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Cleveland Clinic Journal of Medicine

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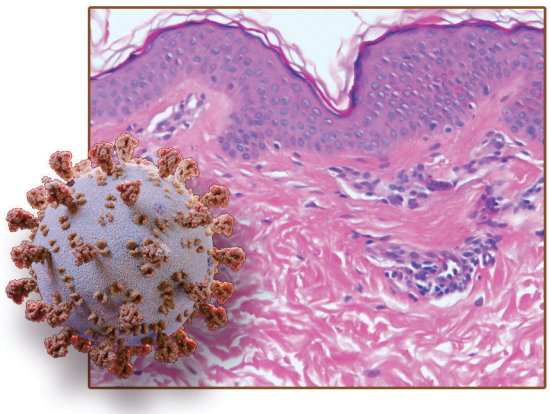

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CME MOC

2023

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Some complexities of diabetes and the heart

Patients with diabetes are at greater risk of coronary artery disease, including severe and diffuse coronary disease, than their peers without diabetes. That's straight and simple. But there the simplicity ends. Patients with diabetes have comorbidities that contribute to the development of coronary artery disease, including chronic kidney disease, obesity (often with obstructive sleep apnea), hypertension, and dyslipidemias. An individual may have none or all of these shared cardiac risk factors. Successful treatment of some of these comorbidities can reduce the risk of coronary and cardiovascular events, and current guidelines call for aggressive management of blood pressure and lipid levels as well as treatment of proteinuria in an effort to reduce progression of kidney disease.

Diabetes is defined by the presence of hyperglycemia or an elevated level of glycosylated proteins, its biochemical footprint. And for 100 years (insulin was first administered in 1922), the control of blood glucose levels has been the target of diabetic therapies. Control of blood glucose levels results in reduced microvascular complications, but reduction of the hemoglobin A1c level has not been uniformly shown to reduce coronary risk. Some controlled studies have instead indicated that aggressive diabetes control may paradoxically increase cardiac events. While it can be argued that some events may have been related to hypoglycemic stress, specific drugs may also play a contributory role.

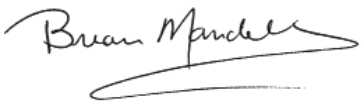
There are many drugs now available that lower the blood glucose. Many share the ability to increase insulin levels and have efficacy in treating type 2 diabetes. Other drugs have unique biologic mechanisms of action that lower blood glucose without relying entirely on insulin for their effect. They are uniquely different in biochemical structure and thus, not surprisingly, differ in their off-target pharmacologic effects. Subanalyses of clinical trials and observational studies led to the hypothesis that different diabetes drugs have different effects on cardiovascular outcomes, with some contributing to cardiovascular morbidity. Although this was contentious for a while, and total clarity is still not apparent for every drug, it led the US Food and Drug Administration to mandate that clinical trials of new diabetes medications need to include cardiovascular outcome data. And we now have a lot of information on the cardioprotective effects of the sodium-glucose cotransporter 2 inhibitors, even in patients without diabetes.

But our patients with diabetes often have comorbidities that can independently contribute to cardiovascular morbidity, and those comorbidities need to be treated—with more drugs. What about off-target effects of those medications that are demonstrably effective at reducing cardiac disease? Might they do the reverse of what I discussed above and, while decreasing cardiac disease, increase the development or worsen the progression of diabetes? It is well known that the thiazides can increase blood glucose levels, and we have generally worked around their usually mild hyperglycemic effect. A thornier issue for some patients (and physicians) has been the back-alley concern that statins can cause or hasten the development of diabetes. I think this has been a particularly challenging issue, because at least in my experience the question is most often raised by the well-read, Internet-savvy patient who already has concerns with the safety profile of statins—perceived muscle problems and dementia risk. That statins may cause an increased risk of diabetes may, for some patients, be the final nail in the medicine cabinet.

doi:10.3949/ccjm.90b.01023

In this issue of the *Journal*, Dr. Byron Hoogwerf presents a comprehensive discussion of statin use and diabetes risk,[1] contributing clinical and data-enriched context to the relationship between statins and diabetes. He provides us with concrete guidance from his perspective as an experienced clinical diabetologist and trialist as to what we can say to patients and how we can sort out this therapeutic conundrum. It is well worth the read.

As we await the snow in Cleveland, on behalf of the entire *CCJM* editorial team, I wish us all a healthy, much kinder, and peaceful 2023.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Hoogwerf BJ.** Statins may increase diabetes, but benefit still outweighs risk. Cleve Clin J Med 2023; 90(1):53–62. doi:10.3949/ccjm.90a.22069

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Median rhomboid glossitis caused by tongue-brushing

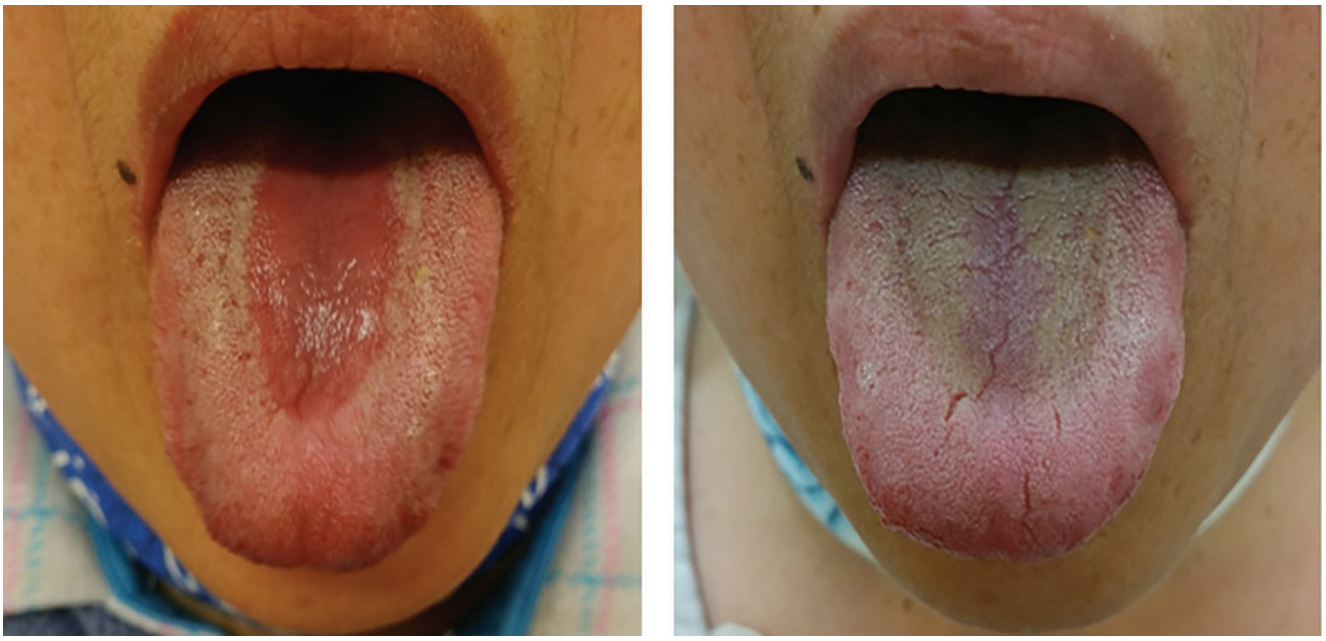

Figure 1. (A) The patient's tongue on presentation at the hospital, and (B) 1 month after discontinuing tongue-brushing.

A previously healthy 57-year-old woman presented to the hospital with a month-long history of painful sensations in the tongue. She was not a smoker. She did not use any prosthesis contacting the palate and was not in the habit of holding any food or material on the tongue. She had started vigorous brushing of the tongue 1 month earlier because her child had told her that she had halitosis. She had not received any treatment before she came to the hospital.

Physical examination revealed a plaque of smooth, erythematous, and well-circumscribed papillary atrophy on the dorsal midline of the tongue (**Figure 1A**). There were no lesions or inflammation on the hard palate. Laboratory tests were normal and testing for candidal infection was negative for yeast-like fungi. A clinical diagnosis of median rhomboid glossitis was made. The patient was advised to stop brushing her tongue, and at a follow-up visit 1 month later, her symptoms and the lesion had improved (**Figure 1B**), and no further evaluation was warranted.

doi:10.3949/ccjm.90a.21111

KEY FEATURES

Median rhomboid glossitis is present in up to 1% of the population[1] and is more prevalent in men,

immunosuppressed patients, patients with diabetes, and patients taking broad-spectrum antibiotics.[1,2] It is characterized by a papillary atrophy of the dorsum of the tongue, typically anterior to the circumvallate papillae. It occurs as a well-demarcated area of depapillation, elliptical or rhomboid in shape, on the midline of the tongue.[1] The condition is usually asymptomatic and is often first noticed by a dentist during routine examination. However, some patients may present to the physician's office with persistent pain, irritation, or pruritus.[2]

In patients with median rhomboid glossitis due to chronic candidal infection, prolonged contact of the tongue lesion with the hard palate can result in a lesion on the hard palate, referred to as a "kissing lesion." This is considered a marker of immunosuppression, and human immunodeficiency virus infection should be suspected.[1] However, the cause of median rhomboid glossitis is not limited to candidal infection, and idiopathic cases have also been reported.[3] It may also be caused by minor trauma.[4] Vigorous tongue-brushing may result in loss of filiform papillae and so should be discouraged.

The differential diagnosis includes erythroplakia, geographic tongue, and granular cell tumor, but these conditions can be differentiated by their appearance and clinical course, and unnecessary evaluation and referral can be avoided if the clinician is aware of median rhomboid glossitis.

Median rhomboid glossitis may improve spontaneously, as in this patient. If initial testing is negative for candidal infection, patient follow-up may be useful, but empiric antifungal treatment should be avoided as it contributes to resistance.[3]

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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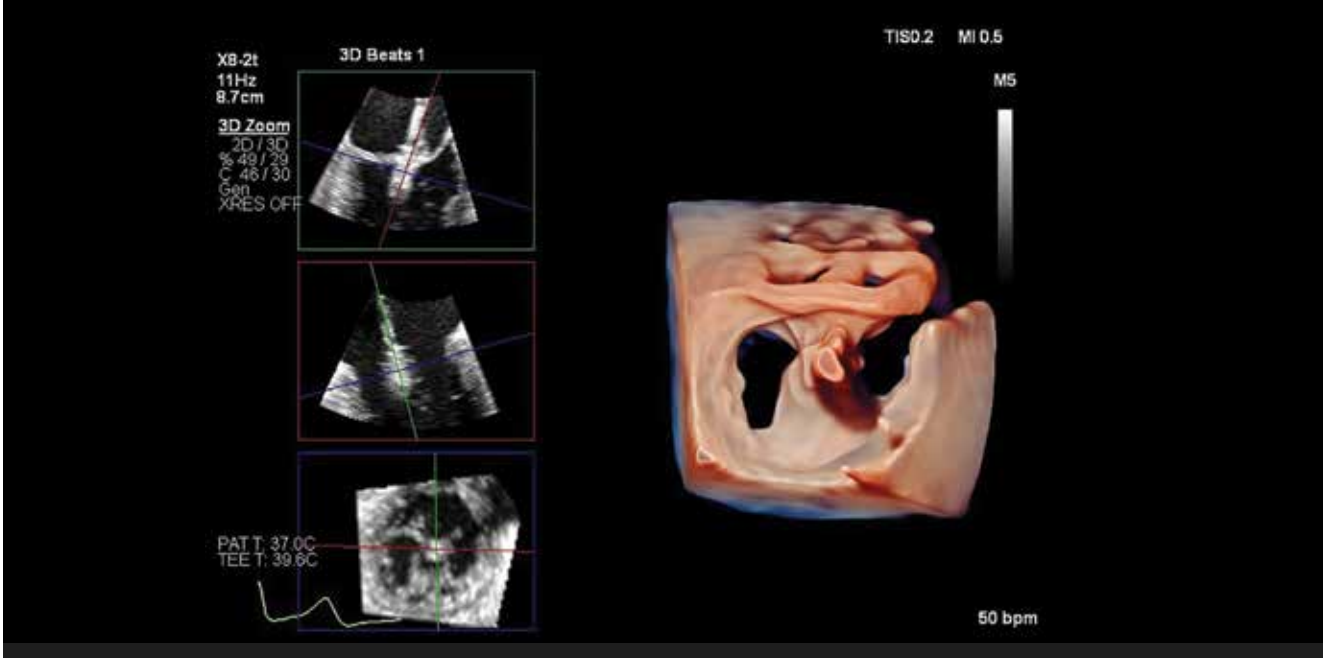

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What are my obligations to my incarcerated patient?

A 45-year-old man is brought to the emergency department with a self-inflicted forearm laceration. He is incarcerated and under the care of the Department of Corrections (DOC). The patient has a history of self-harm and iron deficiency anemia, and his baseline hemoglobin is 6 to 7 g/dL (reference range 13.0–17.0). On presentation to the emergency department, his vital signs are stable, he has no symptoms of blood loss, and his hemoglobin is 5.2 g/dL. A DOC representative presents a court order that authorizes a blood transfusion when the hemoglobin level is less than 6 g/dL, but the patient refuses the transfusion. As his caregiver, am I obligated to follow the court order against the patient's wishes?

A: The caregiver's obligation is to the patient. An incarcerated patient's autonomy deserves the same respect as the autonomy of someone not incarcerated. Loss of decision-making autonomy in healthcare is not part of a prison sentence.[1,2]

As stated by former Associate Justice of the Supreme Court Benjamin Cardozo in *Schloendorff v. Society of New York Hospital*, "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."[3] The real-world application of this principle is rarely straightforward, however.

PIVOTAL STEP: DETERMINE CAPACITY

The first step in any situation involving an incarcerated patient and a court order is to determine the patient's capacity to make decisions about his or her own care. In this case, the decision is refusal or acceptance of the transfusion authorized by the court. Psychiatric consultation may be helpful when there is comorbid psychiatric disease, but any physician (and in some US states nurse practitioners and physician assistants) who is familiar with the patient is authorized to determine capacity.

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Scenario 1

The patient has the capacity to make a decision regarding the treatment outlined in the court order—in this case, a blood transfusion.

A patient who has decision-making capacity has the same right as a nonincarcerated patient to refuse evaluation and treatment, but a court order can complicate the situation, as in the following examples:

- A court order has no bearing on the patient's capacity status. An order that authorizes medical treatment in specific scenarios is not a ruling on a patient's capacity, nor does its existence imply that the patient does not have capacity.
- A court order can be used to override a patient's right to object to a course of treatment, but it does not mandate the treatment. That is, the presence of a court order does not require a caregiver to act if the caregiver considers the treatment to be inconsistent with the patient's clearly stated preferences.

Even in *Washington v. Harper*, a 1990 US Supreme Court case that ultimately mandated antipsychotic treatment of a mentally ill incarcerated individual, the Court wrote that the interests of the incarcerated individual are "adequately protected, and perhaps better served, by allowing the decision to medicate to be made by medical professionals rather than a judge."[4] There are a few scenarios, though, in which a court's decision may overrule that of the caregiver. (See sidebar, "Exceptions to the rule").[4–6]

In our case, the patient's refusal of a transfusion is unlikely to result in irreversible harm. However, respect for an autonomous patient's preferences includes respect for their decision even if it is likely to result in death

EXCEPTIONS TO THE RULE

If the caregiver elects to go against the patient's preferences, the court order authorizing the treatment gives the caregiver legal coverage. In general, however, if a patient has the capacity to make the medical decision, the caregiver should respect the patient's autonomy and the decision. If the caregiver opts not to administer the court-authorized treatment, they should inform their organization's legal team so they can be prepared should a dispute arise.[5]

In rare situations, the court has compelled treatment of a patient with decision-making capacity in order to maintain security in a prison setting or to protect the due process of law (*Washington v. Harper*[4] or *Saenz v. Wisconsin Department of Corrections*[6]). These circumstances differ from the ones presented in this article, and caregivers outside of DOC facilities are unlikely to face such situations. Additionally, a court order that compels treatment of a specific patient does not compel a specific caregiver to administer that treatment.

or other irreversible harm. As with nonincarcerated patients, all reasonable efforts should be made to ensure that the patient's preference is informed, consistent, and congruent with their basic values.

Scenario 2

The patient lacks the capacity to refuse the treatment outlined in the court order.

This situation sets in motion a series of steps. The first is to identify the patient's healthcare power of attorney. If one does not exist or cannot be found, there are other options:

- A patient who lacks medical decision-making capacity may still have the capacity to designate a power of attorney. If the patient lacks the capacity to identify a surrogate, state-specific hierarchies of family members should be contacted,[7] and incarceration does not change or exclude this hierarchy. If it is technically feasible and medically necessary, the surrogate decision-maker should be allowed access to the patient in order to make appropriate medical decisions even if such visitation would not normally be allowed.[8]
- If no surrogate can be identified or contacted, caregivers must move forward with what they believe is in the patient's best interest. Correctional officers do not become the surrogate decision-makers and do not have the authority to make medical decisions for people in their custody. This is true for patients in all healthcare settings, including healthcare facilities within correctional institutions. As with patients who are not incarcerated, the default assumption is that a patient would want to be evaluated and treated.

In this setting—ie, the patient lacks the capacity to make the decision and name a surrogate, there is no surrogate decision-maker, and a court order instructs treatment—the caregiver is still not obliged to order the treatment and may choose not to follow a court order that they feel is medically unnecessary. On the other hand, if the caregiver does feel that the treatment is in the patient's best interest, the court order gives the caregiver legal protection to treat even when it is against the patient's wishes.

Scenario 3

The patient lacks decision-making capacity and physically resists treatment the caregiver believes is necessary.

When a patient who lacks decision-making capacity physically resists treatment the caregiver believes is needed, the same process should be followed as for other patients, using necessary mechanisms to ensure safety.[8] Sometimes this requires sedation, which is emotionally challenging even when it is used for a nonincarcerated patient. Given the additional complexities surrounding the care of incarcerated patients, forcing sedation may feel ethically questionable. Caregivers may opt to consult their legal teams or ethics committees for input in these cases. This is unnecessary, however, if the patient has been determined not to have capacity to make the decision.

OTHER CHALLENGES

When providing care in correctional settings, caregivers must abide by rules set by DOC authorities. These rules may include limiting the amount of information provided to the patient or requiring that the patient be restrained. The need to abide by the rules of correctional authorities may be reasonable, but the rules can complicate the delivery of medically appropriate care. Caregivers have the right to challenge the rules, but under the current system, final decision-making power lies with correctional employees. Further challenges may occur if caregivers feel pressure from correctional officers to make specific decisions. In these instances, it is prudent to involve the legal team or ethics committee.

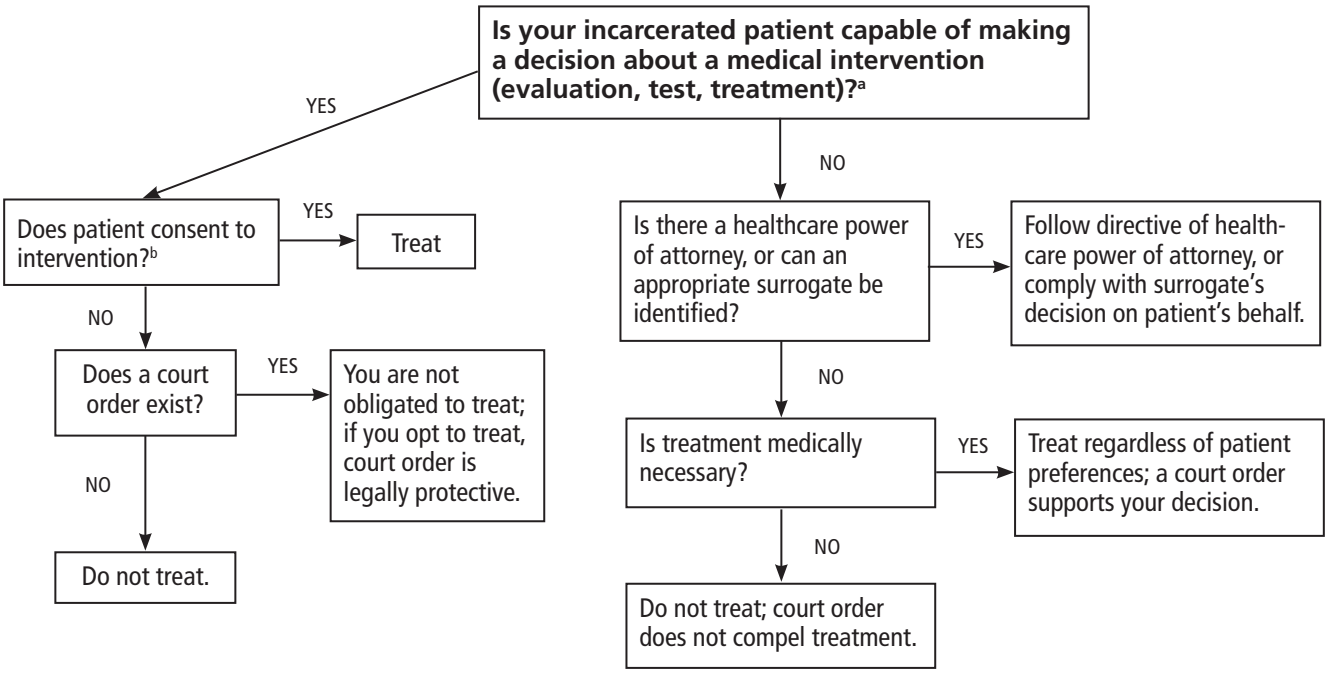

Figure 1. Navigating healthcare of an incarcerated patient.

[a]Any physician, and in some US states nurse practitioners and physician assistants, can determine capacity.
[b]This applies for medical evaluations, diagnostic tests, and treatments.

In the case of a life-threatening emergency, when there may not be time to clearly assess the patient's capacity or preferences or when an appropriate surrogate cannot be found, the default position should be to avoid irreversible decisions and preserve the patient's life until a more thorough assessment can be made. In the absence of sufficient information, it is reasonable to assume that most patients prefer life to death, so a decision to treat is still based on the best guess of the patient's likely preference.

THE BOTTOM LINE

The United States incarcerates more people per capita than any other country.[7] Caregivers in all specialties and all settings should be aware of their roles in caring for this large and vulnerable group, especially as the incarcerated population is aging rapidly and will require more medical care.[9,10] Indeed, incarcerated individuals are among the few Americans who possess a constitutional right to healthcare.[8]

Caring for patients who are incarcerated can create complex, uncomfortable situations. These cases are easier to navigate with the use of a decision-making tool (**Figure 1**) and awareness that patients who are incarcerated have the same rights of self-determination as those who are not. A prison sentence, a jail sentence, or a court order does not abolish an individual's entitlement to or refusal of healthcare.

RETURNING TO THE INITIAL CASE

This incarcerated 45-year-old patient consistently refused transfusion despite conversations with multiple caregivers. Although his hemoglobin was lower than the court-noted threshold, it was not greatly reduced from his baseline, and he was asymptomatic. The patient's stability allowed time for a thorough capacity evaluation, which was done with psychiatric assistance due to his history of self-harm.

The patient was able to state his reasons for refusal: "I don't want someone else's blood inside of me . . . [and] there is a shortage of blood in the world; my blood can regenerate, it has before." He denied suicidal ideation and was deemed to have the capacity to refuse transfusion. Ultimately, the transfusion was deferred despite the court order. ■

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Which patients hospitalized with alcohol withdrawal syndrome should receive high-dose parenteral thiamine?

A: All patients hospitalized with alcohol withdrawal syndrome who have severe or complicated withdrawal (eg, severe symptoms, hallucinations, seizures, or withdrawal delirium) and evidence of malnutrition or malabsorption and patients admitted to the intensive care unit to treat alcohol withdrawal should receive high-dose parenteral thiamine to treat Wernicke encephalopathy.[1,2]

We suggest using clinical criteria to risk-stratify all other patients hospitalized with alcohol withdrawal syndrome for Wernicke encephalopathy, as high-risk patients warrant treatment regardless of severity of withdrawal. Pharmacokinetic data indicate that currently available oral thiamine formulations are absorbed too slowly to replenish depleted brain stores, and parenteral thiamine administration is required.[3] There is no consensus on the optimal dose and duration of parenteral thiamine, but its short half-life and water solubility suggest that divided dosing (2 or 3 times daily) would lead to better tissue repletion than once-daily dosing.[3–6]

WERNICKE ENCEPHALOPATHY: UNDERDIAGNOSED AND UNDERTREATED

Wernicke encephalopathy is an acute neurocognitive syndrome caused by depletion of intracellular stores of thiamine (also known as vitamin B_1), an enzymatic cofactor essential in carbohydrate metabolism.[4] Patients with alcohol use disorder, with or without malnutrition, are at increased risk for Wernicke encephalopathy, which autopsy studies suggest is underdiagnosed.[1] Due to nonspecific symptoms and other causes of encephalopathy (including infection, withdrawal delirium, and hepatic encephalopathy) in high-risk patients, it is estimated that only 5% of cases of Wernicke encephalopathy found on autopsy are diagnosed antemortem.[1] Untreated, Wernicke encephalopathy is fatal in up to 20% of patients, and progression to Korsakoff syndrome, a devastating anterograde and retrograde amnesia, occurs in more than half of survivors, many of whom require long-term institutional care.[1,3,4,7] If treated early, the neuropsychiatric abnormalities of Wernicke encephalopathy are often reversible,[2,4] highlighting the importance of promptly identifying high-risk patients.

Clinical manifestations include confusion, oculomotor abnormalities, and gait disturbances; hypothermia and hypotension may also occur.[1] The classic triad of encephalopathy, nystagmus, and ataxia occurs only rarely and late in the disease course, and there are no reliable laboratory or imaging criteria to establish the diagnosis of Wernicke encephalopathy.[4] Serum thiamine levels correlate poorly with tissue stores, and test results may not be available for several days. For these reasons and owing to the urgency of treatment, laboratory measurement is of limited value and is not routinely recommended to guide treatment decisions.

WHICH PATIENTS SHOULD ALWAYS BE TREATED?

Given the challenge in accurately diagnosing Wernicke encephalopathy, the American Society of

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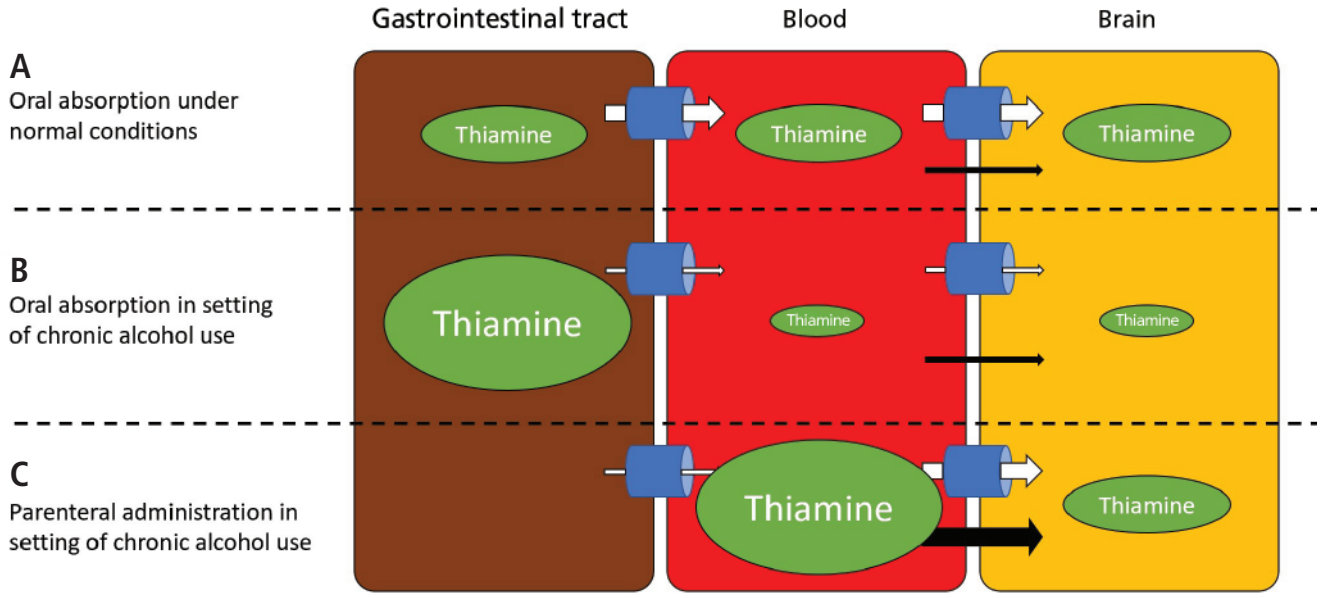

Figure 1. The three compartments above represent the gastrointestinal tract lumen on the left, the blood in the middle, and the brain on the right. The size of the green ovals is proportional to the concentrations of thiamine in each compartment, and the width of the arrows is proportional to the amount of uptake by each mechanism. The three rows diagram a schematic representation of (A) oral thiamine absorption under normal conditions, (B) oral thiamine absorption in the setting of chronic alcohol use, and (C) parenteral thiamine administration in the setting of chronic alcohol use. Under normal conditions, most uptake from the gastrointestinal tract to the blood and from the blood to the brain occurs via a membrane-bound transporter (white arrows) and little occurs via passive diffusion (black arrows). The relative proportions are altered in chronic alcohol use and with the administration of parenteral thiamine.

Addiction Medicine's 2020 guidelines recommend parenteral thiamine administration in patients hospitalized for alcohol withdrawal syndrome and any of the following[2]:

- Symptoms of severe or complicated withdrawal
- Evidence of malnutrition
- Evidence of malabsorption
- Admission to the intensive care unit to treat alcohol withdrawal syndrome.

This recommendation will result in some patients without thiamine deficiency receiving high-dose parenteral treatment. However, considering the availability, low cost, and safety of parenteral thiamine, empiric administration is recommended in high-risk populations to avert the dire consequences of untreated Wernicke encephalopathy.[2]

WHICH PATIENTS SHOULD BE RISK-STRATIFIED?

All patients admitted with alcohol withdrawal syndrome are at high risk for thiamine deficiency and should be risk-stratified for Wernicke encephalopathy because high-dose parenteral thiamine is warranted in all high-risk patients.[2] In a 1997 paper, Caine et al[8] compared autopsy findings with neurologic and neuropsychological assessments from 106 patients with alcohol use disorder to develop and validate operational criteria for the diagnosis of Wernicke encephalopathy in patients with alcohol use disorder. We favor this approach to risk stratification owing to the high sensitivity of history and physical examination findings alone. Any 2 of the following 4 criteria had sensitivity of 100% for predicting diagnosis of Wernicke encephalopathy[8]:

- Dietary deficiencies (body mass index ≥ 2 standard deviations below normal, history of grossly impaired oral intake, or low serum thiamine level)
- Oculomotor abnormalities (ophthalmoplegia, nystagmus, or gaze palsy)
- Cerebellar dysfunction (ataxia, unsteadiness, dysmetria, dysdiadochokinesia, or impaired heel-shin testing)

- Altered mental state or mild memory impairment (disorientation in 2 of 3 fields, confusion, abnormal digit span, or coma).

THIAMINE TREATMENT: ROUTE, DOSING, AND DURATION

Chronic alcohol use, with or without malnutrition, reduces intestinal thiamine absorption by up to 50%, severely limiting the ability of even large oral doses to correct tissue deficiencies (**Figure 1A and 1B**).[4] In the setting of chronic alcohol use, parenteral administration of thiamine offers 2 benefits: it overcomes reduced gastrointestinal absorption and creates a large concentration gradient between the blood and brain that drives an increase in the passive diffusion of thiamine across the blood-brain barrier, allowing replenishment of depleted stores (**Figure 1C**).[4] These observations support the administration of parenteral thiamine to treat Wernicke encephalopathy. When comparing intravenous and intramuscular administration, our practice is to administer intravenous thiamine when feasible, with intramuscular administration as an acceptable alternative.

There is no consensus on the optimal dose or duration of parenteral thiamine required to treat Wernicke encephalopathy. In their 2020 guidelines, the American Society of Addiction Medicine cites 100 mg/day intravenously or intramuscularly for 3 to 5 days as typical dosing in the absence of data from high-quality randomized controlled trials.[2] In addition, small studies done in the 1980s and 1990s suggest that parenteral doses below 250 mg daily may not consistently reverse signs and symptoms of Wernicke encephalopathy.[3] This concern has led some to recommend higher doses up to 500 mg 2 or 3 times daily, without strong evidence.[3,4,5,7] A recent single-center randomized controlled trial comparing different dosages of parenteral thiamine found no evidence of an effect of dose on neurologic and cognitive outcomes in patients at risk for Wernicke encephalopathy; however, this study was limited by small sample size, high attrition, and short duration of follow-up.[6] Fortunately, adverse effects from parenteral thiamine administration are uncommon. Although early case reports of anaphylaxis from rapid administration of intravenous thiamine have raised concern, the risk is now believed to be exceedingly rare, especially when thiamine is administered over 30 minutes.[4]

In the absence of data from high-quality dose-ranging studies, pharmacokinetic principles can inform dosing decisions. Because thiamine is a water-soluble vitamin with an elimination half-life of only 96 minutes, it is rapidly cleared from the system.[5] Given the importance of a large concentration gradient to drive passive diffusion across the blood-brain barrier, parenteral administration in divided doses (2 or 3 times daily) provides more opportunities to replenish tissue stores than once-daily dosing.

Clinical response to high-dose parenteral thiamine in patients with Wernicke encephalopathy is often brisk.[1] Once treatment is initiated, oculomotor abnormalities, if present, typically resolve the fastest, with improvement often evident within days.[1] Encephalopathy and ataxia take longer to improve, and gait impairment may persist as a lasting sequela.[1]

ORAL THIAMINE AT DISCHARGE

Unfortunately, high-quality evidence is lacking to inform which patients hospitalized with alcohol withdrawal syndrome should receive oral thiamine or multivitamin supplementation at hospital discharge.[9] Reflecting this uncertainty, current professional society guidelines do not offer definitive recommendations for prescribing oral thiamine at discharge for patients hospitalized with alcohol withdrawal syndrome.[2] We suggest engaging in shared decision-making to incorporate patient preferences and limit polypharmacy in determining who should receive oral thiamine supplementation at discharge.

THE BOTTOM LINE

Wernicke encephalopathy remains an underdiagnosed, undertreated, and potentially fatal and disabling complication of alcohol use disorder. Prompt recognition and treatment of Wernicke encephalopathy is an essential component of the care of patients hospitalized with alcohol withdrawal syndrome.[2,4] In the absence of high-quality evidence from randomized controlled trials, recommendations for thiamine administration and dosing are based on expert consensus and pharmacologic principles.[1,5,7] In the setting of chronic alcohol use with or without malnutrition, our practice is to administer intravenous thiamine in divided doses (2 or 3 times daily) for up to 5 days to ensure adequate replenishment of brain stores in all patients hospitalized with alcohol withdrawal syndrome who are high-risk for Wernicke encephalopathy. ■

Acknowledgment: *This article is dedicated to patient J.S.*

DISCLOSURES

Dr. Ganatra disclosed ownership interest (stock, stock options in a publicly held company) with Abbott Laboratories, AbbVie Pharmaceuticals, Alcon Lab, Anthem, Becton Dickinson, BioMarin, Bristol-Myers Squibb, Dexcom, Eli Lilly, Intuitive Surgical, Johnson & Johnson, Medtronic, Merck & Co, Stryker, and Thermo Fisher Scientific. The 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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REVIEW

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Bone turnover markers to monitor oral bisphosphonate therapy

ABSTRACT

Bisphosphonates are widely used as first-line therapy to slow bone loss and decrease fracture risk in postmenopausal women with osteoporosis. Nonadherence to oral bisphosphonates diminishes the benefit of reduced bone loss and fracture risk of these medications. Strategies to enhance osteoporosis monitoring and adherence to therapy are crucial to improve outcomes. Dual-energy x-ray absorptiometry (DXA) is the gold standard for monitoring bone mineral density but is slow to detect change after initiation of oral bisphosphonate therapy. Bone turnover markers (BTMs) are by-products released during bone remodeling and are measurable in blood and urine. We review how the rapid change in BTMs can be a useful short-term tool to monitor the effectiveness of oral bisphosphonate therapy, which may ultimately improve adherence to therapy and outcomes.

KEY POINTS

- Oral bisphosphonates slow bone loss and reduce the risk of fracture in postmenopausal women with osteoporosis.
- Nonadherence to bisphosphonate therapy diminishes the benefits of these medications.
- BTMs are a simple, low-risk, and convenient way to monitor effectiveness and adherence to oral bisphosphonate therapy in addition to DXA.
- Bisphosophonates induce a rapid dose-dependent decrease in bone resorption markers, making them an excellent tool to ascertain adherence to and efficacy of oral antiresorptive therapy.

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Primary osteoporosis and its precursor, low bone mass, affect more than 53 million Americans, the majority of whom are postmenopausal women.[1,2] The prevalence of osteoporosis in adults over age 50 is 12.6%, while prevalence of low bone mass is as high as 43.1% in the same age group.[1] Lifestyle and pharmacologic intervention can halt osteoporosis at any point, stabilize or improve bone density, and greatly reduce fracture risk.

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Oral bisphosphonates (eg, alendronate, risedronate, and ibandronate) are the most prescribed treatment for postmenopausal women with osteoporosis and individuals with low bone mass and high fracture risk. Alendronate and risedronate have broad-spectrum efficacy to reduce hip, spine, and nonvertebral fractures. Their long-established safety and efficacy profile, generic availability, and affordability make them excellent first choices for patients at high fracture risk.[3–5] Ibandronate is also an appropriate initial therapy in patients needing treatment for spine-specific bone loss.[6] Although a number of randomized controlled trials show a reduction in the number of osteoporosis-related fractures and an increase in bone mineral density (BMD) with oral bisphosphonate therapy, adherence to these medications may be as low as 43%.[7–9] A recent systematic review of 89 publications confirmed that early treatment discontinuation is a global problem.[10] In this study, about 35% to 70% of individuals remained on oral

bisphosphonate therapy at 6 months and only 18% to 75% had continued use 1 year after initiation.[10]

Low adherence to oral bisphosphonate therapy significantly hinders its effectiveness in reducing fractures. However, capturing the efficacy of treatment (or lack thereof) using current surrogate markers is a challenge. Current guidelines vary widely regarding repeat dual x-ray absorptiometry (DXA) for treatment monitoring, with most indicating every 1 to 3 years because it takes time for a significant bone density change.[11,12] Moreover, there is no numeric cutoff to indicate a clinically effective treatment response or a practical way to assess adherence based on the change in bone density.

We propose that clinicians consider using bone turnover markers (BTMs) to assess the effect of and adherence to oral bisphosphonate therapy. BTMs decrease with oral bisphosphonate therapy, and changes in BTMs are more rapidly detected than bone density is with BMD testing.[3] Furthermore, many studies have found a positive association between BTMs and fracture reduction.[13–15]

BONE TURNOVER MARKERS: CLINICAL OVERVIEW

BTMs are collagenous and noncollagenous components released in the bloodstream during the process of bone remodeling. They reflect a kinetic measurement of bone formation and resorption. BTMs are elevated during childhood, growth, and fracture healing. In these scenarios, elevations in bone resorption and bone formation markers are balanced. In other words, markers of both formation and resorption increase proportionately, thus maintaining a state of equilibrium. Measuring BTMs in these states is of no diagnostic value.

BTMs (resorption and formation markers) decrease in response to hormone replacement therapy and oral or parenteral antiresorptive therapy. In contrast, bone formation markers increase within days of starting anabolic therapy with teriparatide and abaloparatide, and bone resorption markers increase months later. Romosozumab, another anabolic agent approved for osteoporosis, increases bone formation markers and decreased bone resorption markers.[16]

SPECIMEN REQUIREMENTS FOR MONITORING

It is important for clinicians to be aware of the unique pharmacokinetic properties associated with the BTM they plan to monitor. Some BTMs such as C-terminal telopeptide of type I collagen (CTX) or urine N-terminal telopeptide of type I collagen (NTX) show variation with circadian rhythm and meals, so blood or urine samples should be drawn after an overnight fast. Discontinuation of multivitamins and supplements containing biotin for 24 hours before CTX or urine NTX measurement is prudent to prevent assay interference. Fasting is not indicated for measurement of N-terminal propeptide of type I procollagen (PINP) and bone-specific alkaline phosphatase (BSAP), and multivitamins and biotin-containing supplements need not be discontinued. Serum-based BTMs tend to show less individual and analytical variability when compared with urine-based markers.[17] Renal and liver dysfunction alters the clearance of the majority of BTMs. Thus, it is important to be aware of the limitations associated with specific markers. **Table 1** provides a summary of common BTMs and their properties.[18–20]

BONE TURNOVER MARKERS AND ORAL BISPHOSPHONATE THERAPY

BTMs are lowered by bisphosphonate therapy. In our clinical practice, we consider at least a 25% decrease in CTX, PINP, or BSAP and at least a 30% decrease in urine NTX at 3 to 6 months from baseline levels (ie, prior to starting therapy) to be an indication of adequate therapeutic response to bisphosphonate therapy. Therapeutic intervention is considered effective when the marker continues to remain suppressed from baseline along with BMD stability at 12 months. The magnitude of change in the markers on antiresorptive therapy correlates to the reduction in fracture risk.[13–15] **Table 2** presents the case of an 82-year-old postmenopausal woman treated with oral alendronate for osteoporosis. The patient tolerated the oral bisphosphonate well, did not report gastrointestinal upset, and no fractures occurred during the treatment period.

When using a BTM for monitoring, it is important to determine the critical difference or least significant change (LSC). The LSC is the smallest difference between a measurement and a previous measurement that is associated with a true change in the patient. The International Osteoporosis Foundation and European Calcified Tissue Society (IOF-ECTS), the Endocrine Society, and the American Association of Clinical Endocrinology, whose contemporary guidelines are followed worldwide, recently proposed using CTX or PINP for monitoring adherence to bisphosphonate treatment.[3,4,21] According to the IOF-ECTS guidelines, if the magnitude of decline in BTMs is greater than the LSC, then treatment should be continued; if the decrease is smaller, clinicians should reassess possible problems with treatment, including adherence.[21,22]

TABLE 1
Common bone turnover markers, their properties, and pros and cons

Markers of bone formation	Measured in	Diurnal variation	Renal function variation	Pros	Cons
Bone-specific alkaline phosphatase (BSAP)	Serum	No	No	No postprandial changes Stable sample due to half-life of 1–2 days Widely available	Roughly 20% cross-reaction with other types of alkaline phosphatase
N-terminal propeptide of type I procollagen (PINP)	Serum	Yes	Yes	Well studied in clinical trials Relatively low intra-individual variability PINP measures response to therapy more effectively than BSAP	Hepatic function can affect levels depending on the assay and form of propeptide being measured Increased in patients on hemodialysis
Procollagen type I carboxy-terminal propeptide (PICP)	Serum	Yes	Renal variation unknown		Less studied than other bone formation markers
Osteocalcin	Serum and urine	Yes	Yes	Correlates well with bone turnover	Less stable; must process within hours Production is dependent upon vitamin K and can decrease in response to vitamin K antagonists (eg, warfarin)
Markers of bone resorption	**Measured in**	**Diurnal variation**	**Renal function variation**	**Pros**	**Cons**
C-terminal telopeptide of type I collagen (CTX)	Serum and urine	Yes	Yes	Stable biomarker Rapidly decreases with antiresorptive therapy	Postprandial variability Can be impacted by hepatic function
N-terminal telopeptide of type I collagen (NTX)	Serum and urine (24-hour urine collection or second morning void)	Yes	Yes	Minimal postprandial variability	Fasting measurements recommended Impacted by hepatic function
Pyridinoline and deoxy-pyridinoline	Urine (24-hour urine collection or second morning void with creatinine correction)	Yes	Yes	Can be renally adjusted	Impacted by hepatic function
Tartrate-resistant acid phosphatase 5b	Serum	Yes	No	No change with renal function	Predominately from but not exclusive to bone Unstable at room temperature Increases immediately after exercise

Based on data from references 18–20.

Calculating the least significant change

Calculating the LSC is not straightforward. The calculation relies on intra-individual variability (ie, the amount of normal day-to-day variation in a patient) as well as the impression of the assay (ie, reproducibility of the assay from day to day).[21,23,24] The intra-individual variability of many markers is not well known or established, and the impression of the assay is variable among laboratories. Clinicians should therefore become familiar with the LSC of the individual

TABLE 2
An 82-year-old postmenopausal woman treated with oral alendronate for osteoporosis

Background:
- Left proximal humerus fracture 4 years prior due to a fall from standing height during a syncopal event
- Left femural neck T-score of –2.5 on dual-energy x-ray absorptiometry
- No history of celiac disease, paraproteinemia, or bariatric surgery
- Renal function and vitamin D levels were normal
- Patient concerned about falls and balance; another fall 6 months prior without fracture.

After ruling out secondary causes of osteoporosis, oral alendronate 70 mg once weekly was initiated.

Bone mineral density and bone turnover markers:

	Before treatment	At 3 months	At 1 year
T-scores:			
Lumbar spine	–1.6		–1.7
Left femoral neck	–2.5		–2.4
Right femoral neck	–2.2		–2.1
Bone turnover marker: C-terminal telopeptide of type I collagen	520 pg/mL	177 pg/mL (66% reduction from baseline)	273 pg/mL (48% reduction from baseline)

markers they utilize in clinical practice by consulting with their laboratory counterparts.

Not uncommonly, clinicians evaluate patients after they have already started oral bisphosphonate therapy. In such cases, the IOF-ECTS proposes targeting post-treatment BTMs to be reduced to at least the lower half of the premenopausal reference interval.[21,23,24]

Additionally, many women with osteoporosis and high fracture risk have baseline BTMs that may already be in the lower half of the reference range before they start therapy. In this scenario, it is hard to rely on a change in BTMs because little research has been conducted on the impact of fracture risk reduction when the markers are low before treatment initiation. For these patients, it is prudent to rely on BMD changes to make clinical decisions. A few studies and guidelines have proposed checking an alternative marker at baseline (eg, if the PINP is below the reference level, measure BSAP as an alternative approach).[21,23,24]

BONE TURNOVER MARKERS AND BISPHOSPHONATE 'DRUG HOLIDAY'

Due to concerns about long-term side effects of antiresorptive therapy, such as jaw osteonecrosis and atypical femur fractures, clinicians may recommend that patients with a significant therapeutic response pause therapy and enter a bisphosphonate "drug holiday." The optimal duration of the pause has not been established and needs to be individualized based on clinical circumstances, such as a significant decline in DXA or an increase in BTMs.

Thus, monitoring for rising BTMs during a pause in bisphosphonate therapy may be useful in determining when to restart therapy. Some experts feel that a rise in the markers to pretreatment levels provides early feedback about the loss of therapeutic effect and signals a need to resume osteoporosis treatment. Of note, adequately powered clinical studies to support this approach are lacking. Additionally, as stated earlier, this approach may not apply to patients with osteoporosis who had low BTMs before treatment was started. With that in mind, when BTMs start to rise to pretreatment levels, our approach has been to re-evaluate the patient for development of new clinical risk factors for fracture and, sometimes, to repeat DXA earlier to initiate discussion about resuming therapy.[3,4]

BONE TURNOVER MARKERS TO MONITOR PATIENT ADHERENCE

Nonadherence to bisphosphonate therapy usually occurs after 6 to 7 months of treatment, well before DXA is repeated for treatment monitoring.[9,10,25] Clowes et al[26] showed that measuring BTMs can help increase adherence to oral bisphosphonate therapy. This association was supported by another study, which found an increase in persistence with oral risedronate when a positive BTM response was shared with patients.[27] However, not all published studies have observed this effect.[28]

TABLE 3
A 63-year-old postmenopausal woman treated with oral alendronate for osteoporosis

Background:
- History of breast cancer treated with lumpectomy, radiation therapy, and 5 years of tamoxifen
- Outside DXA scans showed a progressive decline in her lumbar spine T-score from –3.1 to –3.3
- Femoral neck bone density was stable
- Past medical history was otherwise unremarkable
- No history of lactose intolerance, celiac disease, or chronic glucocorticoid use
- She did not take calcium supplements, but took over-the-counter vitamin D
- No history of antifracture therapy.

The patient was prescribed oral alendronate 70 mg once weekly.

Bone mineral density and bone turnover markers:

	Before treatment	3 months	1 year
T-scores:			
Lumbar spine	NA		–2.6
Left femoral neck	NA		–1.5
Right femoral neck	NA		–1.5
Bone turnover marker: C-terminal telopeptide of type I collagen	653 pg/mL	361 pg/mL (45% reduction from baseline)	188 pg/mL (72% reduction from baseline)

NA = Not available: baseline dual-energy x-ray absorptiometry (DXA) was done at an outside facility and thus was not appropriate for comparison.

Because BTMs respond rapidly to changes in treatment, their utilization is endorsed by contemporary societal guidelines as an effective feedback tool to improve patient adherence.[3,4,21,24] A positive treatment response (suppressed markers) reinforces to patients that treatment is effective and helps promptly identify patients not responding to treatment (unsuppressed markers).

As is often encountered in the real-world setting, a patient's baseline BMD testing may have been done at an outside facility. **Table 3** provides details of a 63-year-old postmenopausal woman referred to our endocrinology clinic with DXA done outside our facility and with a reported T-score of −3.3 at the lumbar spine. Repeat DXA at our facility showed a lumbar spine T-score of −2.6. Since DXA done at different facilities cannot quantify bone density changes without cross-calibration, a BMD change could not be assessed. Given this scenario, we felt that her early and persistent BTM response was particularly valuable in developing confidence that her treatment was effective. No gastrointestinal upset was reported, and no fractures occurred during treatment.

LIMITATIONS OF BONE TURNOVER MARKERS

BTMs should not be used as a screening test for osteoporosis in the general population. Up to 20% of postmenopausal women with osteoporosis taking calcium and vitamin D supplementation may have baseline BTMs below the premenopausal mean reference range and will not be identified appropriately for therapy, highlighting a key problem with this approach.[23]

When interpreting BTMs, one should keep in mind that they fluctuate in response to any process that manipulates the bone remodeling process. Therefore, BTM testing may be unhelpful in patients with recent glucocorticoid use (resorption markers rapidly increase, formation markers decrease), recent fracture (resorption markers double in weeks, formation markers double in roughly 3 months and stay elevated up to 1 year), or autoimmune conditions affecting bones (eg, rheumatoid arthritis), where markers do not correlate with disease progression or treatment effect.[16,29]

DISCLOSURES

Dr. Algeciras-Schimnich has disclosed consulting for Fujirebio and Roche Diagnostics. The 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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EDITORIAL

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Making best use of bone turnover markers to monitor oral bisphosphonate therapy

We now have more agents than ever before to treat osteoporosis, including newer anabolic drugs such as teriparatide, abaloparatide, and romosozumab that increase bone formation and are extremely effective at preventing fractures. But the oral bisphosphonates remain the most widely prescribed antifracture drugs and continue to pose clinical challenges such as measuring therapeutic efficacy and ensuring patient adherence.

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Poor gastrointestinal absorption, potential gastrointestinal and musculoskeletal adverse effects, irregular dosing regimens, and patient fear of rare but serious complications of therapy such as atypical femoral fracture and osteonecrosis of the jaw—all have a potential negative impact on patient adherence to therapy.

In this issue of the *Cleveland Clinic Journal of Medicine*, Ashcherkin and colleagues[1] review how bone turnover markers (BTMs) can be used to monitor oral bisphosphonate treatment efficacy and patient adherence. However, the clinical applications of bone turnover markers (BTMs) can extend beyond these roles: BTMs can be utilized to determine when to start or end a bisphosphonate "holiday," and they can also measure treatment response.

WHAT ARE BONE RESORPTION AND BONE FORMATION MARKERS?

As discussed by Ashcherkin and colleagues,[1] BTMs are byproducts of bone remodeling released into the bloodstream. The phrase "bone turnover" encapsulates markers of bone resorption and markers of bone formation. Markers of bone resorption are breakdown products resulting from osteoclastic activity in the bone that are released in the bloodstream; likewise, markers of bone formation are byproducts of osteoblastic activity in bone that are released when bone is formed.[2]

Markers of both bone formation and bone resorption can be used clinically, and many clinicians, myself included, use markers of bone formation such as procollagen type 1 to assess a patient's response to an anabolic agent such as teriparatide, abaloparatide, or romosozumab. However, I would like to focus my comments here on bone resorption.

CURRENT RECOMMENDATIONS

Markers of bone resorption include collagen breakdown products C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide of type I collagen (NTX), noncollagen proteins, osteoclastic enzymes, and osteocyte activity markers.[2] The International Osteoporosis Foundation has proposed that the serum CTX level be used as a reference marker of bone resorption and that procollagen type 1 be used as a reference for bone formation.[2] CTX and NTX are released in the bloodstream and can be measured in serum or urine, though some may argue that measuring serum levels of BTMs is preferable.[3] However, the important point here is for the clinician to choose a specific BTM and become familiar with the properties of that test. In other words, one must be familiar with the proper way of collecting the sample, the least significant change, and the advantages and limitations of that particular test.

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THE VALUE OF MARKERS OF BONE RESORPTION

In healthy bone, there should be a balance between resorption and formation. Markers of bone resorption are elevated in situations where there is greater bone resorption than bone formation, such as in postmenopausal osteoporosis, although, as Ashcherkin and colleagues point out,[1] an elevated marker of resorption is hardly specific for postmenopausal osteoporosis and can be seen in a variety of disease states. The value of these byproducts of osteoclastic activity lies in the observation that bone turnover decreases in response to treatment with antiresorptive agents such as bisphosphonates. The relatively rapid decrease in markers of bone resorption (within days of intravenous or injection therapy, and within weeks to months of initiating oral therapy) lies in stark contrast to the slower, less dramatic changes observed on bone density scans.[4–6] In addition to providing information on bone resorption or formation, BTMs are useful in that they can be measured more frequently than bone density scans can be obtained, therefore providing the clinician with more real-time data to aid decision-making.[4]

CLINICAL USE OF MARKERS OF BONE RESORPTION

BTMs cannot be used to diagnose osteoporosis or predict fracture risk. However, they can and should be used to assess patient adherence and biologic response to oral bisphosphonate therapy, as emphasized by Ashcherkin and colleagues. It should be understood that a baseline BTM level must first be obtained as a point of comparison, otherwise posttreatment measurements are meaningless.

Although an area of some debate, an approximately 30% to 55% decrease in a marker of bone resorption 3 to 6 months after starting antiresorptive therapy would generally indicate an adequate therapeutic response.[7] In a patient on alendronate therapy, a follow-up BTM level that has not decreased as anticipated would therefore indicate either poor absorption or poor adherence. That particular patient may benefit from a switch to an intravenous bisphosphonate such as zoledronic acid.

However, markers of bone turnover have additional useful clinical applications. In my clinical practice, I obtain a baseline urine NTX level for all patients with osteoporosis before starting oral or intravenous bisphosphonate therapy. I use follow-up NTX levels to assess response to therapy and make management decisions based on the results. In patients who are on a bisphosphonate holiday, I obtain a repeat NTX level to help determine the need to restart therapy, as an increase in NTX would prompt me to reconsider restarting bisphosphonate therapy.

Whenever the BTM level and the bone density scan are not congruent, I make decisions based on the bone density scan, as this measurement represents the gold standard in bone density ascertainment and osteoporosis care. If a patient clinically has osteoporosis based on bone density scan or fracture history, a lower-than-expected baseline BTM would never dissuade me from treatment. Likewise, if a patient's bone density has increased in response to antiresorptive therapy while the BTM has not decreased as expected, I would certainly not judge that treatment as less than successful based on one BTM test. However, in the face of a stable bone density scan, a rising NTX in a patient who is otherwise clinically stable based on bone density scan and fracture history would indicate that it is time to restart therapy.

One criticism leveled at the use of BTMs in this manner is that we do not yet have sufficient randomized controlled trial data to support this specific use clinically. However, BTMs have been investigated in numerous pharmacodynamic trials, which have demonstrated a significant decline in markers of resorption days to weeks after initiation of antiresorptive therapy.[8–10] Additional data beyond a bone density scan are often needed to make treatment decisions, particularly if a bone density scan cannot be covered by insurance, and measuring BTMs can fill this role adequately. Without the use of BTMs we would otherwise be operating in a clinical vacuum in many instances. As do many others in this field, I maintain that it is better to have at least some data from BTMs to guide management decisions than to have no data whatsoever. Although additional data would be helpful in guiding further use, standardization, and interpretation of these tests, we currently have enough clinical experience to enable the reasonable use of BTMs in clinical osteoporosis management.

DISCLOSURE

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

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Central vision loss in a 44-year-old woman

A 44-year-old woman presented to the emergency department following 1 week of sudden, painless, central vision loss in the left eye and 1 day of headache preceded by intermittent floaters and flashing lights. The headache was a dull, aching pain in the left temple. For the preceding 2 months, she had been treated by an outside ophthalmologist for bilateral anterior uveitis, unresponsive to topical prednisolone. She additionally noted recent hair loss and a rash on the palms. She denied light sensitivity, eye pain, trauma, blurred vision, fever, chills, chest pain, shortness of breath, abdominal pain, nausea, dizziness, blurred vision, or syncope prior to presentation.

Medical comorbidities included 15 years of systemic lupus erythematosus (SLE) and antiphospholipid syndrome that first manifested as a cerebrovascular accident (CVA). Serum analysis at time of SLE diagnosis revealed strongly positive antinuclear antibodies, elevated Sjögren syndrome antibodies, double-stranded DNA, beta-2-glycoprotein immunoglobulin G, anticardiolipin immunoglobulin G, and lupus anticoagulant.

The patient's presentation of vascular thrombosis with positive antiphospholipid antibodies met the Sydney criteria for diagnosis of triple-positive antiphospholipid antibody syndrome. Following appropriate anticoagulation, she experienced occasional skin rashes, Raynaud phenomenon, and sicca symptoms. Other medical comorbidities included migraines and focal epilepsy. Her regular medications included prednisone 7.5 mg daily, methotrexate, hydroxychloroquine, warfarin, and topiramate. She was sexually active.

INITIAL EVALUATION AND MANAGEMENT

At presentation, the patient's temperature was 99.1°F (37.3°C), heart rate 80 beats per minute, blood pressure 131/80 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation 100% on room air. She was alert and oriented and mildly uncomfortable but not in distress. Head examination demonstrated patchy alopecia. Extremity sensation and strength were normal. Skin examination revealed a scaly, erythematous rash on both palms. Her joint examination was unremarkable, and there was no cervical, supraclavicular, axillary, or inguinal lymphadenopathy.

Visual acuity was 20/20 in the right eye and 3/200 in the left eye. Pupils were equally round and reactive to light without an afferent pupillary defect. Confrontation visual field testing revealed central scotoma in the left eye. Extraocular muscles functioned properly in both eyes. Slit-lamp microscope examination demonstrated mild to moderate anterior chamber and vitreous cellular reaction, indicating the presence of anterior and intermediate uveitis. Dilated funduscopic examination demonstrated blunted foveal reflex suggestive of retinal involvement and bilateral panuveitis.

Laboratory test results

Notable results of blood testing at presentation were as follows:

- Hemoglobin 10.6 g/dL (reference range 11.6–15.0)
- Mean corpuscular volume 93.7 fL (78.2–97.9)
- Red blood cell distribution width 15.5% (12.2–16.1)
- Platelet count 296 x 10^9/L (157–371)
- Total leukocyte count 8.2 x 10^9/L (3.4–9.6)
- Neutrophils 6.43 x 10^9/L (1.56–6.45)
- Lymphocytes 1.19 x 10^9/L (0.93–3.07)
- Monocytes 0.53 x 10^9/L (0.26–0.81)
- Eosinophils 0.04 x 10^9/L (0.03–0.48)
- Basophils 0.03 x 10^9/L (0.01–0.08)
- International normalized ratio (INR) 3.6 (0.9–1.1)
- Activated partial thromboplastin time (aPTT) 48 seconds (25–37)

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TABLE 1
Uveitis

Location	Structures	Possible etiology
Anterior uveitis	Iris, ciliary body, anterior chamber	Sarcoidosis, ankylosing spondylitis, inflammatory bowel disease, Lyme disease, syphilis
Intermediate uveitis	Vitreous, peripheral retina	Tuberculosis, multiple sclerosis, sarcoidosis, inflammatory bowel disease, Lyme disease, syphilis
Posterior uveitis	Retina, choroid	Toxoplasmosis, tuberculosis, herpes simplex virus, varicella zoster virus, Lyme disease, syphilis
Panuveitis	All of the above	Sarcoidosis, sympathetic ophthalmia, ocular or hematologic neoplasm, tuberculosis, Behcet disease, Lyme disease, syphilis

- Glucose 152 mg/dL (70–140)
- C-reactive protein 0.4 mg/dL (≤ 0.8)
- Serum creatinine 0.79 mg/dL (0.59–1.04).

Findings on imaging

Computed tomography of the head without contrast revealed no evidence of acute intracranial or orbital bleed, infarction, or mass effect. There was evidence of old infarction in the frontoparietal region and left parietal lobe, mild generalized cerebral atrophy, and ex vacuo ventricular dilation.

DIFFERENTIAL DIAGNOSIS

1 What is the most likely cause of the patient's symptoms?

☐ SLE
☐ Sarcoidosis
☐ Lyme disease
☐ Syphilis

After a full day of an associated headache, the patient experienced unilateral, painless, progressive vision loss for 1 week following a 2-month history of bilateral anterior uveitis that was unresponsive to corticosteroids. Her lab results revealed mild normocytic anemia, appropriate anticoagulation, and mildly elevated random glucose in the absence of diabetes. Given her CVA history and antiphospholipid syndrome diagnosis, imaging studies appropriately ruled out CVA and intracranial bleeding, and ophthalmic examination excluded retinal artery or vein occlusion. Additionally, retinal toxicity owing to chronic hydroxychloroquine use was rejected based on examination and pattern of vision loss (central vs ringed scotoma). Overall, ocular examination and history were consistent with chronic panuveitis.

Uveitis refers to inflammation of the uveal tissues, specifically the iris, ciliary body, and choroid.[1] It also commonly affects tissue or space adjacent to the uvea such as the anterior chamber, vitreous humor, or retina.[2] It is subdivided by anatomic location (**Table 1**).[2] Each form of uveitis may present with vision loss, necessitating a detailed ophthalmologic workup augmented by serum testing to determine underlying cause.[3] Anterior uveitis encompasses inflammation of the iris or ciliary body and typically presents with a red, painful eye and cellular reaction in the anterior chamber on slit-lamp biomicroscopy.[1] Intermediate uveitis includes inflammation of the vitreous and peripheral retina and presents with worsening eye floaters, decreased vision, and cells in the vitreous on examination.[4] Posterior uveitis involves inflammation of the retina and choroid and presents with deteriorating vision and visual field changes.[5] Panuveitis involves global inflammation that may present with symptoms from each of the previous categories.[6]

Systemic lupus erythematosus

Though SLE can involve any structure within the eye, uveitis is an uncommon ophthalmologic manifestation of SLE (0.47%).[7] SLE more commonly causes corneal manifestations such as keratoconjunctivitis due to secondary Sjögren syndrome.[8] Retinal vasculopathy is another common ocular finding that additionally presents with cotton wool spots on funduscopic examination in SLE patients.[8] Given our patient's uveitis and lack of corneal manifestations or retinal vasculopathy, an SLE flare was unlikely to be contributing.

Sarcoidosis

Ocular sarcoidosis occurs in 25% to 50% of patients with systemic sarcoidosis.[9–12] Ocular sarcoidosis typically presents in younger individuals as anterior uveitis

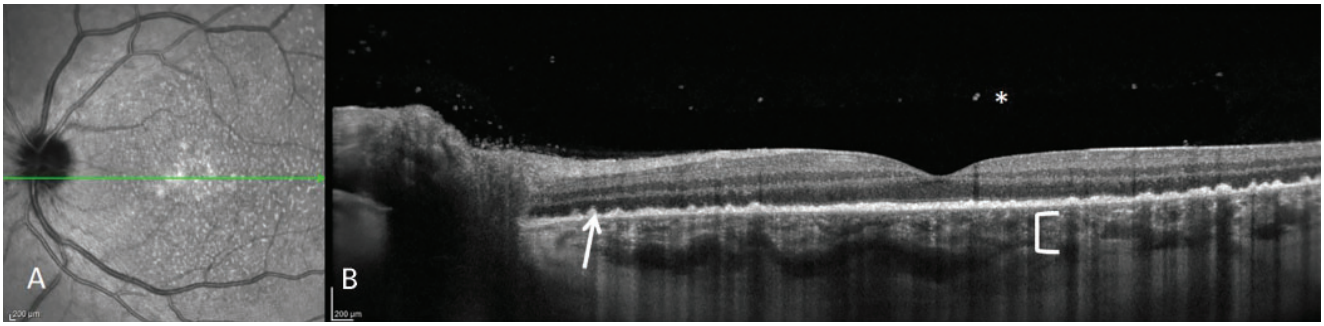

Figure 1. (A) Near infrared reflectance and (B) corresponding macula optical coherence tomography of the left eye, derived from the green line in image (A), demonstrate subretinal infiltrates (white arrow) and increased choroidal hypertransmission (white bracket) due to outer retinal atrophy. Vitritis is shown with a white asterisk.

compared with panuveitis in middle and older age patients.[9] Advanced disease can affect all structures of the eye.[9] Most sarcoid uveitis is bilateral, and approximately 90% of patients experience chronic sarcoid uveitis, as our patient. However, it is rare for adults to present with sarcoid uveitis without concurrent pulmonary manifestations.[13–15] Thus, sarcoidosis is less likely.

Lyme disease

Infection causes roughly 20% of all uveitis, including, but not limited to, viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus), bacteria (Lyme disease, syphilis, tuberculosis, bartonellosis), and parasites (toxocariasis).[16–18] *Borrelia burgdorferi*, the spirochete responsible for Lyme disease, can directly invade the eye to produce acute or chronic visual symptoms.[19,20] The principal symptom of Lyme ophthalmic involvement is decreased vision.[21] Although there are reports in the literature, uveitis due to Lyme is exceedingly rare and should only be suspected if the patient has systemic signs and symptoms in combination with plausible risk factors for Lyme disease, such as outdoor activities, known tick bite, and a characteristic rash.[22,23] The absence of these characteristics places Lyme uveitis low on the differential.

Syphilis

Treponema pallidum is the spirochete responsible for syphilis.[24,25] Ocular syphilis is a form of neurosyphilis characterized by involvement of the eye. It can present at any stage of a syphilitic infection but is quite rare with estimates of 0.6% of patients with syphilis presenting with ocular syphilis.[24] The most common manifestation of ocular syphilis in an HIV-negative patient is posterior uveitis, though anterior uveitis and panuveitis can occur.[26] These can all present as decreased vision, necessitating further ophthalmologic workup and serum treponemal testing.[3]

Our patient's presentation of decreased vision associated with panuveitis, in addition to patchy alopecia and previous rash on the hands raises suspicion for ocular syphilis. Of note, neurosyphilis can present as acute ischemic stroke with the prodromal symptom of a mild headache.[25] Reassuringly, imaging studies ruled out ischemic stroke in our patient.

NEXT STEPS

In the setting of uveitis, further investigation hinges on advanced ocular imaging and appropriate lab testing for an underlying cause, which includes syphilis testing, angiotensin-converting enzyme for sarcoidosis, Lyme serologies, and QuantiFERON gold or purified protein derivative for tuberculosis. Multidisciplinary evaluation is essential and advanced ocular imaging may include macula optical coherence tomography, fundus autofluorescence, and fluorescein angiography to reveal subtle details not appreciated clinically.

Ocular imaging in our patient demonstrated inflammatory cells in the vitreous as well as retinal and subretinal infiltrates (**Figure 1**). When combined with autofluorescence imaging that revealed a pattern of mixed hypo- and hyperautofluorescence of the retina, commonly referred to as "leopard spotting," these findings were characteristic of acute syphilitic posterior placoid chorioretinitis—a hallmark finding of ocular syphilis (**Figure 2**).[27]

2 What is the most appropriate testing sequence for syphilis in this patient?

☐ Nontreponemal (eg, rapid plasma reagin [RPR] or venereal disease research laboratory [VDRL]), treponemal (eg, fluorescent treponemal antibody

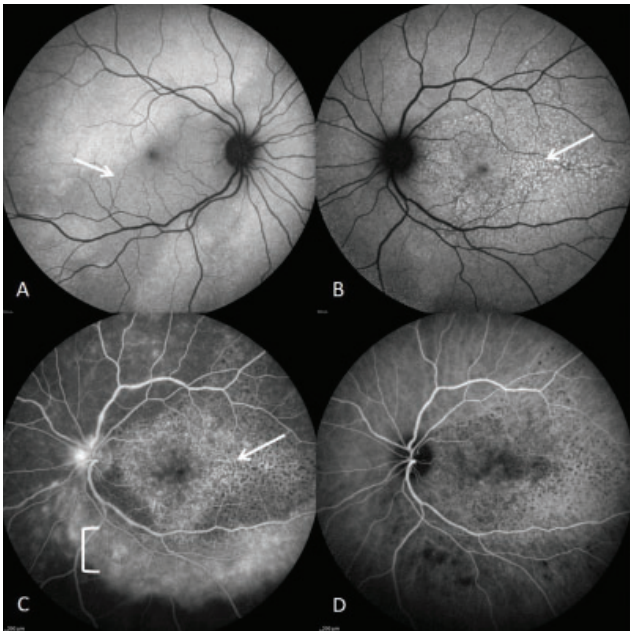

Figure 2. Fundus autofluorescence of right and left eye. (A) In the right eye, there is a placoid appearance in the macula (white arrow). (B) In the left eye, there is a stippled pattern of hyperautofluorescence and hypoautofluorescence scattered throughout the macula (white arrow). (C) Fluorescein angiography and (D) indocyanine green angiography of the right eye demonstrate a stippled pattern of hyperfluorescence with regions of hypofluorescence owing to blocking consistent with the location of the subretinal infiltrates (white arrow in C; similar finding in D). Just inferior to the inferior vascular arcade, there is a band of perivascular hyperfluorescence consistent with perivascular staining (white bracket).

absorption [FTA-ABS]), cerebrospinal fluid (CSF) testing
- ☐ Treponemal, nontreponemal, CSF testing
- ☐ Darkfield microscopy
- ☐ CSF testing, treponemal, nontreponemal

Nontreponemal tests rely on reactivity of antibodies in patient serum to cardiolipin-cholesterol-lecithin antigen.[28] Titration of nontreponemal tests provides quantitative measure of disease. Examples include RPR and VDRL titers. Treponemal tests detect antibodies against specific *T pallidum* antigens. The most common example is the FTA-ABS test.[28]

Treponemal tests have historically been more complex and expensive to perform than nontreponemal tests, leading to traditional screening of an initial nontreponemal test followed by confirmatory treponemal test, if reactive.[28] However, newer versions of treponemal tests are automated, facilitating ease of use.[28]

Thus, the most appropriate testing sequence for this patient is a treponemal test, such as FTA-ABS followed by reverse screening with a nontreponemal test, such as an RPR or VDRL titer.[29,30] Reverse screening is also preferred in suspected late stage syphilis—as with most ocular syphilis—where serum nontreponemal tests may be negative but treponemal tests remain positive.[31]

Because ocular syphilis is a manifestation of neurosyphilis, in patients with suspected neurosyphilis, VDRL can be performed on CSF after positive serum testing, but should not delay initiation of treatment.[32] This is particularly useful in determining diagnosis in patients without ocular symptoms or examination findings.[32] Darkfield microscopy is complex and no longer routinely recommended or available.[33]

Of special consideration in our patient, nontreponemal tests may return false-positive in patients with antiphospholipid syndrome when anticardiolipin antibodies are present.[34] The reverse screening technique is particularly useful in this circumstance, as FTA-ABS and other treponemal tests do not rely on reactivity of cardiolipin in patient serum.[28]

CASE CONTINUED

The patient's serum FTA-ABS returned positive, and serum RPR titer was reactive and remained reactive to a titer of 1:512. The patient revealed having an unprotected sexual encounter 4 months prior. The patient was admitted to inpatient medicine for lumbar puncture to confirm neurosyphilis and treatment. Because of her history of CVA in the setting of antiphospholipid syndrome, the patient required bridging anticoagulation for the lumbar puncture to be performed safely. Lumbar puncture and CSF analysis revealed elevated protein of 68 mg/dL (reference range 0–35), normal glucose of 57 mg/dL (50–80), 37 nucleated cells per microliter (0–5), and CSF VDRL that remained reactive to a titer of 1:1—consistent with neurosyphilis. Serum HIV testing was negative.

3 What should be the next step in this patient's management?

- ☐ Intravenous penicillin G infusions 3 million units every 4 hours
- ☐ Intramuscular procaine penicillin G 2.4 million units daily and oral probenecid 500 mg
- ☐ Intramuscular ceftriaxone injections
- ☐ Close monitoring, testing for additional sexually

transmitted infections, and repeat lumbar puncture studies in 3 months

Intravenous penicillin G infusions of 3 to 4 million units should be given every 4 hours for 10 to 14 days, or penicillin G 24 million units as a continuous infusion for 10 to 14 days.[30] Allergic patients should undergo penicillin desensitization and proceed with either of the above 2 options.[32]

Intramuscular procaine penicillin G injections plus probenecid has not been well studied in the treatment of neurosyphilis, and central nervous system levels of oral/intramuscular penicillin are often undetectable.[35–37] Oral probenecid is believed to increase the bioavailability of penicillin in the CSF by inhibiting excretion of penicillin in the urine through blockade of the organic anion transporter in the proximal convoluted tubule.[35,36] Though early data suggest effectiveness of lumbar puncture penicillin plus probenecid in the treatment of neurosyphilis,[32,38] intravenous penicillin remains the preferred treatment.[37]

Intramuscular ceftriaxone injections are an appropriate alternative to intravenous penicillin G in patients allergic to penicillin who remain poorly responsive after resensitization and challenge.[30,39,40]

Close monitoring. Following penicillin infusion, monitoring for Jarisch-Herxheimer reaction after antibiotic treatment is essential.[30] Endotoxins released from lysed spirochetes induce fevers, chills, myalgias, headache, tachycardia, and vasodilation with resultant mild hypotension and flushing.[30] It occurs within 2 to 24 hours of antibiotic administration and resolves within 12 to 24 hours.[30] Treatment is symptomatic, and acetaminophen is the preferred agent.[30,41]

SYPHILIS

Syphilis is a sexually transmitted systemic disease caused by infection with the spirochete bacteria *T pallidum*.[30] A moniker of "the great imitator" befits syphilis for its numerous and often vague clinical presentations.[30,42] Syphilis classically progresses through 3 stages of increasing severity.[42] Primary syphilis commonly presents with a solitary, painless genital chancre in response to local invasion by the bacteria.[42] Chancres can present on any skin surface that was in direct contact with an infected lesion, including the digits, nipples, and oral mucosa.[42] Secondary syphilis results from systemic hematogenous bacterial dissemination of an untreated primary infection.[43] The clinical manifestations in this stage are often nonspecific, but can include condyloma lata, a generalized maculopapular rash involving the hands and feet, and alopecia, in addition to symptoms of myalgia, headache, and malaise among many others.[43] Primary and secondary syphilis often improve within weeks but can regress into a latent phase only detectable by serologic testing. Months or years later, some patients progress to the tertiary (late) stage, characterized by cardiovascular involvement resulting in aortic aneurysm, valvulopathy, and/or organ infiltration with gummas.[44,45]

Neurosyphilis refers to *T pallidum* spread into the central nervous system and can manifest in any stage of the disease. Five types of neurosyphilis exist, with severity ranging from asymptomatic in early forms to general paresis and tabes dorsalis in the late forms, years or decades after initial infection.[30] CSF nontreponemal testing should be performed in patients with suspected neurosyphilis.

Ocular syphilis is a form of neurosyphilis that often presents as posterior uveitis or panuveitis, though almost any ocular structure can be involved.[46] Posterior placoid chorioretinitis is a characteristic yellowish plaque lesion near the macula that may be identified through fundoscopy in patients with secondary and tertiary syphilis.[47]

Management considerations

Broad testing for sexually transmitted infections and repeat lumbar puncture with basic labs should be considered at 3 months.[48,49] Repeat lumbar puncture is not indicated in most patients, however, should be considered in immunocompromised patients, such as ours. Patients need to be followed with serial nontreponemal tests at 3 months and every 6 months thereafter to confirm disease eradication.[50]

Failure of titers to be reduced by 4-times within 6 to 12 months indicates inadequate response to treatment (eg, 1:64 to 1:16).[32] A clinical cure is indicated by seroreversion—loss of antibodies and negative nontreponemal test. Retreatment is indicated if a patient fails to experience a 4-fold decrease of CSF VDRL titer by 1-year post-treatment, if there is a 4-fold increase in CSF VDRL titer, or if CSF white blood cell count has not decreased after 6 months or normalized after 2 years.[50]

CASE CONCLUSION

Intravenous penicillin was initiated and tolerated well without development of Jarisch-Herxheimer reaction. Two weeks of continuous penicillin infusion yielded full visual recovery to 20/20 acuity in both eyes. Given the patient's immunocompromised status and recommendation of our Infectious Disease

colleagues, repeat CSF evaluation was performed at 3 months to monitor disease resolution, which confirmed eradication.

TAKE-HOME POINTS

- Syphilis is an important consideration for patients presenting with subacute vision loss.
- Identify syphilis using preferred "reverse screening" of treponemal assay followed by nontreponemal assay for confirmation.
- Treatment of neurosyphilis should include penicillin G infusion with close monitoring for Jarisch-Herxheimer reaction.
- Confirm eradication of disease with nontreponemal tests, consider repeat CSF testing for eradication in immunocompromised patients, and pursue broad testing for other sexually transmitted infections and related age-appropriate cancer screening (cervical cancer).

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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REVIEW

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Update in cutaneous manifestations of COVID-19: Special populations

ABSTRACT

Cutaneous abnormalities were among the first clinical findings reported in patients infected with SARS-CoV-2 at the onset of the COVID-19 pandemic, but the significance was initially unclear. Correlations have since been drawn between many of these cutaneous eruptions and their diagnostic or prognostic value. Additionally, COVID-19 vaccines have generated acute and delayed cutaneous reactions with which clinicians should be familiar. In this narrative review, we update the cutaneous abnormalities associated with COVID-19 infection for pediatric and non-White populations, and common cutaneous reactions to COVID-19 vaccines.

KEY POINTS

There has been an increase in cutaneous manifestations together with and following COVID-19 infection and messenger RNA vaccination, respectively.

Unique manifestations have been described in children, including erythema multiforme, acute hemorrhagic edema of infancy, papular acrodermatitis of childhood, and various skin changes in multisystem inflammatory syndrome in children.

Adenoviral vector vaccine appears to result in vaccine-induced thrombotic thrombocytopenia in some patients.

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As the impact of the COVID-19 pandemic has extended across the globe, cutaneous presentations deserve specific attention in both adult and pediatric patient populations.[1–8] The development and dissemination of COVID-19 vaccines has also generated notable cutaneous findings,[9–16] and studies have noted skin phenotype as a factor in cutaneous COVID-19 manifestations.[17–21] Recognition of these reactions and their implications is beneficial to clinicians in shaping patient counseling and anticipatory guidance (**Table 1**).[9,12,17–32]

PEDIATRIC OVERVIEW

The reported prevalence of cutaneous manifestations ranges between 0.25% and 8.1% in pediatric COVID-19 cases,[1,2] with studies suggesting that the face is the most commonly affected site.[3] Review articles have detailed similarities in cutaneous findings and their implications between adult and pediatric patients.[3–6] However, unique manifestations have been described in children, including erythema multiforme, acute hemorrhagic edema of infancy, papular acrodermatitis of childhood, and various skin changes in multisystem inflammatory syndrome in children (MIS-C) that we will detail in this article.[4–6,33,34]

An early review article found that cutaneous involvement was described prior to other systemic symptoms in 77.9% of pediatric COVID-19 cases and simultaneously in 13.2% of cases.[3] Additionally, a cohort study of more than 12,000 children noted that the prevalence of fever in conjunction with cutaneous lesions was lower in adolescents when

TABLE 1
Cutaneous reactions to COVID-19 vaccines in pediatric patients and non-White patients

Category	Clinical presentation	Timing	Prognostic value	Notes
Multisystem inflammatory syndrome in children[22]	Kawasaki-like clinical presentation in pediatric patients[22]	Majority developed fever prior or concurrently with mucocutaneous findings[22]	Cutaneous findings not correlated with more severe clinical course[22]	Patients tend to be older and have more gastrointestinal symptoms than in Kawasaki disease[22]
Non-White patients[17–21,23,24]	Small reports of decreased rates of specific COVID-19 skin findings[23,24] Scalp involvement and telogen effluvium may be more common[17–20]	Hyperpigmentation may provide insight into previous inflammatory process[21]	No definitive data comparing outcomes based on cutaneous findings	Palpation can be identify cutaneous eruptions when erythema is subtle[21]
Messenger RNA COVID-19 vaccines[9,12,25–28]	Acute and delayed local reactions most commonly seen, followed by urticarial and morbilliform eruptions[9]	Median time to onset after first dose was 7 days, occurring in 2 clusters between day 1–3 and day 7–8[9] Shorter median time from second dose, occurring at day 19	Burgeoning data suggest local reactions not strongly associated with immunogenicity[25–28]	Many non-local reactions mimic the skin findings seen in COVID-19 infection[12]
Adenoviral vector COVID-19 vaccines[29–32]	Overall, rare dermatologic adverse events include urticaria and local reactions[29]	Majority of local dermatologic events were transient with a median duration of 2–3 days[29]	Associated petechiae may suggest a rare but life-threatening thrombotic reaction[30,31]	Rare case reports of unusual reactions including generalized Sweet syndrome, leukocytoclastic vasculitis, and a widespread pustular eruption[32]

compared with younger children and infants.[2] Their analyses also suggested that hospitalized COVID-19 pediatric patients more frequently had rash, urticaria, and conjunctivitis at the time of presentation compared with nonhospitalized patients, although specific incidence rates and comparative statistics were not reported.[2]

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Although there is overlap in the cutaneous manifestations between adult and pediatric populations,[7] the most notable cutaneous abnormalities in pediatric COVID-19 patients relate to MIS-C. Reported findings in this syndrome include a nonexudative conjunctivitis, polymorphic rash, oral mucositis, hand and foot anomalies, and perineal and facial desquamation (**Figures 1 and 2**).[35–37] These manifestations suggest that MIS-C shares many similarities with Kawasaki disease. However, children with MIS-C tend to be older, with higher rates of gastrointestinal symptoms, myocarditis, and shock than in classic Kawasaki disease.[8,22,37,38] Mucocutaneous manifestations are important clues to the diagnosis of MIS-C,[22] although not significantly associated with overall disease severity,[36,37] and in some studies have been associated with lower rates of intensive care unit admission, shock, and requirement for invasive mechanical ventilation.[37,38]

NON-WHITE POPULATIONS

As of September 2021, the US Centers for Disease Control and Prevention (CDC) reported that rates of COVID-19 infections were 1.1 and 1.5 times higher in Black and Hispanic populations, respectively, compared with White peers.[39] Notably, these disparities increased when rates of hospitalization and death were considered.[39] Despite this, there has been a

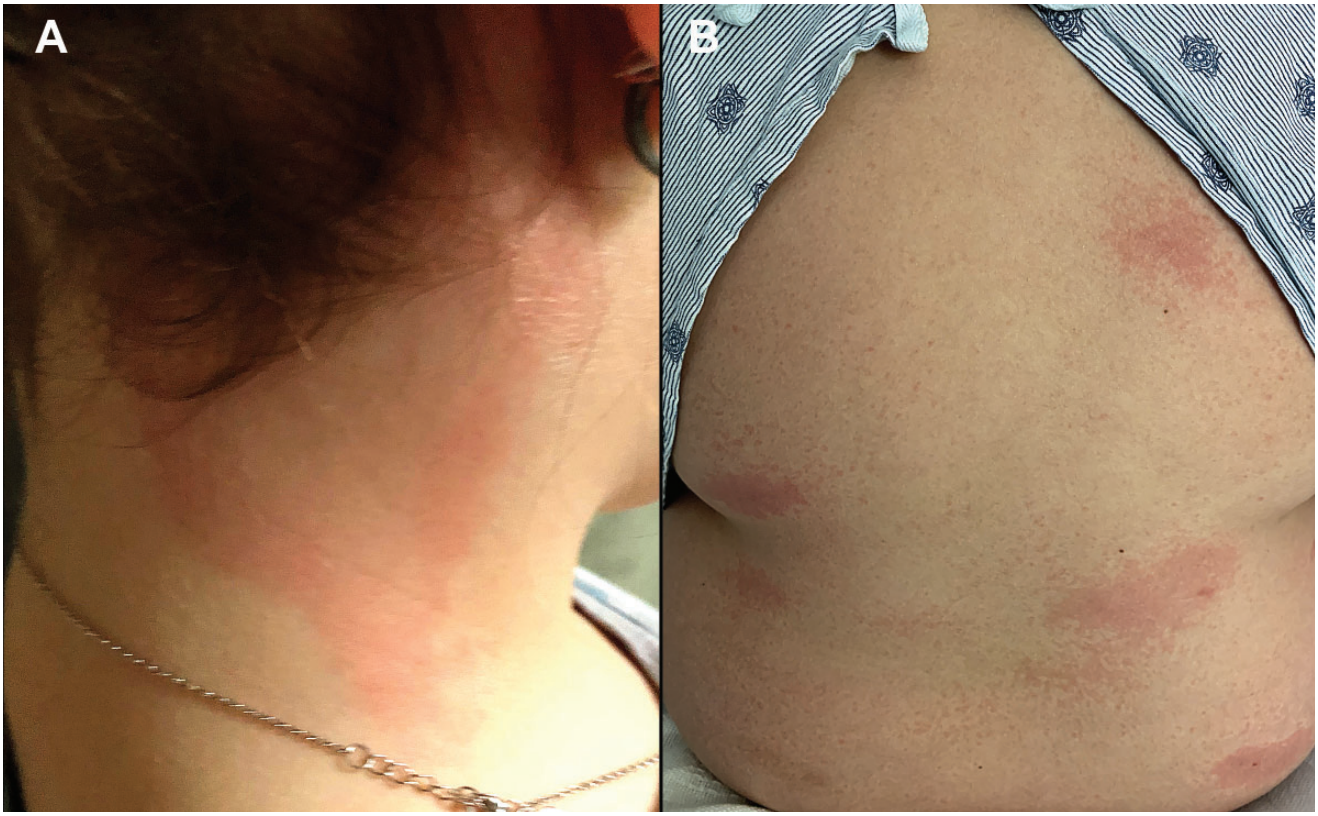

Figure 1. (A) A previously healthy 11-year-old girl with known COVID-19 exposure was hospitalized after 5 days of fever along with bilateral neck erythema and swelling. Workup revealed mildly reduced left ventricular ejection fraction of 47%, elevated erythrocyte sedimentation rate of 60 mm/hr, and a highly elevated C-reactive protein of 15.3 mg/dL, resulting in a diagnosis of multisystem inflammatory syndrome in children. The patient was treated with intravenous immunoglobulin G, steroids, and antithrombotics, with subsequent improvement in left ventricular ejection fraction and rash. She was discharged home with close clinical follow-up. (B) A previously healthy 10-year-old boy was admitted to the pediatric intensive care unit with 5 days of fever, nausea, vomiting, and erythematous, blanchable patches on the back and extremities that began 1 month after confirmed COVID-19 infection. His condition stabilized after treatment with intravenous steroids and immunoglobulin G, and broad-spectrum antibiotics, and he was ultimately discharged home on oral steroids and aspirin, with resolution of the rash confirmed at outpatient follow-up 3 days later.

relative dearth of published information describing these findings.[40] Interestingly, 3 studies based on race and ethnicity found that COVID-19–specific cutaneous manifestations, including chilblain-like lesions, were uncommon in patients with darker skin phenotypes.[23,24,41] As these studies were relatively limited in size, it is not yet clear whether these observations reflect the subtleties of appreciating inflammation in darker skin tones or true variations in presentation. Additionally, multiple small retrospective studies found disproportionate rates of telogen effluvium in patients with darker skin tones during the COVID-19 pandemic, and the presence of medical comorbidities has been described as a risk factor.[17–19] However, larger prospective studies are needed to clarify this association. Furthermore, self-reported rates of scalp erythema and scaling were significantly higher in non-White Brazilian patients with confirmed COVID-19 infection.[20] Our institutional experience suggests cutaneous abnormalities seen in patients with darker phenotypes may be somewhat more variable compared with those described and seen in White patients (**Figures 3 and 4**).

Although more studies are needed to better characterize the skin manifestations of COVID-19 in patients with darker skin and to investigate potential

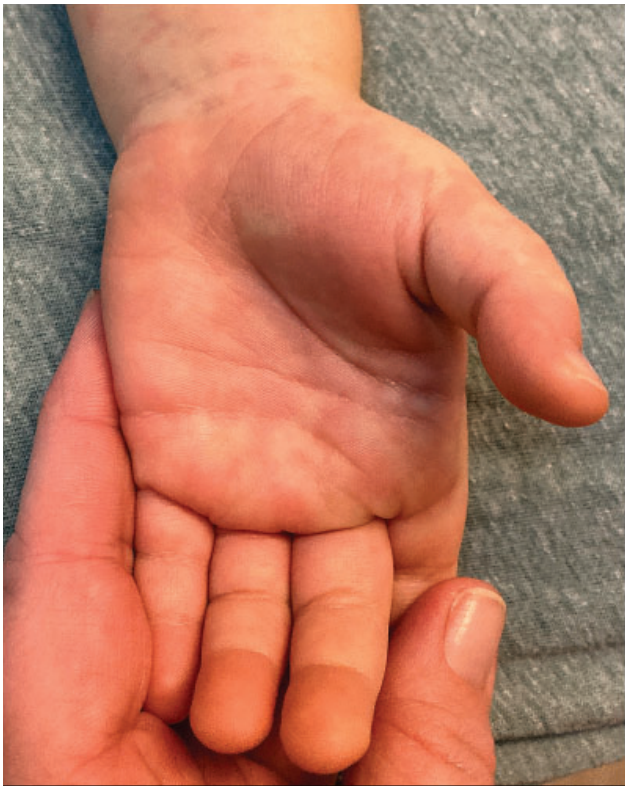

Figure 2. A previously healthy 2-year-old girl was admitted with concern for multisystem inflammatory syndrome in children after 5 days of fever, and vomiting, as well as palmar erythema, (seen in photo) a blanchable erythematous rash, conjunctival injection, periorbital edema, and lip erythema with desquamation and fissuring. Results of laboratory testing were notable for an elevated erythrocyte sedimentation rate of 36 mm/hr, a highly elevated C-reactive protein of 26.9 mg/dL, and COVID-19 immunoglobulin G antibody positivity. Because of cardiopulmonary deterioration during intravenous immunoglobulin G infusion, she was transferred to the intensive care unit and started on steroids, diuretics, antithrombotics, and anakinra, with improvement and eventual discharge after a 13-day hospitalization.

prognostic implications, a recent review highlighted clinical clues for identifying predominant cutaneous findings in patients with darker skin tones and emphasized the importance of palpation when considering diagnoses of urticaria, morbilliform eruptions, or even chilblain-like lesions, as the associated erythema may be more difficult to appreciate.[21] Additionally hyperpigmentation was noted to provide insight into previous skin inflammation and may be concerning to affected patients.[21]

VACCINE REACTIONS

Messenger RNA vaccines

Vast clinical trial data[42–44] noted that self-limited nonspecific, acute, local reactions were the most commonly described cutaneous findings following vaccination with a messenger RNA (mRNA) vaccine. However, a study of 414 cutaneous reactions to mRNA COVID-19 vaccines noted the most frequently reported reactions were delayed large, confluent, local reactions involving the lateral upper arm and deltoid at the injection site (**Figure 5**),[9] often referred to as "COVID arm."[10,12] International registry data suggest delayed cutaneous reactions are more commonly seen with the Moderna mRNA vaccine[9] and in female patients,[9,10] presented on average 1 week after the first vaccine dose, with no reports of severe adverse events in patients who went on to receive a second dose.[9] The reaction is often associated with mild tenderness and pruritus, and less commonly with concomitant fever and malaise, resolving within 1 to 2 weeks without treatment.[11]

In our experience, nonconfluent rashes, rashes involving the lateral arm, or rashes involving other anatomic locations close to the injection site may also occur (**Figure 6**). Notably, when looking at all cutaneous reactions, in the above-mentioned study, 43% of patients who initially had a cutaneous reaction developed another cutaneous reaction after the second dose.[9]

Other commonly reported cutaneous manifestations include findings associated with COVID-19 infection, such as functional angiopathies, urticarial eruptions, and morbilliform rashes.[12] Another important adverse event to be aware of is herpes reactivation, which was reported in 13.8% of cutaneous reactions from a cohort of 405 cases.[13] Reassuringly, a review of 40 cases of herpes reactivation found that none of the patients had a repeat viral flare after the second vaccination dose.[14]

The connection between reactogenicity and immunogenicity of the mRNA vaccines continues to be explored. Recent studies have suggested that systemic adverse effects are correlated with increased antibody production.[15,16,45] However, others have found that the presence and severity of local and systemic adverse reactions are not reliable indicators of a humoral response,[25–27] specifically when adjustments are made for age and sex that have been independently associated with increased antibody production.[28] As the number of vaccinated patients continues to climb and increasingly available metrics of immune response

Figure 3. A 74-year-old man, fully vaccinated against COVID-19 and with a remote history of cutaneous leukocytoclastic vasculitis, was seen in the emergency room after developing new purpuric patches, plaques, and bullae (A) on the face, oral mucosa, trunk, and (B) extremities. Testing confirmed acute breakthrough COVID-19 infection, and skin biopsy results were consistent with immunoglobulin A vasculitis. Hospitalization for intravenous steroids and supportive care was complicated by methicillin-resistant *Staphylococcus aureus* bacteremia and poor food and fluid intake due to oral pain. He was discharged in stable condition after a 22-day hospital stay.

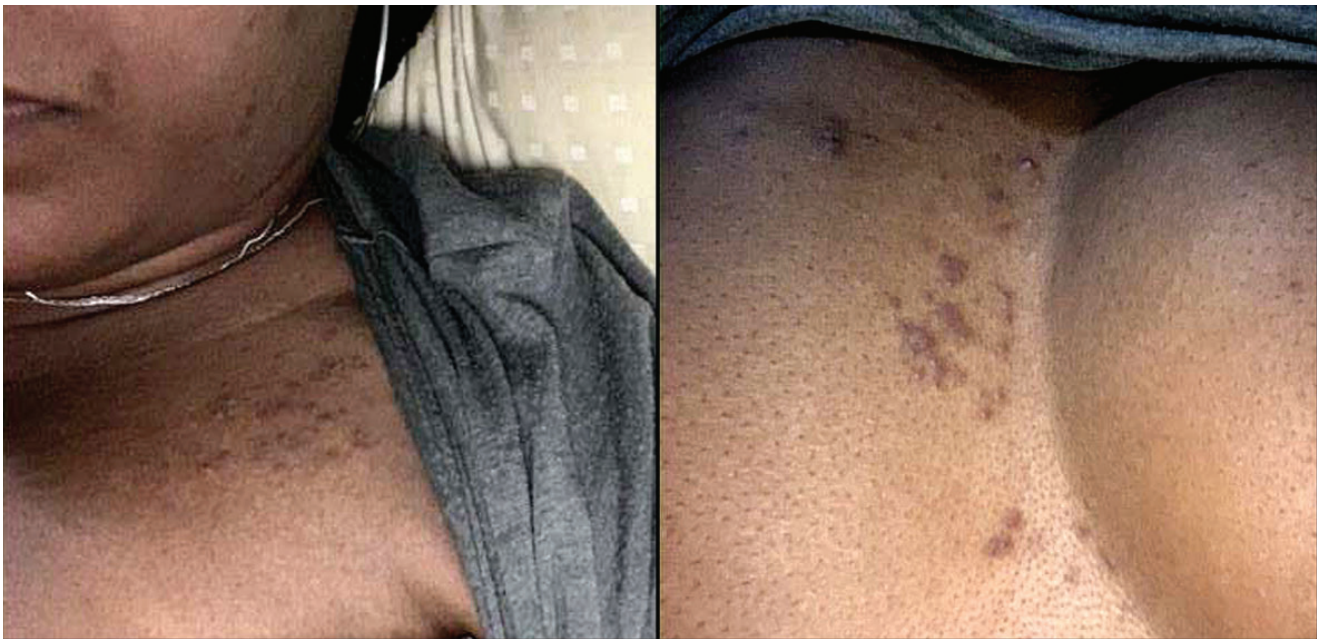

Figure 4. A 40-year-old woman with no known dermatologic history developed a pruritic maculopapular rash on the trunk following hospitalization for COVID-19 infection. Her COVID-19 course was complicated by bilateral pneumonia requiring supplemental oxygen and treatment with remdesivir and dexamethasone. Her rash was managed with oral antihistamines.

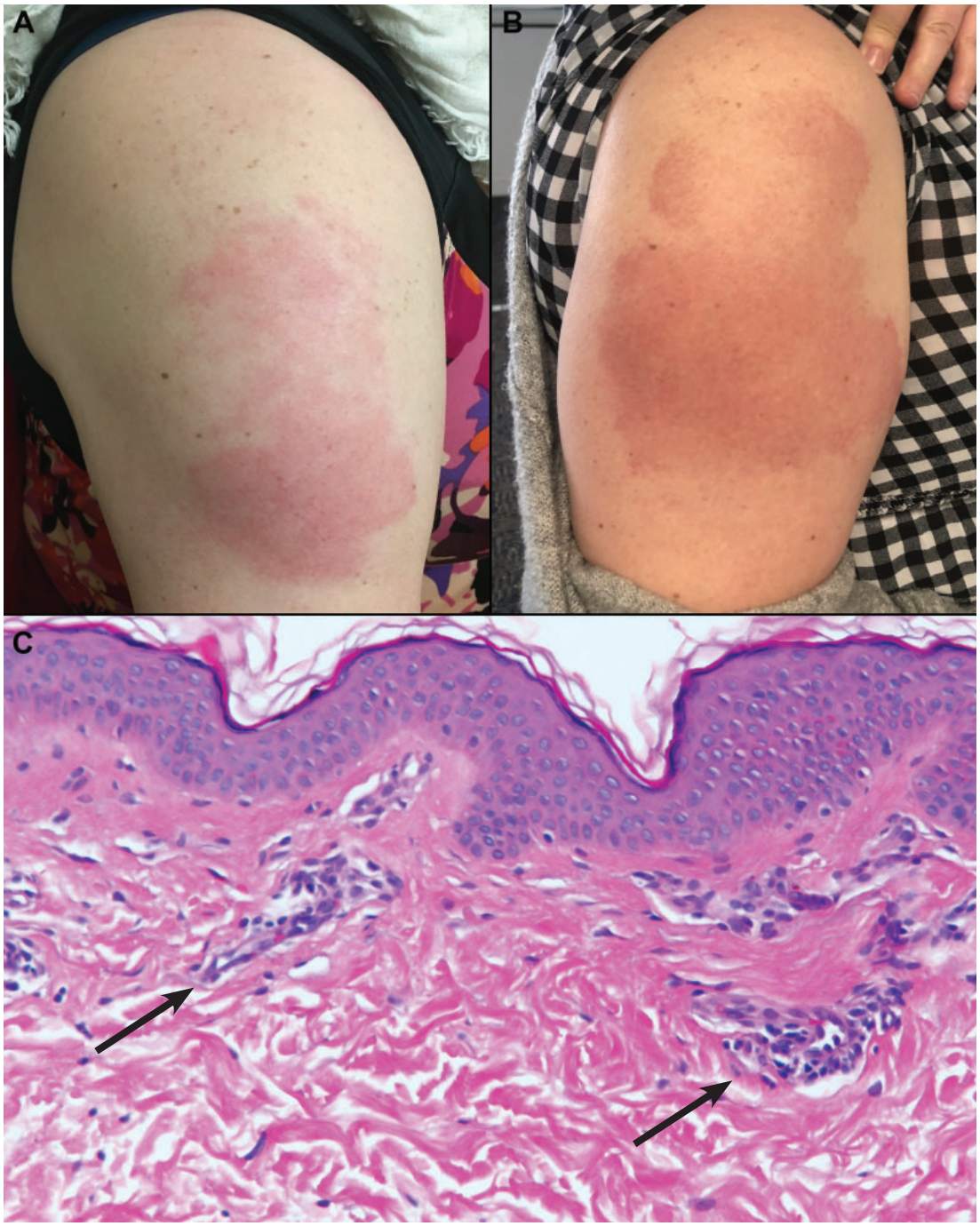

Figure 5. Eight days after her first dose of the Moderna messenger RNA vaccine, a 39-year-old woman developed a warm, confluent, (A) erythematous rash on her arm, characterized by a burning sensation. She also developed a pruritic, erythematous papular eruption on her chest, neck, and upper back 3 weeks after vaccination. Her primary care physician had treated her for presumed cellulitis with clindamycin without improvement. (B) The rash and associated symptoms began to improve by 23 days after vaccination. (C) Biopsy study of the lesions on her chest revealed a mild perivascular inflammatory infiltrate (arrows) consistent with a dermal hypersensitivity reaction. The patient deferred her second dose of Moderna vaccine due to concern for reaction recurrence. She eventually received the Johnson & Johnson COVID-19 vaccine at 10 months after the initial Moderna vaccine dose.

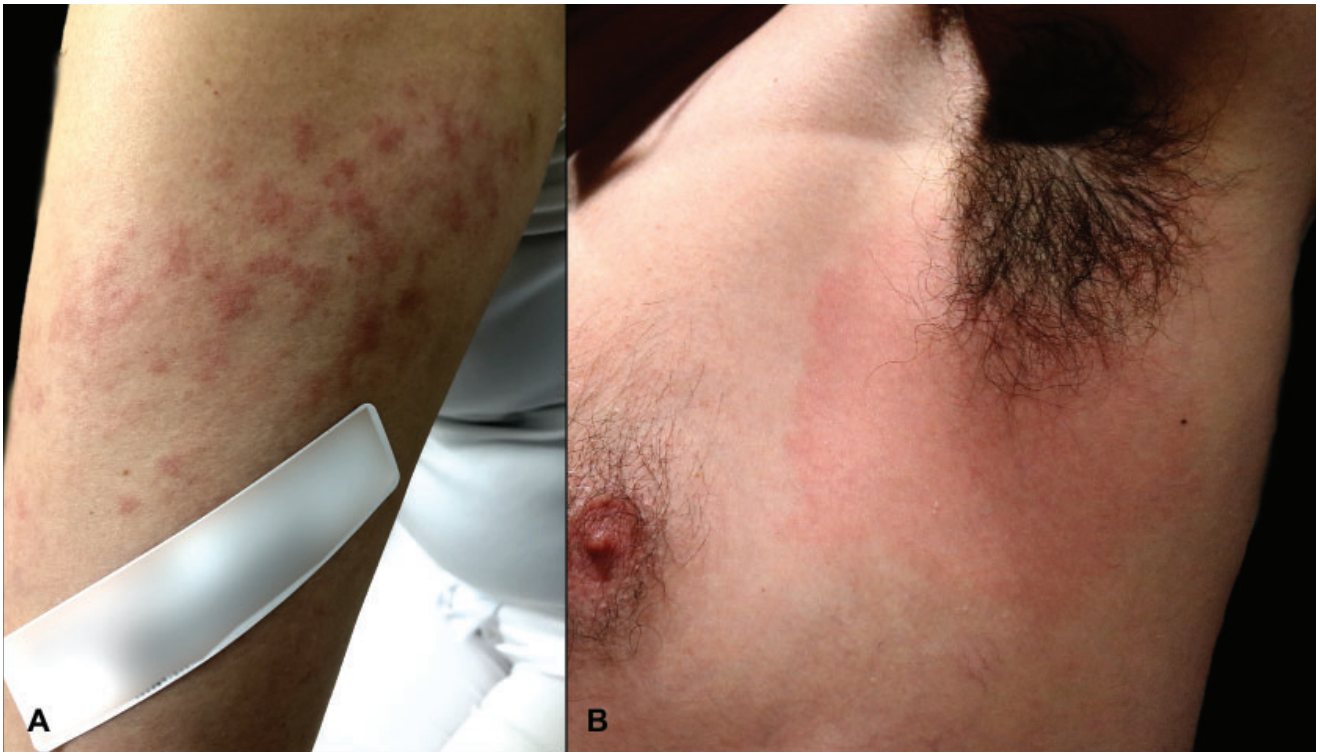

Figure 6. Uncharacteristic COVID-19 vaccine reactions near the injection site. (A) A 28-year-old woman developed a rash localized to the arm after her receiving her second dose of the Moderna vaccine. She developed multiple, ill-defined, erythematous macules and thin papules extending from the vaccination site in the deltoid area distally to the elbow 16 days after vaccination. Treatment with antihistamines, topical steroids, and a methylprednisolone dose pack brought resolution within 1 week. (B) A 51-year-old man developed confluent erythema with mild axillary tenderness and lymphadenopathy 48 hours after a third dose (ie, booster dose) of the Pfizer-BioNTech vaccine. He had experienced no cutaneous reactions after his first or second vaccine doses. His symptoms resolved within 2 days without treatment.

are developed, the relationship between cutaneous reactions and immunogenicity may become clearer.

Owing to more recent approval of the Pfizer-BioNTech COVID-19 vaccine for pediatric patients, data regarding cutaneous reactions in this population are limited. However, clinical study data noted that rash was seen in 0.3% of children ages 5 to 11 years and redness and swelling at the injection site reported in less than 20% of patients.[46] As increased numbers of pediatric patients undergo vaccination, clinicians should be familiar with commonly seen reactions as well as the potential for more severe presentations (**Figure 7**), which may relate to a more intense immune response in younger individuals. Additionally, a recent nationwide analysis of French adolescents ages 12 to 18 suggests that COVID-19 mRNA vaccination could be associated with a lower incidence of MIS-C, although data regarding younger patients are not yet available.[47]

Adenoviral vector vaccine

Although the Johnson & Johnson adenoviral vector vaccine appears to have relatively few dermatologic side effects, with clinical trial data and safety analyses reporting only local adverse reactions and urticaria,[29] rare reports of vaccine-induced immune thrombotic thrombocytopenia have garnered significant attention.[30,31,48] Patients have demonstrated concomitant petechiae, suggesting their presence may be a clue to this reaction.[30,31] Although only a few cases describing vaccine-related cutaneous manifestations of immune thrombotic thrombocytopenia have been reported to date, affected patients are often critically ill, and subsequent deaths have been reported.[49] Thus, any cutaneous manifestation that provides insight to this diagnosis could be valuable. Other cutaneous reactions have also been reported in association with the Johnson & Johnson COVID-19 adenoviral vector vaccine.[32]

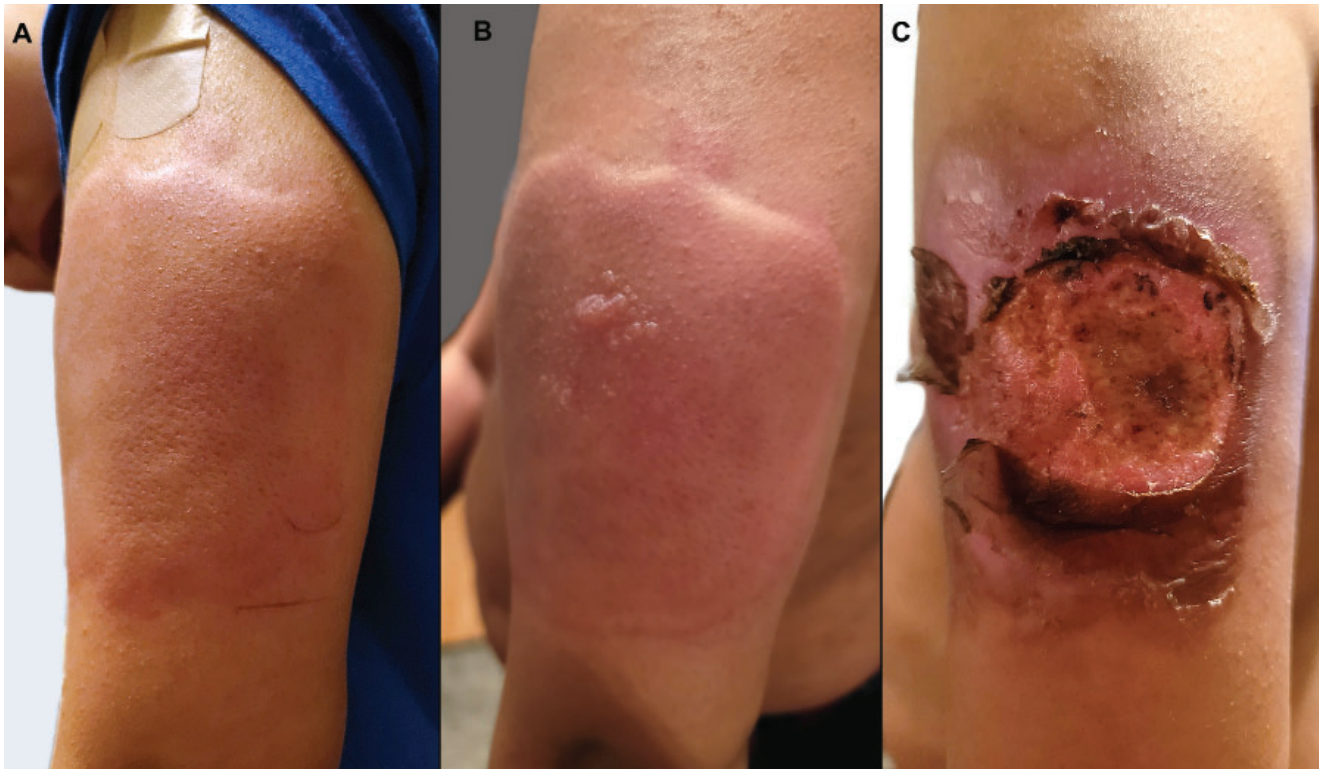

Figure 7. At a well visit with his pediatrician, an 11-year-old boy received 4 age-appropriate vaccines. In the right arm, he received the tetanus, diphtheria, and acellular pertussis vaccine and the meningitis vaccine. In the left arm, he received the Pfizer-BioNTech COVID-19 vaccine (12-year-old dose) and the human papillomavirus vaccine. Within minutes of receiving the vaccines, he developed a large, pruritic, erythematous and edematous plaque on his left arm (A), with subsequent vesiculation (B). Over the next 1 to 2 days, this progressed to a large, painful ulceration (C). He had no systemic symptoms with this reaction, and the lesions eventually healed.

TAKE-HOME MESSAGES

In summary, cutaneous findings of COVID-19 infection in pediatric patients appear to overlap those in adult patients. Although the constellation of cutaneous findings in MIS-C can aid in diagnosis, mucocutaneous involvement is not correlated with more severe disease. While there are reports of fewer cutaneous findings in COVID-19 infection in non-White patients, palpation may be helpful in appreciating subtle inflammation not readily apparent on visual examination. Fortunately, the vast majority of cutaneous mRNA vaccine reactions are short-lived, associated with only minimal or mild symptoms, and in some cases represent molecular mimicry causing rashes similar to those seen with COVID-19 infection. Given the limited number of available studies and variable strength of current data, future research is warranted to more definitively characterize cutaneous manifestations of COVID-19 in pediatric and non-White patients, in addition to cutaneous manifestation following COVID-19 vaccines.

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REVIEW

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Statins may increase diabetes, but benefit still outweighs risk

ABSTRACT

Data have been accumulating on the risk of developing type 2 diabetes in patients receiving statins and on the potential adverse effects of these drugs on glycemic control in patients who already have type 2 diabetes. This article reviews data linking statin use and new-onset diabetes mellitus, the effects of statins on glycemic control in type 2 diabetes, the benefit-risk considerations of statin use and type 2 diabetes, and how these factors affect patient management.

KEY POINTS

The weight of the evidence suggests that statin use is associated with an increased risk of new-onset diabetes mellitus, but the magnitude of the effect has varied across studies, including differences between randomized controlled trials and observational studies.

The risk is generally greater with high-intensity statin therapy and higher statin doses. However, many other variables are also involved, including prediabetes, genetics, central obesity, dyslipidemia, hypertension, lifestyle, and other medications, most notably glucocorticoids.

In patients with type 2 diabetes mellitus, statin use is associated with a small increase in hemoglobin A1c, and this effect may be greater with atorvastatin than with other statins. However, the benefits of statins in preventing atherosclerotic cardiovascular disease outweigh their adverse effects on glycemic control.

Pitavastatin has been associated with a lower risk of new-onset diabetes mellitus, but it lacks data on cardiovascular outcomes from large trials in patients with diabetes.

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After the first of the statins was introduced in 1987, a number of clinical trials demonstrated that these drugs, which effectively lower low-density lipoprotein cholesterol (LDL-C) levels, consistently reduce the risk of atherosclerotic cardiovascular disease events in many types of patients, including those with type 2 diabetes mellitus.[1] One of these trials—the West of Scotland Coronary Prevention Study (WOSCOPS),[2] with 5,974 patients—even reported that statins decreased the risk of new-onset diabetes.

Then, a larger trial—Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[3] with 17,802 participants treated with rosuvastatin or placebo—found a higher incidence of diabetes in the rosuvastatin group.

This observation raised questions and stimulated efforts to find answers. Do statins cause diabetes? If they do, is it true for all statins? Is the risk a function of the potency and dose of the statin? Are there other risk factors for this effect? In patients who already have diabetes, do statins worsen glycemic control? Most importantly, do the benefits of statin use in reducing cardiovascular risk outweigh any increased risk of new-onset diabetes mellitus?

Two caveats are warranted. First, in most studies, new-onset diabetes was diagnosed by the individual investigators and not according to any protocol. It was probably underdiagnosed, but in double-blind trials, the amount of underdiagnosis was likely about the same in each treatment group. Second, there are not enough data on microvascular complications of diabetes mellitus in statin-treated patients to warrant

TABLE 1
Statins and diabetes: Results of 13 trials

Trial and statin	Risk of diabetes with statin use
Trial of atorvastatin	
ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm)	Higher
Trials of simvastatin	
HPS (Heart Protection Study)	Higher
4S (Scandinavian Simvastatin Survival Study)	Higher
Trials of rosuvastatin	
JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin)	Higher
CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)	Higher
GISSI HF (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico*–Heart Failure)	Higher
Trials of pravastatin	
WOSCOPS (West of Scotland Coronary Prevention Study	Lower
LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease)	Lower
MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese)	Higher
ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)	Higher
GISSI PREVENZIONE (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione*)	Lower
PROSPER (Prospective Study of Pravastatin in the Elderly at Risk)	Higher
Trial of lovastatin	
AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)	Lower

Based on information from reference 5.

any discussion of risk vs benefit. The available results are limited and inconsistent regarding statin benefit or harm for microvascular complications, and they vary for retinopathy, nephropathy, and neuropathy.

DO STATINS CAUSE DIABETES? A NEW LOOK AT OLD TRIALS

Investigators have examined data from a number of trials of statin therapy in preventing cardiovascular disease events to look for effects on the incidence of new-onset diabetes mellitus.

The JUPITER trial[3] reported the incidence of physician-reported new-onset diabetes mellitus during the 1.9-year trial duration as 3.0% in the rosuvastatin group and 2.4% in the placebo group ($P < .01$).

Rajpathak et al[4] performed a meta-analysis of 6 trials, including JUPITER[3] and WOSCOPS.[2] The risk of new-onset diabetes mellitus was increased by 6% when WOSCOPS was included (P = NS) and by 13% ($P = .008$) when WOSCOPS was excluded.[4]

Sattar et al[5] performed another meta-analysis of the same 6 trials plus 7 more, for a total of 13. The results varied widely across trials (**Table 1**).[5] In 4 trials, the incidence of new-onset diabetes was higher in the control group than in the statin group, while it was higher in the statin group in the other 9.[5] Individually, none of the findings was statistically significant, but combined, the odds ratio for new-onset diabetes was 1.09 with statins, which was statistically significant (95% confidence interval [CI] 1.02–1.17). The investigators calculated that 255 patients would need

to be treated with statins for 4 years to observe 1 extra case of diabetes.[5]

The Women's Health Initiative[6] recruited 161,808 postmenopausal women without diabetes mellitus at baseline, of whom 153,840 had enough data to be analyzed post hoc. Statin therapy was associated with a 71% higher risk of new-onset diabetes mellitus (self-reported). After adjustment for age, body mass index, family history of diabetes, and other variables, the risk was still 48% higher in statin users.[6]

Lin et al[7] used a database of more than 30,000 patients who had undergone percutaneous intervention for acute coronary syndromes. Propensity score matching (n = 9,043 in each group) was used to evaluate the effects of statin use vs no statin use on new-onset diabetes. In the unmatched cohort, statin use was actually associated with a lower risk of diabetes. However, in the matched cohort the risk of new-onset diabetes was higher in statin users than in nonusers (adjusted hazard ratio 1.27, 95% CI 1.14–1.41, $P \leq .001$). The hazard ratios varied depending on which statin the patients received, and they were all statistically significant except for lovastatin (and the risk was lower in lovastatin users than in those not receiving any statin at all). Hazard ratios were as follows:

- Lovastatin 0.87
- Atorvastatin 1.30
- Fluvastatin 1.38
- Rosuvastatin 1.42
- Pravastatin 1.71.[7]

Engeda et al[8] performed a meta-analysis of 8 randomized controlled trials and 15 observational studies. They found an association between statin use and new-onset diabetes mellitus and also showed that the risk was higher in observational studies (relative risk 1.55, 95% CI 1.39–1.74) than in randomized controlled trials (relative risk 1.11, 95% CI 1.00–1.22).[8]

In summary, the weight of the evidence suggests that statin use is associated with an increased risk of new-onset diabetes mellitus, but the magnitude of the effect varied across studies, including differences between randomized controlled trials and observational studies.

DO ALL STATINS DO IT? DOES RISK VARY BY STATIN INTENSITY?

Statin potency, now more commonly called statin intensity, is based on the amount by which each statin lowers LDL-C and at what dose. Statins are thus classified as high-, moderate-, or low-intensity (**Table 2**),[9] and this classification is widely used in guidelines for giving statins to prevent atherosclerotic cardiovascular disease based on the patient's baseline risk of cardiovascular events.[9]

TABLE 2
Categories of statin therapy

High intensity (lowers LDL-C at least 50%)
Atorvastatin 40–80 mg
Rosuvastatin 20–40 mg
Moderate intensity (lowers LDL-C 30%–49%)
Atorvastatin 10–20[a] mg
Fluvastatin 40 mg twice a day
Fluvastatin XL 80 mg[a]
Pitavastatin 1–4 mg[a]
Pravastatin 40–80 mg
Rosuvastatin 5[a]–10 mg
Simvastatin 20–40 mg
Low intensity (lowers LDL-C less than 30%)
Fluvastatin 20–40 mg[a]
Lovastatin 20 mg
Pravastatin 10–20 mg
Simvastatin 10 mg[a]

[a]Not evaluated in randomized controlled trials at dosage shown.

LDL-C = low-density lipoprotein cholesterol

Based on information in reference 9.

Dose-response relationships among statins and their effects on LDL-C levels have been well known since the first statins came on the market.[10] Since proprotein convertase subtilisin/kexin type 9 inhibitors, which lower LDL-C levels even more than statins do, have not been reported to increase the risks of dysglycemia or new-onset diabetes, any relationships between statins and diabetes risk is likely related to the statin itself and not to the LDL-C reduction.[11]

A number of studies have addressed whether statin dose and intensity are related to the risk of new-onset diabetes mellitus.

Preiss et al[12] reported on 5 large clinical trials comparing statins in higher vs lower doses and showed that each of them had an odds ratio point estimate greater than 1 for higher doses to increase incident diabetes. The odds ratio for the pooled estimate was 1.12 (95% CI 1.04–1.22).[12]

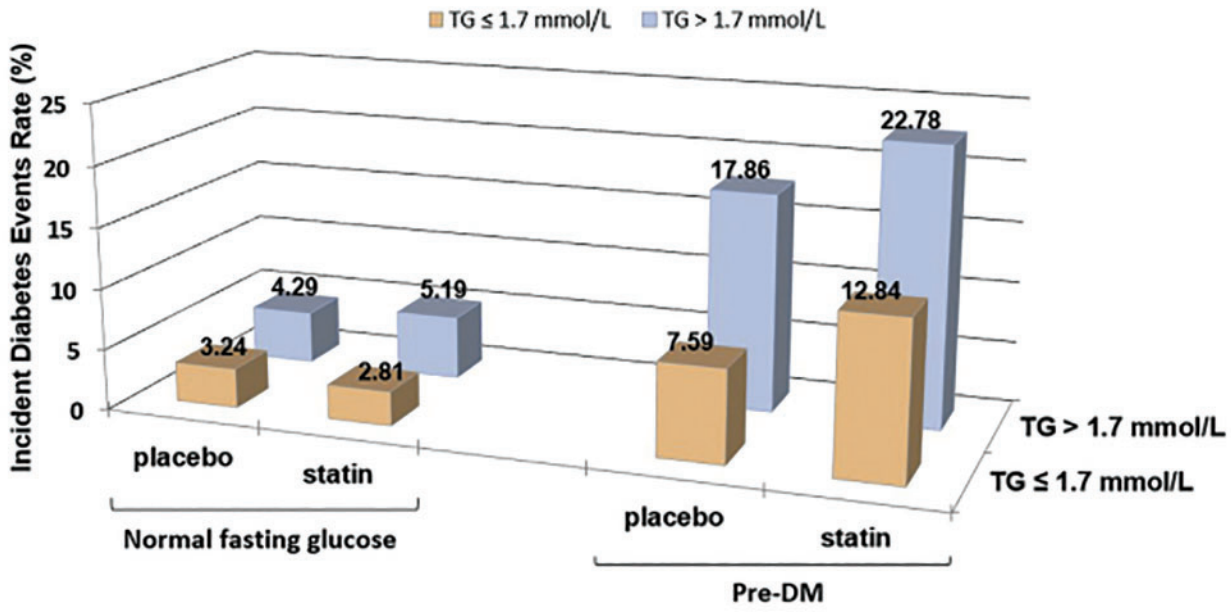

Figure 1. Risk of new-onset diabetes according to statin use, prediabetes, and elevated triglyceride (TG) level in the Treating to New Targets trial and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. For triglycerides, 1.7 mmol/L = 150 mg/dL.

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

Other investigators have analyzed higher- and lower-intensity statins, each compared with placebo.

Sattar et al,[5] in the meta-analysis described above, calculated that the overall odds ratios for incident diabetes were nominally higher with rosuvastatin (1.18), atorvastatin (1.14), and simvastatin (1.11) than with pravastatin (1.03) and lovastatin (0.98); recall that for all 13 studies combined it was 1.09 (**Table 1**).[5] The analysis could not adjust for all confounders such as age, new-onset diabetes mellitus being more common in older patients.[5]

Navarese et al[13] performed a network meta-analysis of 17 randomized controlled trials (14 placebo-controlled and 3 that compared 2 doses of statins) with a total of 113,394 participants. The data generally suggested a relationship between statin intensity as well as higher vs lower doses of some statins and risk of diabetes. The incidence of new diabetes was highest with rosuvastatin and lowest with pravastatin.

Carter et al[14] performed a population-based study using information from several databases in Ontario, Canada. Data from 471,250 patients who did not have diabetes at baseline and were treated with a statin supported the idea that the risk was greater with rosuvastatin, atorvastatin, and simvastatin than with lovastatin and fluvastatin in both primary and secondary cardiovascular disease prevention cohorts. The incidence of diabetes was also a function of duration of exposure.

In summary, the weight of the evidence from randomized controlled trials and observational studies suggests that higher-intensity statins and higher doses of statins are associated with higher risk of new-onset diabetes mellitus.

RISK FACTORS FOR DIABETES IN NON–STATIN-TREATED PATIENTS

Phenotypic and laboratory variables that may be associated with risk of new-onset diabetes mellitus in general include the following:

- Fasting blood glucose levels
- Postprandial glucose levels
- Triglyceride levels
- Hypertriglyceridemia, including elevated ratio of triglyceride to high-density lipoprotein cholesterol
- Hypertension

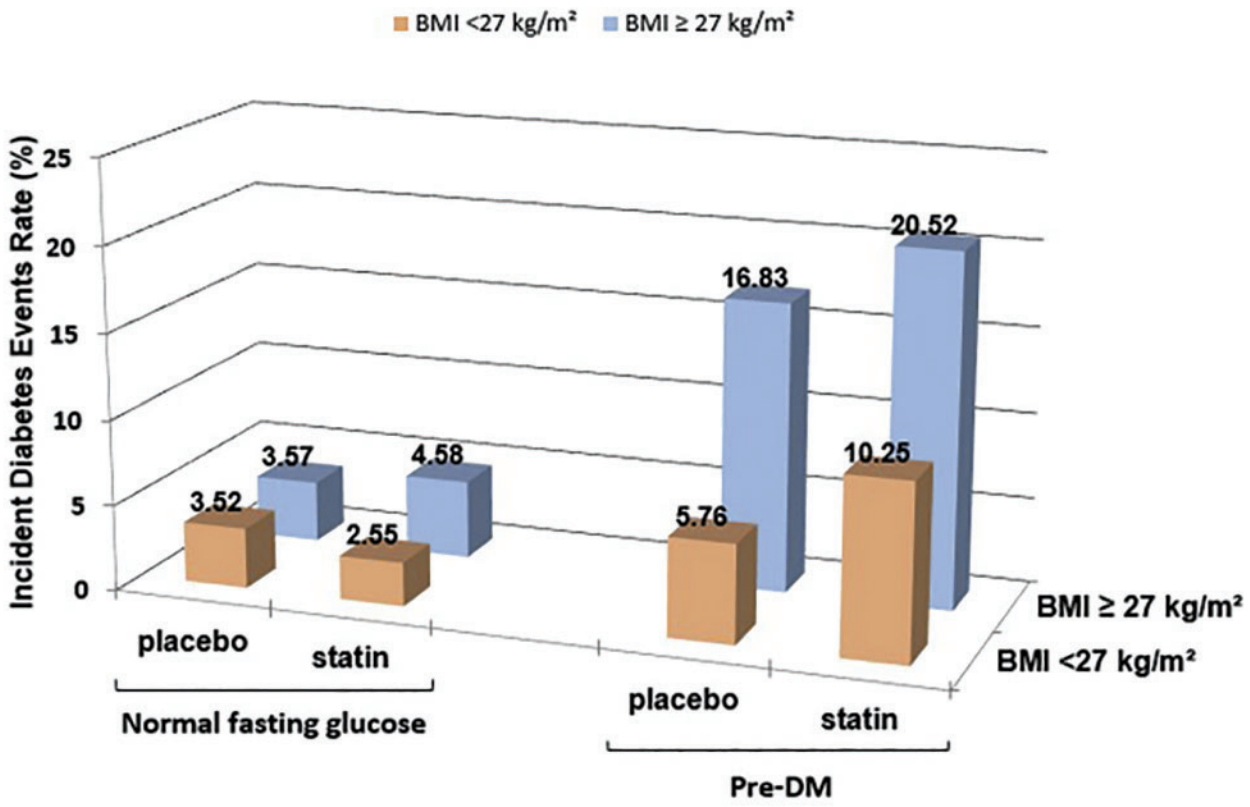

Figure 2. Risk of new-onset diabetes by statin use, prediabetes, and body mass index (BMI) in the Treating to New Targets trial and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

- Elevated measures of obesity, including body mass index and waist-to-hip ratio
- Smoking
- Depression
- Hyperuricemia
- Sleep disturbances
- Gestational diabetes
- Polycystic ovary disease.
- Biomarkers of insulin resistance.[15,16]

RISK FACTORS FOR DIABETES IN STATIN-TREATED PATIENTS

Many of the same risk factors associated with the development of diabetes in the general population are also present in statin users who develop associated diabetes.[17–20]

Kohli et al,[21,22] in an analysis of 2 large trials of atorvastatin,[19,20] reported that the risk of new-onset diabetes in patients who had high triglyceride levels or high body mass index depended on whether they had prediabetes, ie, fasting blood glucose or hemoglobin A1c levels higher than normal but not high enough to be classified as diabetes. Statins had little effect on the incidence of diabetes in those who did not have prediabetes (**Figure 1, Figure 2**).[21] The risk continued to diverge over time between the group with prediabetes and the group without prediabetes, and was greatest in those with prediabetes receiving atorvastatin 80 mg daily (**Figure 3**).[21]

Among the 15,056 participants who did not have diabetes at baseline, 5,924 (39%) had a fasting glucose level between 100 mg and 126 mg (designated prediabetes) and 9,132 (61%) had normal fasting glucose levels.[22] Statin treatment was balanced between groups. As in other studies, the participants with prediabetes were older and more likely to have features of metabolic syndrome, hypertension, higher

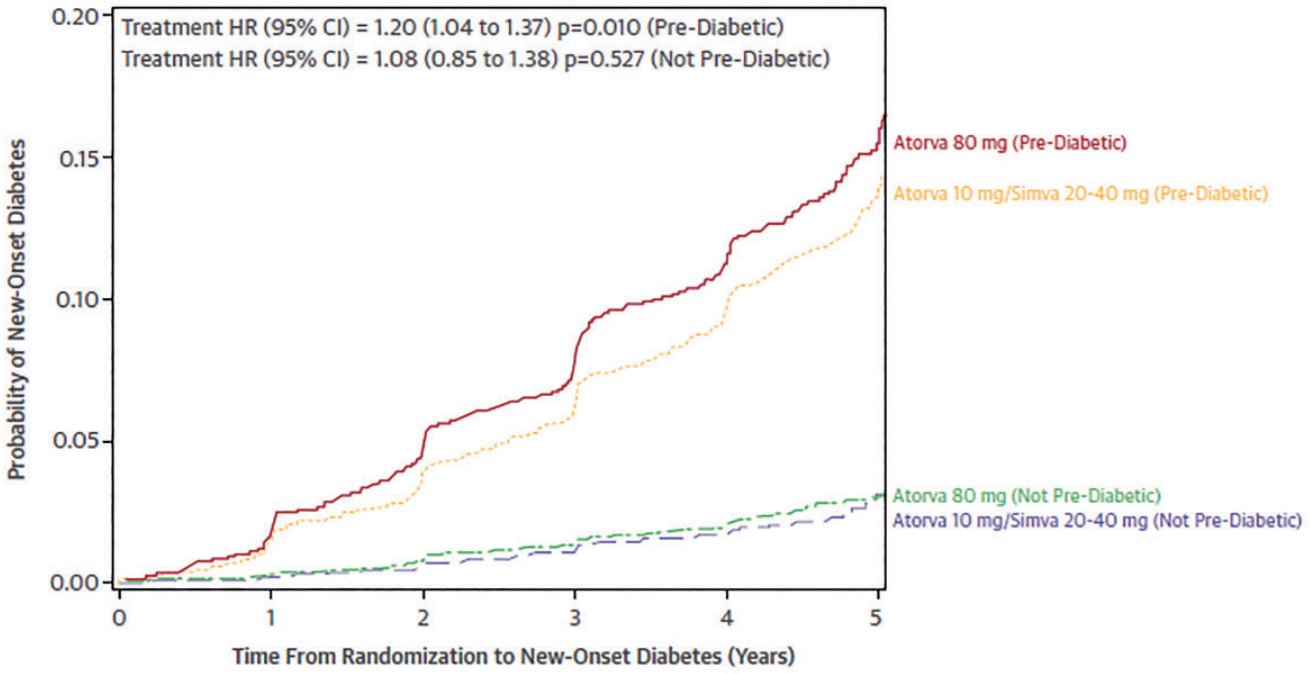

Figure 3. Risk of new-onset diabetes by statin use, prediabetes, and body mass index in the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trials (Atorva = atorvastatin; CI = confidence interval; HR = hazard ratio).

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

triglyceride levels, and lower HDL-C levels. During a mean 5-year follow-up, 14.2% of participants with prediabetes developed new diabetes compared with 2.9% of those without prediabetes.[22]

High-intensity statin use in prediabetes was associated with a higher risk of new diabetes, but in patients with normal fasting glucose levels there was no difference in diabetes risk between those who received high-intensity vs low-intensity statins.[22]

Arsenault et al[23] assessed 18 biomarkers associated with the risk of cardiovascular disease in the Treat to New Targets trial and found that plasma lipids, adiponectin, and lipoprotein-associated phospholipase A2 might be also useful for predicting incident diabetes in statin-treated patients.

In summary, variables associated with increased risk of progression to diabetes in general cohorts are also associated with an increased risk of diabetes in statin-treated patients. The statin-associated risk of diabetes is most evident in patients with high fasting blood glucose levels and prediabetes. These observations suggest that statin use is an additional risk factor for new-onset diabetes.

DO STATINS WORSEN GLYCEMIC CONTROL?

Statin use was associated with increasing hemoglobin A1c and fasting blood glucose levels in patients with established type 2 diabetes in some studies.[24–31] Several small randomized controlled trials had designs that allowed analyses of statin effects on glycemic control.

Simsek et al[24] reported that hemoglobin A1c values increased by 0.3% with both atorvastatin 80 mg/day and rosuvastatin 40 mg/day over 18 weeks.

The AFORRD trial (Atorvastatin in Factorial With Omega-3 EE90 Risk Reduction in Diabetes),[25] in 800 patients with type 2 diabetes, reported that hemoglobin A1c increased by the same amount (0.3%) with atorvastatin 10 mg over 4 months.

Teramoto,[26] in contrast, found that hemoglobin A1c decreased with pitavastatin.

Three meta-analyses addressed the effects of statins on glycemic control in type 2 diabetes.

Zhou et al[27] analyzed 26 statin trials that included 3,232 participants and concluded that statin therapy "had no remarkable influence" on hemoglobin A1c. The mean change was 0.04%.[27]

Erqou et al[28] performed a meta-analysis of 9 placebo-controlled trials of atorvastatin, simvastatin, and pravastatin. Overall, the hemoglobin A1c levels were 0.12% higher in the statin groups than in the control groups after an average follow-up of 3.6 years, with most of the effect related to atorvastatin use. This analysis is confounded by inadequate information on any changes in use of glucose-lowering agents.

Cui et al[29] performed a network meta-analysis of 23 trials to assess the overall effects of statin and statin dosage on hemoglobin A1c. Overall, in statin users, hemoglobin A1c increased by 0.11%. The greatest effect was with high-intensity atorvastatin, which was associated with a mean increase of 0.63%. Pitavastatin was associated with a reduction in hemoglobin A1c compared with all other statins.

The Fremantle Diabetes Study,[30] an observational study in Australia, found that low-intensity statins (n = 119) were not associated with any change in hemoglobin A1c, moderate-intensity statins (n = 195) were associated with a mean increase of 0.22% (P = .022), and high-intensity statins (n = 11) were associated with a mean increase of 1.05% (P = .023).

Sukhija et al[31] reported changes in fasting blood glucose in a large database of US Veterans Affairs patients with type 2 diabetes mellitus. In unadjusted analyses, fasting blood glucose increased from 102 mg/dL to 141 mg/dL in statin users and from 100 mg/dL to 129 mg/dL in statin nonusers.

In summary, any conclusions about the effects of statins on glycemic control, especially hemoglobin A1c, in type 2 diabetes are confounded by the type of analyses, the limited data on any changes in glucose-lowering agents, and study durations and size. Overall, the data support the conclusion that there is a small aggregate effect of statins in increasing hemoglobin A1c. This effect may be greatest with high-dose atorvastatin and least with pitavastatin.

HOW MIGHT STATINS INCREASE DIABETES RISK?

Historically, type 2 diabetes has been largely characterized by 2 major metabolic abnormalities: insulin resistance and declining beta-cell function. However, many other abnormalities including inflammation, glucagon dysregulation, and altered renal thresholds for glycosuria are also associated with it.

Mechanistic studies in animals and humans have sought links between statin use and diabetes risk. One of the more likely possible explanations is statin-associated insulin resistance.[32–35] This hypothesis has not been tested in the large studies of new-onset diabetes mellitus or studies of changes in hemoglobin A1c in type 2 diabetes mellitus.

BENEFIT OUTWEIGHS RISK

Diabetes has been consistently shown to be associated with an increased risk for cardiovascular disease, and many clinical trials have shown that statin treatment is associated with a reduction in cardiovascular disease risk.[1] Most patients with type 2 diabetes mellitus are at high risk of atherosclerotic cardiovascular disease because they also have other risk factors such as obesity, hypertension, and the high triglyceride-to-low HDL-C ratio often associated with insulin resistance. Thus, the obvious concern revolves around whether the risk of developing diabetes with statin alters the benefit-risk considerations and whether statin use significantly attenuates the benefits of statins on atherosclerotic disease risk and events.

Conclusions about the effects of statins on glycemic control are confounded by the type of analysis, study duration and size, and other factors

Ridker et al[36] analyzed the JUPITER[3] data and concluded, "the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes."[36] The benefit-risk question has also been addressed in thoughtful reports by Navarese et al[37] and Collins et al.[38] Each of these groups concluded that the evidence supports the contention that in patients with a high risk for atherosclerotic disease, the benefits of statin use outweigh the risk of new-onset diabetes. Navarese et al noted that the benefit-risk considerations are less clear for patients without diabetes and 0 to 1 risk factors.[37] Collins et al stated that "the absolute benefits of statin therapy depend on the individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved."[38]

GUIDELINES SUGGEST SHARED DECISION-MAKING

The 2018 guidelines[9] suggest that in patients at low risk of atherosclerotic cardiovascular disease based on a low 10-year risk score and no diabetes, starting a statin is recommended only after discussing it with the patient. This approach aligns with the considerations raised by Navarese et al.[37]

TABLE 3
Starting statin therapy: Things to consider and discuss

For all patients when considering statin therapy:
Screen to determine baseline glycemic status
Consider nonstatin therapies to lower cholesterol (resins, ezetimibe, bempedoic acid)
Consider variables associated with an increased risk of diabetes, including potentially adverse antihypertensive drugs (thiazides and beta-blockers) and potentially beneficial antihypertensive drugs (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers)
When starting statin therapy in patients without diabetes, discuss:
The possibility of developing diabetes mellitus
Types and doses of statins
Benefits of statins in reducing the risk of cardiovascular disease generally far outweigh risks on the development of new-onset diabetes
For patients with diabetes mellitus, discuss:
The possible adverse effects of statins on glycemic control, which are small
The benefits of statins in reducing the risk of atherosclerotic cardiovascular disease, which significantly outweigh a small increase in hemoglobin A1c
Adverse glycemic effects of statins can be mitigated by glucose-lowering therapies, especially those with favorable cardiovascular profiles

Based on recommendations from references 9, 40, and 41.

If patients have a calculated 10-year risk of 7.5% or higher but no other significant risk factors, besides elevated LDL-C, the guidelines suggest a discussion about starting a moderate-intensity statin, eg, pravastatin 40 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 1 to 4 mg daily. Each of these is associated with a lower risk of new-onset diabetes mellitus than the high-intensity statins.

Some data suggest that pitavastatin actually lowers the risk of diabetes, but this drug lacks the extensive cardiovascular disease outcomes data in patients with diabetes that exist for the other statins,[1] and this fact may be a point of discussion between the healthcare team and patient.

If patients have a calculated 10-year risk of 7.5% to 19.9%, especially when associated with additional risk factors, then the guidelines favor starting an intermediate-intensity statin. As noted above, the risk of new diabetes with statin use is higher in people who already have multiple atherosclerotic cardiovascular disease risk factors.[9,37]

In patients without type 2 diabetes and at low 10-year risk of atherosclerotic cardiovascular disease, if statin use is agreed on between the healthcare team and patient, a low-intensity statin is likely the best consideration.

In patients without type 2 diabetes but with multiple risk factors and a high risk for atherosclerotic cardiovascular disease over 10 years, the use of moderate- or high-intensity statins is justified, as the benefits of statins outweigh the risk of developing diabetes.

The guidelines do not discuss how statin therapy may change in a patient who develops new-onset diabetes mellitus related to statin use, but it has been addressed by Collins et al.[38] In cardiovascular disease risk calculators, diabetes is a yes-or-no question, and having diabetes approximately doubles one's risk. However, this may be overly simplistic, as the relationship between glucose and cardiovascular risk is continuous and graded.[39] In general, benefits of both moderate-intensity and high-intensity statins on reducing the risk for atherosclerotic cardiovascular disease events outweigh risks associated with hyperglycemia.

In patients with type 2 diabetes who are treated with moderate- or high-intensity statins, careful follow-up of hemoglobin A1c and appropriate glucose-lowering therapy should be implemented. Glucose-lowering therapies with established benefits on atherosclerotic cardiovascular disease are preferred.

Backes et al[40] have distilled these recommendations into a digestible format, which I have combined with those of the guidelines in **Table 3**.[9,40,41]

DISCLOSURES

Dr. Hoogwerf has disclosed ownership interest in Eli Lilly and consulting for Mannkind and Zealand Pharmaceuticals.

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