the evidence of safety and efficacy of testosterone in women with HSDD, a testosterone formulation for women will join the list of FDA-approved products.

ALIGNING PRACTICE WITH EVIDENCE

It is important for physicians and other healthcare practitioners caring for women to ensure that their practice aligns with the evidence regarding testosterone treatment for women. There is a great need for comprehensive sexual health treatment, given the significant numbers of women suffering from sexual problems. For those select women with HSDD, transdermal testosterone, properly dosed and monitored, can provide important improvements in quality of life and sexual function.

Dosage should be in the physiologic range for a premenopausal woman

Testosterone should not be touted as a treatment for improving energy, well-being, or other outcomes that are not supported by data, especially with formulations that put women at risk of supraphysiologic levels. Smith and Batur's review provides a clinically relevant and valuable summary to communicate this important message.

DISCLOSURES

Dr. Parish has disclosed membership on advisory committees or review panels for AMAG and consulting for Strategic Science Technologies.
Dr. Kling reports no relevant financial relationships which, in the context of her contribution, could be perceived as a potential conflict of interest.

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The role of SGLT-2 inhibitors in managing type 2 diabetes

ABSTRACT

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are an exceptionally versatile class of medication, and their glycemic and nonglycemic benefits could help millions of patients with type 2 diabetes. Of note, they have been shown to improve cardiac and renal outcomes, much-needed benefits in patients with type 2 diabetes, who are at a higher risk for developing cardiac and renal dysfunction than those who do not have diabetes. The indications for SGLT-2 inhibitors may continue to expand as ongoing clinical trials provide more insight into these drugs.

KEY POINTS

SGLT-2 inhibitors improve glycemic control, reduce hospitalizations for heart failure, and slow the progression of renal disease.

Consider an SGLT-2 inhibitor as first- or second-line therapy (after metformin) in patients with type 2 diabetes with cardiovascular disease or renal disease, or both, regardless of glycemic control.

Consider an SGLT-2 inhibitor in overweight or obese patients with type 2 diabetes.

Be aware of the possibility of genital infections and diabetic ketoacidosis with SGLT-2 inhibitor use.

doi:10.3949/ccjm.88a.20088

Options for treating type 2 diabetes mellitus have expanded with the introduction of the sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like protein-1 (GLP-1) receptor agonists. These drugs improve glycemic control and possess cardiovascular and metabolic benefits.

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This article will discuss and interpret recent studies regarding the benefits of SGLT-2 inhibitors and their role in the treatment of type 2 diabetes. By doing so, we aim to provide guidance for clinicians, particularly primary care physicians and general internists, in their decision-making in managing type 2 diabetes.

SODIUM-GLUCOSE COTRANSPORTER-2

The kidneys play a role in regulating blood glucose levels by filtering out glucose in the glomerulus and then reabsorbing it in the proximal tubule. They can filter and reabsorb approximately 180 g of glucose per day, and less than 1% is excreted into the urine.[1,2] The transporters responsible for reabsorbing glucose from the tubular lumen into the blood stream are the sodium-glucose cotransporters 1 and 2 (SGLT-1 and SGLT-2, respectively). SGLT-1 is located in the distal segment of the proximal tubule and reabsorbs approximately 10% of the glucose that is filtered by the glomerulus, while SGLT-2 is located in the proximal portion of the proximal tubule and reabsorbs about 90%.[3]

In type 2 diabetes, expression of SGLT-2 is increased, which increases the ability of the kidneys to reabsorb glucose.[3] This in turn causes glucose to not spill into the urine un-

TABLE 1

Absolute change in hemoglobin A_{1c} with SGLT-2 inhibitor monotherapy compared with placebo

Empagliflozin[a]		Canagliflozin[b]		Dapagliflozin[c]		Ertugloflozin[d]	
Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose
–0.74%	–0.85%	–0.90%	–1.20%	–0.54%	–0.60%	–0.50%	–0.50%

[a]Empagliflozin low dose = 10 mg, high dose = 25 mg.[6]
[b]Canagliflozin low dose = 100 mg, high dose = 300 mg.[5]
[c]Dapagliflozin low dose = 5 mg, high dose = 10 mg.[7]
[d]Ertugloflozin low dose = 5 mg, high dose = 15 mg.[8]

til the plasma glucose level reaches about 220 mg/dL, instead of the usual threshold of about 180 mg/dL. Conversely, drugs that inhibit SGLT-2 promote glycosuria in exchange for lower plasma glucose. An advantage of these drugs is that their mechanism of action is independent of insulin secretion, beta-cell function, and insulin resistance.[4]

Drugs that inhibit SGLT-2 promote glycosuria in exchange for lower plasma glucose

EFFECT ON GLYCEMIC CONTROL

Currently, there are 4 approved SGLT-2 inhibitors on the market: empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin. No head-to-head trials have compared glycemic control with the individual drugs within the class, but in placebo-controlled trials, SGLT-2 inhibitors lowered hemoglobin A_{1c} by 0.6 to 1.2 percentage points when used as monotherapy (**Table 1**),[5–8] by 0.5 to 0.9 percentage points when added to metformin therapy,[4,9–11] and by 0.4 to 0.6 percentage points when added to insulin and other oral antihyperglycemic agents.[12–14]

Because SGLT-2 inhibitors lower glucose independently of insulin, hypoglycemia is rare when they are used as monotherapy or in conjunction with noninsulin secretagogue oral agents.[4–7,9,10] The incidence of hypoglycemia increases with the use of insulin or insulin secretagogues such as sulfonylureas, but severe hypoglycemic episodes remain uncommon.[12–14]

Nevertheless, when SGLT-2 inhibitors are used in combination with insulin or insulin secretagogues, one should consider reducing the dose of insulin or insulin secretagogue to prevent hypoglycemia:

- For patients using basal insulin, some suggest decreasing the basal insulin dose by 20% if the fasting plasma glucose level is less than 106 mg/dL and decreasing it by 10% if the fasting plasma glucose level is between 106 and 145 mg/dL
- For patients using bolus insulin, consider reducing the dose by 20% if the blood glucose level is less than 106 mg/dL before meals, and by 10% if it is between 106 and 145 mg/dL
- For patients using both insulin and an insulin secretagogue, consider reducing the dose of insulin secretagogue or discontinuing it altogether, particularly if blood glucose levels are less than 106 mg/dL before starting the SGLT-2 inhibitor.[15]

EFFECT ON CARDIOVASCULAR OUTCOMES

Approximately one-third of patients with type 2 diabetes have cardiovascular disease: about 20% have coronary artery disease and 15% have heart failure.[16] Patients with type 2 diabetes who also have heart failure have worse quality of life and a poorer prognosis.[17,18] Cardiovascular disease is responsible for half of the deaths in this patient population,[16] and those with type 2 diabetes who develop heart failure have a 9 to 12 times greater mortality risk than those who do not.[19,20] Therefore, the ability of SGLT-2 inhibitors to reduce cardiovascular deaths and hospitalizations for heart failure is crucial in managing this population.

Four large randomized clinical trials (**Table 2**)[21–24] have provided insight into the effects

TABLE 2

Cardiovascular outcomes in 4 major trials of SGLT-2 inhibitors

	EMPA-REG OUTCOME[21]	CANVAS[22]	DECLARE-TIMI 58[23]	VERTIS-CV[24]
Population	Type 2 diabetes + cardiovascular disease	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease
Number of patients	7,020	10,142	17,160	8,246
History of cardiovascular disease	99%	65.6%	40.6%	100%
History of heart failure	10.1%	14.4%	10.2%	23.7%
Outcomes with SGLT-2 inhibitor				
MACE (relative risk reduction)	14%	14%	Not significant	Not significant
MACE (number needed to treat)	63	217	Not available	Not available
Cardiovascular death (relative risk reduction)	38%	Not significant	Not significant	Not significant
Hospitalization for heart failure (relative risk reduction)	35%	33%	27%	30%
Hospitalization for heart failure (number needed to treat)	71	312	125	91

CANVAS = Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACE = major atherosclerotic cardiovascular events; VERTIS CV = Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes

of SGLT-2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes.

EMPA-REG OUTCOME (the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[21] found that empagliflozin reduced the incidence of major atherosclerotic cardiovascular events (composite of cardiovascular death, hospitalization for heart failure, and ischemic stroke) by 14%, cardiovascular death by 38%, and hospitalization for heart failure by 35%. There was no significant difference in efficacy between empagliflozin 10 mg and 25 mg.

CANVAS (the Canagliflozin Cardiovascular Assessment Study)[22] found that canagliflozin reduced major atherosclerotic cardiovascular events by 14% and hospitalizations for heart failure by 33% but did not reduce cardiovascular deaths significantly.

DECLARE-TIMI 58 (the Dapagliflozin Effect on Cardiovascular Events trial)[23] found that dapagliflozin did not reduce the rate of major atherosclerotic cardiovascular events, but it did reduce cardiovascular deaths by 17% and hospitalizations for heart failure by 27%.

VERTIS CV (the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial)[24] found that ertugliflozin did not significantly reduce major atherosclerotic cardiovascular events or cardiovascular deaths, but it reduced hospitalizations for heart failure by 30%.

In summary, SGLT-2 inhibitors have been shown to have moderate benefits in terms of preventing major adverse cardiovascular events and a robust benefit in preventing hospitalizations for heart failure.

A further look at heart failure

Individually, these trials lacked the statistical power to evaluate differences in efficacy between subgroups such as those with established atherosclerotic cardiovascular disease (ASCVD) vs those with cardiovascular risk factors but without established ASCVD.

A meta-analysis[25] of EMPA-REG OUTCOME,[21] CANVAS,[22] and DECLARE-TIMI 58[23] found that in patients with established ASCVD, major atherosclerotic cardiovascular events were reduced by 14% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.80–0.93, $P = .0002$) but no treatment effect was found in the multiple cardiovascular risk factors group. The composite outcome of cardiovascular death or hospitalization for heart failure showed a 23% relative risk reduction, regardless of whether the patients had ASCVD or heart failure. When patients with and without a history of heart failure were compared, the difference in the rate of the composite outcome of cardiovascular death or hospitalizations for heart failure was not statistically significant.[25]

Overall, SGLT-2 inhibitors' effect on major adverse cardiac events appears to be confined to patients with established ASCVD, but their effect on reducing hospitalizations for heart failure appears to be independent of established ASCVD, risk factors, or history of heart failure.

Approved SGLT-2 inhibitors: empagliflozin, canagliflozin, dapagliflozin, ertugliflozin

Heart failure type and the benefit of SGLT-2 inhibitors

In view of the clear benefit of SGLT-2 inhibitors in preventing heart failure hospitalizations, a subanalysis of the DECLARE-TIMI 58 trial was undertaken to further assess this benefit in regard to heart failure phenotype (heart failure with reduced ejection fraction vs heart failure with preserved ejection fraction).[26]

Treatment differs for the 2 groups. For those with heart failure with reduced ejection fraction, agents such as angiotensin-converting enzyme inhibitors and beta-blockers reduce the risk of death. However, no treatments to date have been shown to lower the mortality rate in heart failure with preserved ejection fraction, and the guidelines are limited to recommending treatment of any underlying comorbidities such as hypertension, atrial fibrillation, coronary artery disease, and diabetes.[27] The answer to whether SGLT-2 inhibitors benefit both types of heart failure will have an enormous impact on the future management of heart failure.

DECLARE-TIMI 58,[26] in a subgroup analysis, found that dapagliflozin significantly reduced hospitalizations for heart failure and cardiovascular deaths in those with heart failure with reduced ejection fraction more than in those with preserved ejection fraction or unclassified heart failure (HR 0.62 vs 0.88, $P = .046$). On the other hand, it appeared to reduce hospitalizations for heart failure in all patients regardless of their heart failure phenotype.

DAPA-HF (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction)[28] evaluated the efficacy of dapagliflozin in patients with heart failure with reduced ejection fraction regardless of diabetes diagnosis The incidence of the primary outcome (composite of worsening heart failure—unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy for heart failure—or death from cardiovascular causes) was 26% lower in the dapagliflozin group than in the placebo group (HR 0.74, $P < .001$) with a number needed to treat of 20. Hospitalizations for heart failure alone were reduced by 30%. These benefits were comparable in patients with or without diabetes in the study based on a subgroup analysis.[28]

In May 2020, the US Food and Drug Administration (FDA) expanded the indications for dapagliflozin to include heart failure with reduced ejection fraction.[29]

EMPEROR-Reduced (the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)[30] investigated the efficacy of empagliflozin in patients with heart failure with reduced ejection fraction with or without diabetes. The incidence of the primary outcome (composite of adjudicated cardiovascular death or hospitalization for heart failure) was

25% lower in the empagliflozin group (HR 0.75, $P < .001$) with a number needed to treat of 19. Hospitalizations for heart failure were reduced by 30%. These results were similar to those of the DAPA-HF trial.

CVD REAL 2 (the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study)[31] reinforced the cardiovascular benefits of SGLT-2 inhibitors. This was a large multinational observational study including cohorts from regions that were not well represented in the clinical trials mentioned above such as Asia Pacific and the Middle East. Also, the study population more closely resembled that of clinical practice in which the majority (approximately 74%) did not have established cardiovascular disease.

Nonetheless, SGLT-2 inhibitors, compared with other glucose-lowering drugs, significantly reduced the risk of death from any cause (49% relative risk reduction), hospitalization for heart failure (36% reduction), composite of all-cause death and hospitalization for heart failure (40% reduction), myocardial infarction (19% reduction), and stroke (32% reduction) in patients with type 2 diabetes.[31] Despite differences in study population and design, the results were similar to those in previous clinical trials and were also consistent across countries.

The CVD REAL 2 study suggests that the cardiovascular benefits of SGLT-2 inhibitors may apply to a broader population of patients.[31]

POSSIBLE MECHANISMS OF CARDIOVASCULAR BENEFIT

How SGLT-2 inhibitors exert their cardioprotective benefits is not fully understood, but several mechanisms have been hypothesized.

Osmotic diuresis. By increasing glycosuria and natriuresis, SGLT-2 inhibitors increase urine output and therefore decrease plasma volume and ventricular preload.[32]

Inhibition of the sodium-hydrogen exchanger. Cytosolic sodium concentration and sodium-hydrogen exchanger activity are both increased in the myocytes in people with diabetes and heart failure,[33] and sodium-hydrogen exchanger inhibition has been shown to reduce hypertrophy in heart failure.[34]

Inhibition of fibrosis. Cardiac fibrosis is widely regarded as an essential factor in the development of heart failure. In a study using human cardiac fibroblasts, empagliflozin suppressed gene expression of key profibrotic markers such as type I collagen and connective tissue growth factor.[35] This inhibition may lead to protection from cardiac fibrosis independent of glycemic status.

Bottom line. SGLT-2 inhibitors should be considered for all patients with type 2 diabetes who do not have contraindications to them, given their efficacy in preventing hospitalizations for heart failure in all patients regardless of ASCVD or heart failure history. They should be considered even more strongly in patients with established ASCVD. Guidelines for integrating SGLT-2 inhibitors into diabetes management are discussed further below.

EFFECT ON RENAL OUTCOMES

Another benefit of the SGLT-2 inhibitor class of medications is renal protection. Diabetes is the leading cause of kidney failure in the United States,[36] and dialysis carries a poorer prognosis than some cancers.[37] Furthermore, early diabetic kidney disease shortens life by 16 years compared with those without diabetes or kidney disease.[38] Thus, preventing or slowing the progression of diabetic kidney disease is a key aspect of diabetes management.

About one-third of patients with type 2 diabetes have cardiovascular disease

CREDENCE (the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial)[39] was a large, randomized, placebo-controlled, multicenter trial that assessed the effect of canagliflozin on renal outcomes in patients with type 2 diabetes and chronic kidney disease. All the participants had to have an estimated glomerular filtration rate (eGFR) of 30 to 90 mL/min/1.73 m^2 and a urine albumin-to-creatinine ratio of 300 to 5,000 mg/g. The primary outcome was a composite of end-stage renal disease, doubling of serum creatinine, or death from renal or cardiovascular disease.

The risk of the primary composite outcome was 30% lower in the canagliflozin group (HR 0.70, 95% CI 059–0.82, $P < .001$). One of the secondary composite outcomes, end-stage renal disease, doubling of creatinine, or renal

death, was reduced by 34% (HR 0.66, 95% CI 0.53–0.81, $P < .001$).

In addition, canagliflozin slowed the progression of chronic eGFR decline.[39] SGLT-2 inhibitors have been shown to induce an initial decline in eGFR but with subsequent return to baseline and then an overall preservation of eGFR over time.[40]

Of note, in the CREDENCE trial, patients whose eGFR was 30 to 44 mL/min/1.73 m^2 still benefited from canagliflozin; the primary outcome was reduced by 25% in this subgroup (HR 0.75, 95% CI 0.59–0.95), and the number needed to treat was 19. Initially, canagliflozin was contraindicated in patients with eGFR less than 45 mL/min/1.73 m^2. However, in January 2020, the 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m^2 with urinary albumin excretion less than 300 mg/day.

Canagliflozin is the only SGLT-2 inhibitor studied in a large trial with a primary renal outcome. The EMPA-REG OUTCOME and the DECLARE-TIMI 58 trials had prespecified secondary renal composite outcomes that showed favorable results for renal benefit, but it is prudent to note that the composite outcomes consisted of different criteria.

SGLT-2 inhibitors have moderate benefits in preventing cardiovascular events and a robust benefit in preventing hospitalizations for heart failure

The EMPA-REG trial[41] found a 39% reduction compared with placebo for the renal composite outcome of progression to macroalbuminuria, a doubling of serum creatinine level accompanied by an eGFR of ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

The DECLARE-TIMI 58 trial[42] had a renal composite outcome consisting of sustained decrease in eGFR by at least 40% to less than 60 mL/min/1.73 m^2, end-stage renal disease, and renal death; there was a 47% reduction compared with placebo.

The VERTIS-CV trial[24] had a renal composite outcome that included renal death, renal replacement therapy, or doubling of serum creatinine. A statistically significant renal benefit was not found, although ertugliflozin did show a trend for reducing the rate of eGFR decline over time, similar to the other 3 SGLT-2 inhibitors.

Meta-analysis. In the meta-analysis by Zelniker et al[25] of the first 3 cardiovascular outcome trials (EMPA-REG OUTCOME,[21] CANVAS,[22] and DECLARE-TIMI 58[23]), the composite outcome of worsening renal function, end-stage renal disease, or renal death was reduced by 45%, suggesting a renal protective benefit of SGLT-2 inhibitors as a class.

The American Diabetes Association[43] currently recommends empagliflozin, canagliflozin, and dapagliflozin as second-line therapy after metformin in patients with type 2 diabetes and chronic kidney disease whose eGFR is at least 45 mL/min/1.73 m^2 (except for canagliflozin 100 mg, which can be used if eGFR is at least 30 mL/min/1.73 m^2 and urinary albumin excretion is more than 300 mg/day).

The CVD REAL 3 study[44] (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGTT-2 Inhibitors) evaluated the renal outcomes of SGLT-2 inhibitors in real-world clinical practice settings around the world. The rate of eGFR decline was significantly less in the SGLT-2 inhibitor group than with other glucose-lowering drugs, and the composite outcome of a 50% eGFR decline or end-stage renal disease was reduced by 51% (HR 0.49, 95% CI 0.35–0.67). These results were consistent across countries and baseline eGFR.

MECHANISM OF RENAL PROTECTION

The mechanism by which SGLT-2 inhibitors protect the kidneys is also not fully understood and is probably multifactorial.

A proposed mechanism is correction of glomerular hyperfiltration, which is a risk factor for progression of diabetic nephropathy.[45] SGLT-2 inhibitors inhibit uptake of glucose and sodium in the proximal tubule, leading to an increase in delivery of sodium to the distal tubule and juxtaglomerular apparatus. The juxtaglomerular apparatus perceives this increase in sodium as a decrease in glomerular perfusion, causing the afferent arteriole to vasoconstrict, which in turn attenuates the hyperfiltration.[46]

This afferent arteriolar constriction manifests as a transient reduction in eGFR of approximately 3 to 4 mL/min/1.73 m^2 in the first few weeks of SGLT-2 therapy and a reduction in albuminuria. Renal function subsequently stabilizes, and ultimately the progression of renal disease is slower with SGLT-2 inhibitors

than with placebo in the long term. This effect was seen in the cardiovascular outcome trials of all 4 SGLT-2 inhibitors[39,41,42] as well as in the CVD REAL 3 study.[44]

An ongoing clinical trial is assessing the efficacy of empagliflozin in patients with chronic kidney disease. A trial evaluating dapagliflozin in patients with chronic kidney disease was recently terminated early due to the overwhelming benefit of dapagliflozin in this population. The results of this trial are of great interest, as they may further expand the utilization of this drug.

EFFECT ON METABOLIC OUTCOMES

SGLT-2 inhibitors have been shown to promote weight loss and lower blood pressure. Taking these drugs as monotherapy for 24 to 26 weeks, patients lost approximately 2.3 to 3.5 kg. Systolic blood pressure decreased by 1.4 to 3.7 mm Hg, and diastolic blood pressure decreased by 0.6 to 2.0 mm Hg.[5–8] Reductions in weight and blood pressure persist in patients with eGFR less than 60 mL/min/1.73 m^2 even when the glucose-lowering effect of SGLT-2 inhibitors is attenuated.[47]

SGLT-2 inhibitors have not been approved for use solely as weight-loss medications. However, when they are used in combination with other antiobesity medications they seem to have an additive effect on weight loss and blood pressure compared with SGLT-2 inhibitor monotherapy.

Hollander et al[48] compared the effect of canagliflozin, phentermine, canagliflozin and phentermine combined ("can-phen"), and placebo in patients without type 2 diabetes. Patients lost an average of 0.6 kg on placebo, 1.9 kg on canagliflozin, 4.1 kg on phentermine, and 7.3 kg on can-phen over 26 weeks. Compared with placebo, can-phen produced a statistically significant weight loss of 6.9% ($P < .001$). In addition, there was a statistically significant reduction in systolic blood pressure in the can-phen group compared with placebo (difference of –4.2 mm Hg, $P = .015$).

Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists has been studied in patients with type 2 diabetes, with the primary outcome of glycemic control and secondary outcomes including changes in weight and blood pressure.

A meta-analysis[49] of 4 large, randomized controlled trials showed that patients who received combination therapy lost significantly more weight than those who received SGLT-2 inhibitor monotherapy (difference = –1.61 kg, $P = .01$), and they had significantly reduced systolic blood pressure (difference = –3.32 mm Hg, $P < .001$).[49] Hemoglobin A_{1c} reduction was also greater in the combination therapy group compared with monotherapy (difference = –0.74%, $P < .001$).

STUDIES IN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD is a chronic liver disease that can ultimately progress to liver cirrhosis, and there are no FDA-approved pharmacotherapies for it to date. Such treatments are needed, especially considering that the prevalence of NAFLD is high in the type 2 diabetes population.

Empagliflozin, dapagliflozin, and canagliflozin have been studied for their effect on NAFLD. Overall, they have been shown to decrease alanine aminotransferase and improve steatosis and fibrosis along with reducing hemoglobin A_{1c} and body weight.[50] Further randomized controlled trials are needed to evaluate the benefit of SGLT-2 inhibitors in NAFLD in patients with and without diabetes.

To date, no treatments have been shown to lower mortality in heart failure with preserved ejection fraction

The mechanism by which SGLT-2 inhibitors improve NAFLD remains unclear. A popular theory is that a chronic inflammatory state underlies type 2 diabetes and its complications, and patients with NAFLD show significant increases in inflammatory markers as well.[51] Therefore, it is speculated that SGLT-2 inhibitors have several features that can provide anti-inflammatory benefits to improve NAFLD. One feature is the reduction in weight as well as subcutaneous and visceral fat,[52] as weight reduction is known to reduce inflammatory markers.[53]

In addition, SGLT-2 inhibitors decrease serum uric acid levels.[21] Uric acid has been associated with oxidative stress and vascular injury in in-vitro and animal studies[54] leading to the hypothesis that lowering of serum uric acid may improve the inflammatory state. Fralick et al[55] showed that SGLT-2 inhibitors

decreased the rate of gout in patients with type 2 diabetes compared with those who were prescribed a GLP-1 receptor agonist.

Bottom line. SGLT-2 inhibitors should be considered in patients with type 2 diabetes who are also overweight or obese. They may also have an added benefit of improving NAFLD. In cases in which further hemoglobin A_{1c} reduction and weight loss is preferred, combination therapy with GLP-1 receptor agonists is a reasonable option. In those without type 2 diabetes, canagliflozin plus phentermine seems to have a synergistic effect in promoting significant weight loss. Subsequent studies evaluating the combination of other SGLT-2 inhibitors and phentermine and assessing the effect of this combination therapy in the type 2 diabetes population is of interest.

ADVERSE EFFECTS OF SGLT-2 INHIBITORS

Several adverse events related to the use of SGLT-2 inhibitors have been reported. Some are drug-specific and others are class-specific.[21–23]

Early diabetic kidney disease shortens life by 16 years

Fractures, amputations with canagliflozin. The hazard ratio for the risk of fractures with canagliflozin was 1.26 (95% CI 1.04–1.52), and the hazard ratio for the risk of amputations was 1.97 (95% CI 1.41–2.75) in the CANVAS trial.[22] However, the hazard ratios for these 2 events were not significant in the CREDENCE trial.[39] Moreover, the increased risk for fractures and amputations has not been seen in randomized control trials of empagliflozin, dapagliflozin, and ertugliflozin. Thus, the FDA removed the boxed warning about the amputation risk with canagliflozin in August 2020.[56]

Genital infections. As a class, SGLT-2 inhibitors increase the risk of genital infections.[8,21–23] Urinary tract infections were generally not significantly increased as a class, but an increase in female urinary tract infections was seen with empagliflozin.[21]

Fournier gangrene. In a postmarketing analysis based on the FDA adverse event reporting system and published case reports, SGLT-2 inhibitors as a class were associated with an increased risk of Fournier gangrene: 55 cases of Fournier gangrene were identified from March 2013 to January 2019: 21 cases were attributed to canagliflozin, 16 to dapagliflozin, and 18 to empagliflozin.[57] This increased risk of Fournier gangrene has not been shown in any of the randomized clinical trials, but due to the severe and fatal nature of this infection, it is crucial to have a high index of suspicion for it in order to detect these cases in the early stages.

Diabetic ketoacidosis. SGLT-2 inhibitor-associated diabetic ketoacidosis may present atypically (ie, with a lower-than-expected glucose level) which can result in missed diagnoses and delays in treatment.[58]

A proposed mechanism of SGLT-2 inhibitor-associated diabetic ketoacidosis is that the increased urinary excretion of glucose suppresses insulin secretion by the beta cells which in turn decreases the antilipolytic activity of insulin. This stimulates production of free fatty acids that are then converted to ketone bodies.[59] In addition, the decrease in insulin activity increases the activity of carnitine palmitoyl-transferase I (CPT-I) through inhibition of acetyl-CoA carboxylase. CPT-I promotes the transport of fatty acids into the mitochondria which ultimately increases ketone body production.[59] There is also evidence that SGLT-2 inhibitors increase glucagon secretion. As glucagon suppresses acetyl-CoA carboxylase, CPT-I activity is increased, leading to ketone body production.[60]

According to the American Association of Clinical Endocrinologists position statement on SGLT-2 inhibitors and diabetic ketoacidosis, this complication occurs infrequently, and the benefits of SGLT-2 inhibitors clearly outweigh the risk, so continued use of SGLT-2 inhibitors in type 2 diabetes is recommended.[58] However, evidence is emerging that surgery may increase the risk of ketoacidosis in patients taking SGLT-2 inhibitors.[61]

In March 2020, the FDA approved a label change for all SGLT-2 inhibitors on the market, recommending temporary discontinuation of the drug before scheduled surgery. Empagliflozin, canagliflozin, and dapagliflozin should be discontinued 3 days before scheduled surgery and ertugliflozin should be discontinued 4 days before. The drug can be reinitiated after surgery when oral intake has returned to baseline.[62]

Benefit outweighs risk. SGLT-2 inhibitors have an abundance of additional benefits

TABLE 3

Risks and benefits of SGLT-2 inhibitors

	Benefits					Risks	
	Hemoglobin A_{1c}	Weight and blood pressure	Heart failure hospitalizations	Cardiovascular events	Progression of renal disease	Fracture, amputation	Genital infection
Empagliflozin	Decrease	Decrease	Decrease	Decrease	Decrease	No change	Increase
Canagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change[a]	Increase
Dapagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change	Increase
Ertugliflozin	Decrease	Decrease	Decrease	No change	No change	No change	Increase

[a]Changed from "increases risk" to "no change" after the removal of the black box warning by the US Food and Drug Administration.

aside from improving glycemic control. Based on the safety data we have thus far, the risk-benefit ratio unquestionably favors the use of SGLT-2 inhibitors, and they should be recommended for any patient with type 2 diabetes who does not have any absolute contraindications (**Table 3**). Relative contraindications may include recurrent urinary tract or genital infections. For canagliflozin, risk factors for amputation such as prior history of amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers should be considered before initiation and then monitored for signs and symptoms of foot infections if initiated. Fournier gangrene is a severe and fatal infection; any patient on an SGLT-2 inhibitor should be counseled about the symptoms, and providers need to have heightened awareness of the possibility of Fournier gangrene in order to detect this condition early.

REVIEW OF THE GUIDELINES

In 2020, diabetes treatment algorithms were issued by the American Diabetes Association[43] and the American Association of Clinical Endocrinologists.[63]

American Diabetes Association

- In patients who have established ASCVD, high ASCVD risk (age ≥ 55 with coronary, carotid, or lower extremity artery stenosis > 50%, or left ventricular hypertrophy), heart failure, or chronic kidney disease, SGLT-2 inhibitors are considered for use as second-line therapy (first-line is metformin) regardless of baseline hemoglobin A_{1c}. The 3 SGLT-2 inhibitors with cardiovascular and renal benefits are empagliflozin, canagliflozin, and dapagliflozin.
- In patients whose hemoglobin A_{1c} is above their individual target and who do not have established ASCVD, high ASCVD risk, heart failure, or chronic kidney disease, SGLT-2 inhibitors are considered for use as second-line therapy.

American Association of Clinical Endocrinologists

- In patients with established ASCVD, high ASCVD risk, or chronic kidney disease, SGLT-2 inhibitors and GLP-1 receptor agonists are recommended as first-line therapy independent of glycemic control.
- If entry hemoglobin A_{1c} is less than 7.5%, monotherapy is recommended with metformin, a GLP-1 receptor agonist, or a SGLT-2 inhibitor (strength of the recommendation is equal).
- For those with stage 3 chronic kidney disease, canagliflozin is recommended.
- For those with heart failure with reduced ejection fraction, dapagliflozin is recommended.
- If entry hemoglobin A_{1c} is 7.5% to 9.0% or higher or if uncontrolled on monotherapy, dual therapy is recommended with SGLT-2 inhibitor and GLP-1 receptor agonists as the top choices in the hierarchy along with metformin. The 2 drug classes are also the top choices for triple therapy.

A trial of dapagliflozin in chronic kidney disease was recently terminated early due to benefit

Bottom line

SGLT-2 inhibitors are recommended for use as either first-line or second-line therapy regardless of baseline hemoglobin A_{1c} in patients who have established ASCVD, high ASCVD risk, chronic kidney disease, or heart failure. They are also recommended for use in those who would benefit from weight loss and in those whom prevention of hypoglycemia is a priority according to the ADA.

FUTURE DIRECTIONS

Use in type 1 diabetes? Currently, SGLT-2 inhibitors as a class are not recommended for use in type 1 diabetes. Large, randomized, placebo-controlled studies have been undertaken with dapagliflozin,[64] empagliflozin,[65] and canagliflozin[66] as adjunct therapy to insulin in patients with type 1 diabetes. Common results included reduction in hemoglobin A_{1c} and weight without increases in hypoglycemia events. However, the incidence of diabetic ketoacidosis was higher in the SGLT-2 inhibitor groups in all 3 studies.[64–66] None of these drugs have been approved by the FDA for use in type 1 diabetes. Future studies involving type 1 diabetes and SGLT-2 inhibitors include adjunctive use with closed-loop insulin pumps and combination therapy with GLP-1 receptor agonists.

Sotagliflozin is an SGLT-1 and SGLT-2 dual inhibitor being studied for treatment of type 1 diabetes and type 2 diabetes. Besides the distal segment of the proximal tubule of the kidneys, SGLT-1 is also located in the proximal intestine, and inhibition results in reduced glucose absorption and delays postprandial hyperglycemia. In a phase 3 clinical trial,[67] its efficacy and safety were tested as an add-on therapy to insulin in patients with type 1 diabetes. Although the drug was effective in improving glycemic control, the rate of diabetic ketoacidosis was higher compared with placebo.[67] Sotagliflozin was rejected by the FDA as adjunct therapy for type 1 diabetes. There is currently an ongoing clinical trial studying the efficacy of sotagliflozin in type 2 diabetes.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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EDITORIAL

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SGLT-2 inhibitors: A new era in managing diabetic kidney disease starts now

DIABETIC KIDNEY DISEASE is a major cause of chronic kidney disease and the most common cause of end-stage kidney disease. Before the sodium-glucose cotransporter-2 (SGLT-2) inhibitors were introduced, the nephrology community had not had much to celebrate in the management of diabetic kidney disease since the landmark trials of renin-angiotensin system blockers 20 years ago.[1–3] Since that time, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers have been the cornerstone of managing proteinuric diabetic and nondiabetic kidney disease. Fast-forward 20 years, and SGLT-2 inhibitors have emerged as a major addition to our toolkit in the management of diabetic kidney disease.

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In this issue, Tsushima et al[4] discuss the role of SGLT-2 inhibitors in managing patients with type 2 diabetes and highlight the updated 2020 treatment guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists.[5,6] The authors thoroughly highlight the overwhelmingly beneficial cardiovascular, kidney, and metabolic effects of this new class of medications that is taking many different medical specialties by storm.

Here, we would like expand the discussion on the kidney effects of the SGLT-2 inhibitors. We will highlight only the SGLT-2 inhibitors that have data on primary and secondary renal outcomes; however, we suspect that the benefits are a class effect. We also summarize the 2020 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, which emphasize early and extended use of SGLT-2 inhibitors in patients with diabetic kidney disease.[7]

doi:10.3949/ccjm.88a.20190

THE WRITING WAS ON THE WALL

Positive results in randomized controlled trials of these new agents

As reviewed by Tsushima et al,[4] large randomized controlled trials proved SGLT-2 inhibitors to be beneficial in patients with type 2 diabetes in terms of primary cardiovascular outcomes and secondary renal end points (**Table 1**).[8–14] These results paved the way for the CREDENCE trial[12] (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation), which was the first major randomized, placebo-controlled multicenter study to evaluate primary renal composite end points consisting of end-stage kidney disease, a doubling of serum creatinine level, or death from a renal or cardiovascular cause.

The results were overwhelmingly positive, with a 30% relative risk reduction (hazard ratio [HR] 0.70, 95% confidence interval [CI] 059–0.82, P = .00001) with canagliflozin compared with placebo. This astonishing outcome was in patients who were already taking maximally tolerated doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. To accentuate the point, the landmark trials

TABLE 1

Renal outcomes of the major trials of sodium-glucose cotransporter 2 inhibitors

Trial	Agent	Composite kidney outcome	Primary or secondary end points	Hazard ratio (95% CI)	Number needed to treat
EMPA-REG OUTCOME[8]	Empagliflozin	Doubling of the serum creatinine level, initiation of kidney replacement therapy, or death from renal disease	Secondary	0.54 (0.40–0.75)	194
CANVAS[10]	Canagliflozin	Sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from renal causes	Secondary	0.60 (0.47–0.77)	286
DECLARE-TIMI 58[11]	Dapagliflozin	Sustained ≥ 40% reduction in eGFR to < 60 mL/min/1.73 m^2, new end-stage kidney disease, or death from renal cause	Secondary	0.53 (0.43–0.66)	78
EMPEROR-Reduced[9]	Empagliflozin	Sustained ≥ 40% reduction in eGFR, chronic dialysis, renal transplant, or sustained eGFR < 10–15 mL/min/1.73 m^2	Secondary	0.50 (0.32–0.77)	68
CREDENCE[12]	Canagliflozin	End-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes	Primary	0.70 (0.59–0.82)	22
DAPA-CKD[13]	Dapagliflozin	Sustained ≥ 50% reduction in eGFR, end-stage kidney disease, or death from renal or cardiovascular cause	Primary	0.61 (0.51–0.72)	19
EMPA-KIDNEY[14]	Empagliflozin	End-stage kidney disease, a sustained reduction in eGFR to < 10 mL/min/1.73 m^2, renal death, or a sustained decline of ≥ 40% in eGFR	Primary	Ongoing	Ongoing

CANVAS = Canagliflozin Cardiovascular Assessment Study; CI = confidence interval; CREDENCE = Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD = Dapagliflozin in Patients With Chronic Kidney Disease; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events; eGFR = estimated glomerular filtration rate; EMPA-KIDNEY = Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction

of renin-angiotensin system inhibitors such as the Irbesartan Diabetic Nephropathy Trial[2] and the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan study[3] demonstrated a 33% and 25% reduction in doubling in serum creatinine, respectively, while canagliflozin had a 40% reduction.

Even more intriguing is the newly published DAPA-CKD (Dapagliflozin in Patients With Chronic Kidney Disease) trial, which has confirmed the renal benefits of CREDENCE, and has expanded the population eligible for treatment with an SGLT-2 inhibitor.[13]

INSIGHTS FROM DAPA-CKD

The DAPA-CKD trial[13] was a large, multicenter, randomized controlled trial that enrolled 4,304 participants to receive dapagliflozin (10 mg once daily) or placebo. In contrast to the CREDENCE trial, which in-

cluded only patients with type 2 diabetic proteinuria (with albumin-to-creatinine ratios of 300–5,000 mg/g) with an estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min/1.73 m^2, the DAPA-CKD trial enrolled patients with chronic kidney disease with lower eGFRs (between 25 and 75 mL/min/1.73 m^2), less proteinuria (albumin-to-creatinine ratios of 200–5,000 mg/g), with or without type 2 diabetes. Approximately two-thirds of participants enrolled had type 2 diabetes, and 98% of all participants were on a stable dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

The primary composite outcome was a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from kidney or cardiovascular causes.

The independent data monitoring committee stopped the trial after a median of 2.4 years, after primary efficacy end points were achieved. There was a 39% reduction in the primary composite outcome in the dapagliflozin group (HR 0.61, 95% CI 0.51–0.72, $P < .001$), and the number needed to treat was 19 (95% CI 15–27). Results were similar regardless of diabetes status, and the beneficial kidney outcomes were independent of glycemic control. Dapagliflozin also achieved a 31% risk reduction in all-cause mortality (HR 0.69, 95% CI 0.53–0.88, $P = .004$) and a 44% risk reduction in worsening renal function or death from kidney failure (HR 0.56, 95% CI 0.45–0.68, $P < .0001$). Interestingly, the incidence of serious adverse events in the dapagliflozin group was similar to that in the placebo group (33.9% vs 29.5%), with ketoacidosis not reported in the dapagliflozin group and severe hypoglycemia not observed in the nondiabetic population.

MOVING THE GOAL POST: THE 2020 KDIGO GUIDELINE

Given the emerging data, Kidney Disease: Improving Global Outcomes (KDIGO) recently published their inaugural 2020 practice guidelines for diabetes management in chronic kidney disease patients.[7] KDIGO goes beyond what the American Diabetes Association and American Association of Clinical Endocrinologists guidelines say, recommending SGLT-2 inhibitors and metformin as first-line drugs for diabetic kidney disease. We summarize here the key points as they pertain to antihyperglycemic therapies in patients with diabetes and chronic kidney disease.

Lifestyle modification and drugs

Glycemic control for management of patients with type 2 diabetes and chronic kidney disease should include lifestyle therapy; first-line drug treatment includes metformin *and* an SGLT-2 inhibitor, and additional drug therapies as needed for glycemic control. Specifically:

- SGLT-2 inhibitors get a grade 1 (highest) recommendation, level of evidence A (high-quality)
- Metformin gets a grade 1 recommendation, level of evidence B (moderate-quality); dose reduction is required when eGFR drops below 45 mL/min/1.73 m^2, and metformin should be discontinued if eGFR is less than 30 mL/min/1.73 m^2
- Long-acting glucagon-like peptide 1 receptor agonists are recommended for patients who have not achieved their individualized glycemic targets despite use of metformin and SGLT-2 inhibitors, or who cannot use those medications (grade 1B recommendation).

Metformin is a preferred first-line agent due to its glucose-lowering control, tolerability, and low cost. SGLT-2 inhibitors are relatively weak antiglycemic drugs with smaller reductions of hemoglobin A_{1c}. The recommendation to add SGLT-2 inhibiters in combination with metformin is primarily for the beneficial effects of slowing the progression of nephrologic and cardiovascular disease and not for hemoglobin A_{1c} control.

Hemoglobin A_{1c} targets are individualized, ranging from less than 6.5% to less than 8.0% in patients with diabetes and chronic kidney disease not treated with dialysis (grade 1C recommendation: recommended, but low-quality evidence).

DAPA-CKD was stopped early because the primary efficacy end points were achieved

KEY TAKEAWAYS AND PRACTICE POINTERS

We believe that frontline clinicians should initiate SGLT-2 inhibitors for patients with type 2 diabetes and diabetic kidney disease

who have an eGFR of at least 30 mL/min/1.73 m^2. Maximal treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is highly recommended before starting the SGLT-2 inhibitor but is not an absolute requirement in patients who cannot tolerate renin-angiotensin system blockade.

Deferring initiation of SGLT-2 inhibitors to a specialist (a nephrologist or endocrinologist) will result in a faster progression of diabetic kidney disease irrespective of glycemic control, and it is crucial to initiate these medications as early as possible. SGLT-2 inhibitors are contraindicated if the eGFR is less than 25 mL/min/1.73 m^2 (see below), and later initiation even with acceptable but lower eGFR ranges may be more problematic as it relates to the expected acute drop in eGFR.

Efficacious doses of SGLT-2 inhibitors that have been studied in diabetic kidney disease are canagliflozin 100 mg, empagliflozin 10 mg, or dapagliflozin 10 mg.

Prescribers should be aware of the initial reversible drop in eGFR of approximately 5 to 8 mL/min/1.73 m^2 (up to a 20% drop) in the first 2 weeks after starting SGLT-2 inhibitors, which is due to the hemodynamic effects of the drug. This decrease is analogous to the hemodynamic effects of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. This mild reduction in eGFR does not require discontinuation of the drug.

SGLT-2 inhibitors and metformin are now the first-line drugs for diabetic kidney disease

We anticipate the lower limit of kidney function below which SGLT-2 inhibitors cannot be started will continue to be challenged. Currently, canagliflozin and empagliflozin initiation is contraindicated if the eGFR is less than 30 mL/min/1.73 m^2, while dapagliflozin lowered the eGFR threshold to less than 25 mL/minute/1.73 m^2 as a result of the DAPA-CKD trial.[13] The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY)[14] is recruiting patients whose eGFR can be as low as 20 mL/min/1.73 m^2.

- SGLT-2 inhibitors should be continued until kidney replacement therapy needs to be started.
- The expected glycosuria may result in osmotic diuresis; therefore, patients will need to be educated about potential volume depletion. Additionally, clinicians may consider reducing or stopping concomitant diuretic therapy in the short term.

Educate the patient about the "sick day rule." SGLT-2 inhibitors should be held in periods of illness accompanied by decreased oral intake or increased volume losses. Hypovolemia and altered arteriolar hemodynamics may predispose patients to ischemic tubular kidney injury.

The risks and benefits of therapy should be assessed in patients with a history of urinary tract infections, genitourinary yeast infections, or diabetic ketoacidosis.

FUTURE DIRECTIONS

The scope of the KDIGO guidelines was limited to diabetic kidney disease, and the work group did not incorporate recommendations for patients who have chronic kidney disease but no diabetes. All of the aforementioned studies exclusively studied proteinuric diabetic kidney disease, with the exception of the DAPA-CKD trial, in which only one-third (n = 1,398) of the participants did not have diabetes, and which still demonstrated kidney benefits in this subgroup.

In subgroup analysis of the DAPA-CKD trial, 50% of nondiabetic kidney disease patients (HR 0.50; 95% CI 0.35–0.72) vs 36% of diabetic kidney disease patients (HR 0.64, 95% CI 0.52–0.79) met the primary composite outcome (sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from kidney or cardiovascular causes). Neither diabetic ketoacidosis nor severe hypoglycemia was observed in participants without type 2 diabetes.

Questions remain about whether SGLT-2 inhibitors have kidney benefits in patients with diabetes who have chronic kidney disease without proteinuria, or in patients without diabetes who have chronic kidney disease without proteinuria.

EMPA-KIDNEY[14] will hopefully shed more light on this population. The study is actively enrolling 6,000 patients who have chronic kidney disease with or without type 2 diabetes with eGFRs of 20 to less than 45 mL/min/1.73 m^2, and eGFRs of 45 to less than 90 mL/min/1.73 m^2 with less albuminuria (albumin-creatinine ratios ≥ 200 mg/g). The primary composite outcome includes several hard kidney disease outcomes. The EMPA-KIDNEY results are expected in the summer of 2022.

Another important patient population that has been excluded from these trials is kidney transplant recipients. Type 2 diabetes was listed as the cause of their end-stage kidney disease in 31% of patients who received kidney transplants in 2019.[15] These patients may benefit from SGLT-2 inhibitors, but concerns include the risk of genitourinary infections and the uncertainty and additional testing that may be required to differentiate acute rejection from the expected rise in serum creatinine at time of initiation. We hope to get more information about this subgroup in the future.

A NEW ERA IN THE TREATMENT OF DIABETIC KIDNEY DISEASE

SGLT-2 inhibitors have blown the doors wide open in the management of diabetic kidney disease. Further, additional classes of medications appear to be on the horizon. A novel nonsteroidal mineralocorticoid receptor antagonist (finerenone),[16] an endothelin receptor antagonist (atrasentan),[17] and glucagon-like peptide 1 receptor agonists are some promising agents for slowing the progression of diabetic kidney disease. The long-awaited future of multitargeted treatment for diabetic kidney disease is finally here!

DISCLOSURES

Jonathan J. Taliercio, DO, is an EMPA-KIDNEY and SONAR co-investigator. Georges N. Nakhoul MD, MEd, is an EMPA-KIDNEY co-investigator. George Thomas, MD, is an EMPA-KIDNEY principal investigator. All other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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