

Does microalbuminuria screening in diabetes prevent complications?

■ EVIDENCE-BASED ANSWER

Screening diabetic patients for microalbuminuria identifies those who may benefit from treatments that delay progression to renal failure (strength of recommendation: **B**, based on extrapolation from Level 1 treatment studies of patients with microalbuminuria).

No research has determined the best method for screening for microalbuminuria, or whether screening in primary care populations will produce better long-term outcomes. No studies have examined the role of microalbuminuria screening after angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) have been instituted for other indications.

■ EVIDENCE SUMMARY

Patients with diabetes mellitus have a 20% to 40% lifetime risk for development of nephropathy, and microalbuminuria is the earliest easily detectable marker of renal damage.¹ Improved control of blood sugar^{2,3} and blood pressure⁴ decreases but does not completely prevent development of microalbuminuria and progression to overt kidney failure. ACE inhibitors and ARBs have been shown to diminish this progression even in the absence of hypertension (the latter in type 2 diabetes only) (**Table**).

No prospective randomized trials of screening have been reported. There is uncertainty about what method of screening is most effective and practical in primary care settings.¹⁰ Expert opinion recommends diagnosing microalbuminuria after 2 positive test results,¹ but whether repeated tests improve diagnostic accuracy is still controversial.¹⁰

A large randomized controlled trial showing better long-term renal and vascular disease outcomes would be needed to give screening for microalbuminuria a strength of recommendation of **A**. Recruiting patients for such a study, and interpreting its results, would be difficult: many subjects would have other indications, such as hypertension or congestive heart failure, warranting use of potentially renoprotective medications.

■ RECOMMENDATIONS FROM OTHERS

The American Diabetes Association recommends annual screening for microalbuminuria—after 5 years of established type 1 disease, and at time of diagnosis for type 2 diabetes without macroalbuminuria. Initial screening can use 1 of 3 methods: measurement of the albumin-to-creatinine ratio in a random, spot collection; 24-hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance; timed (eg, 4-hour or overnight)

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What is a Clinical Inquiry?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and individuals with particular expertise.

Questions chosen for Clinical Inquiries are those considered most important, according to results of web-based voting by family physicians across the U.S.

Answers are developed by a specific method:

- First, extensive literature searches are conducted by medical librarians.
- Clinicians then review the evidence and write the answers, which are then peer reviewed.
- Finally, a practicing family physician writes a commentary.

TABLE

Reno- and cardioprotective efficacy of treatments for diabetic patients with microalbuminuria

DM type	Medication	NNT	Time (years)	To prevent endpoint
1	ACE inhibitor (Captopril)	7.9*	2	Clinical proteinuria ⁵
2	ACE inhibitor (Enalapril)	6.3*	5	Macroalbuminuria ⁶
2	ACE inhibitor (Enalapril)	2.4*	7	Significant proteinuria ⁷
2	ARB (Losartan)	3.6	3.4	End-stage renal disease ⁸
2	ACE inhibitor (Ramipril)	4	4.5	Cardiovascular disease ^{9†}

*Normotensive subjects
†Myocardial infarction, revascularization procedure, stroke, cardiovascular death, congestive heart failure requiring hospitalization, overt nephropathy, renal dialysis, or laser treatment for retinopathy
DM, diabetes mellitus; NNT, number needed to treat; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

collection. At least 2 of 3 tests measured within a 6-month period should show elevated levels before a patient is said to have microalbuminuria.¹

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■ CLINICAL COMMENTARY

Blood pressure control and ACE inhibition improve mortality and morbidity for patients with diabetes mellitus type 2. Therefore, maximize ACE inhibitor or ARB doses, as tolerated, and aim for a blood pressure of 110–120/70–80 mm Hg (130/85 mm Hg is the maximum).

Using this plan, I do not routinely screen for microalbuminuria—which is, at best, a surrogate marker for nephropathy and poor blood pressure control—unless I believe it will work as an educational and motivational tool for patients who are less committed to self-care.

If serum creatinine becomes elevated, a 24-hour urine collection to examine volume, creatinine clearance, and protein can be used to help develop a negotiated care plan with the patient, which may or may not include referral. Until there is different evidence about screening and treatment options for microalbuminuria, I see no need to screen when the above plan is in effect.

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Is MRI useful for evaluation of acute low back pain?

■ EVIDENCE-BASED ANSWER

Magnetic resonance imaging (MRI) is rarely helpful in the evaluation of acute low back pain. Limited evidence suggests that MRI may be useful in further assessing “red flags” in the history or physical exam.

MRI has a high sensitivity and specificity in the detection of cancer or infection, but it is not particularly specific when evaluating lumbar radiculopathy. Poor specificity can lead to finding clinically irrelevant abnormalities.¹ The overall evidence for the appropriate use of MRI in low back pain is limited and weak^{2,3} (strength of recommendation: **C**, based on limited randomized controlled trials).

■ EVIDENCE SUMMARY

Radiologic imaging of any kind is seldom needed in the evaluation of acute low back pain unless there

TABLE

Red flags for underlying causes of low back pain

Condition	Red flags
Cancer	Age >50 History of cancer Unexplained weight loss Failure to improve after 4 to 6 weeks of conservative low back pain therapy
Spinal infection	Fever >38°C History of intravenous drug abuse Urinary tract infection
Neurologic emergencies or urgencies	Cauda equina symptoms Progressive neurologic deficit Suspicion of ankylosing spondylitis Unrelenting night pain or pain at rest Pain with distal numbness or leg weakness
Fracture	History of osteoporosis Chronic oral steroid use Serious accident or injury

Adapted from Institute for Clinical Systems Improvement¹⁰

are “red flags” suggestive of cancer, infection, or fracture (**Table**). Conduct a thorough history and review of systems to risk-stratify patients that may benefit from imaging.

One study of patients with low back pain identified risk factors for cancer, including age >50 years, prior cancer, unexplained weight loss, pain lasting >1 month, and no relief with bed rest.⁴ An elevated erythrocyte sedimentation rate of >50 mm/hr in the setting of these risk factors should prompt the clinician to order an MRI or bone scan.⁵

An analysis of systematic reviews and original articles by Jarvik and Deyo reported sensitivities for MRI (83% to 93%) and for radionuclide scanning (74% to 98%) in detecting cancer.⁶ MRI exhibits the best sensitivity (96%) and specificity

With patients who warrant a high level of suspicion of cancer, consider MRI, CT, or bone scan

(92%) for infection. MRI may be helpful for further evaluation of an acute neurologic deficit, suspected cauda equina syndrome, suspected active sacroiliitis, and worsening low back pain not responding to 4 or more weeks of conservative therapy.^{7,8}

Consider contrast enhancement with gadolinium when evaluating inflammatory conditions, or for patients who have had spine surgery.⁹ The lower specificity of MRI for radiculopathy means that MRI can detect disk herniations that do not cause the patient's signs or symptoms. In one study, MRI demonstrated herniated disks in 25% of asymptomatic persons.¹

Unfortunately, there are too few studies to guide clinicians in the appropriate use of MRI in the evaluation of low back pain.^{2,4} Higher quality evidence is needed before firm guidelines can be made for the use of MRI in the evaluation of low back pain.

RECOMMENDATIONS FROM OTHERS

Institute for Clinical Systems Improvement guidelines recommend considering plain films for patients with risk factors for cancer or infection.

Additional indications are listed in the **Table**. Plain films, however, do not rule out cancer. With patients who warrant a high level of suspicion of cancer, consider using MRI, computed tomography, or bone scan. Consider MRI or computed tomography also for patients with cauda equina syndrome or a rapidly progressing neurologic deficit, while concurrently consulting neurosurgery or surgery.¹⁰

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CLINICAL COMMENTARY

When a patient has acute low back pain, with or without known trauma, I rarely find it useful to order an MRI. I have found conservative thera-

py with anti-inflammatory agents and exercise (when a patient is able to do so) provides relief. Further intervention is rarely necessary.

For more difficult cases—when pain has been present for months and is getting worse despite conservative therapy, or for patients who demonstrate symptoms of cauda equina syndrome—I find MRI useful to help tailor therapy and make decisions regarding appropriate referral. I agree with the author that, even for patients with radicular pain, an MRI rarely changes the treatment plan. Paying attention to the risk factors identified above and performing an MRI when they are present seems to be the best recommendation.

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Do calcium supplements prevent postmenopausal osteoporotic fractures?

■ EVIDENCE-BASED ANSWER

Calcium supplementation (1000–1200 mg daily) decreases menopause-related bone loss and reduces the rate of vertebral and nonvertebral fractures. Calcium is more efficacious in conjunction with vitamin D (700–800 IU daily), particularly in elderly patients, who have a high rate of vitamin D deficiency (strength of recommendation: **A**, based on randomized controlled trials).

■ EVIDENCE SUMMARY

Calcium supplementation lessens bone loss in postmenopausal women. One double-blind, randomized controlled trial included healthy women who were 6 or more years postmenopausal and had a dietary intake of less than 400 mg of calcium per day.¹ Women who received daily calcium citrate (500 mg) for 2 years had significantly less bone loss at the spine, hip, and radius than women taking placebo. In addition, calcium carbonate supplementation maintained bone density at the hip and radius but not the spine when compared with placebo. This dose of calcium was not associated with better outcomes in women within the first 5 years after menopause, but the dose was less than most generally recommended ranges.

Another randomized controlled trial of healthy women, postmenopausal for at least 3 years, showed that calcium supplementation at 1000 mg per day for 2 years decreased bone density loss in the hip and eliminated loss in the spine.² The effect may be greatest in the first year of supplementation and less in subsequent years.³

Several studies have shown calcium supplementation has a beneficial effect on reducing fractures in postmenopausal women. A randomized controlled trial of healthy, community-dwelling people 65 years of age and older (55% women)

showed daily supplementation with 500 mg calcium and 700 IU vitamin D for 3 years decreased nonvertebral fractures vs. placebo (response rate [RR]=0.54; 95% confidence interval [CI], 0.12–0.77; number needed to treat [NNT]=15).⁴

Another randomized controlled trial of elderly ambulatory women showed that supplementation with 1200 mg calcium and 800 IU vitamin D per day for 18 months decreased hip fractures (RR=0.26; 95% CI, 0.03–0.44; NNT=48) and other nonvertebral fractures (RR=0.25; 95% CI, 0.09–0.38; NNT=26).⁵

A third randomized controlled trial in postmenopausal women with low calcium intake and previous vertebral fractures showed that 1200 mg of calcium supplementation reduced the incidence of additional fractures (RR=0.23).⁶

Not all studies agree. The Study of Osteoporotic Fractures showed no beneficial effect of calcium supplements on fracture risk. This cohort study found that calcium supplements were actually associated with an increased risk of hip fracture (RR=1.5; 95% CI, 1.1–2.0) and vertebral fracture (RR=1.4; 95% CI, 1.1–1.9).⁷

Observational studies like this are subject to bias; reviews of the more rigorous randomized trials support calcium supplementation in order to decrease the risk of vertebral fracture by approximately 35% and nonvertebral fractures by approximately 25%.^{8,9} Daily supplementation of calcium (500–1200 mg) along with vitamin D (700–800 IU) is the regimen best supported by the evidence. Since the absorption of calcium decreases with single doses above 500 mg, the studies that used 1000–1200 mg of calcium split the daily doses.¹⁰

■ RECOMMENDATIONS FROM OTHERS

Guidelines have been published by the National Osteoporosis Foundation (1999),¹¹ the National Institutes of Health Consensus Development Panel on Osteoporosis (2000),¹² and others, all recommending 1200–1500 mg of elemental calcium and 400–800 IU of vitamin D be taken daily through a combination of diet and supplementa-

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tion. The United States Preventive Services Task Force¹³ recommends that 1000–1500 mg of calcium be used daily; they make no specific recommendation regarding vitamin D supplementation.

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■ CLINICAL COMMENTARY

Calcium and vitamin D are the foundation of osteoporosis treatment and prevention. Nearly every trial evaluating the use of antiresorptive and anabolic agents for the treatment and prevention of osteoporosis have evaluated these therapies in combination with calcium and vitamin D. As evaluated in this clinical inquiry, studies have also demonstrated benefit of these agents together in the absence of other medications.

Clinicians should ensure adequate dosing of calcium and vitamin D in all patients they are evaluating for osteoporosis treatment and prevention.

Clinicians should remember some people do get a significant portion of their daily nutritional requirements through diet, and incorporation of calcium and vitamin D as a part of a healthy diet should be the first recommendation. Checking the vitamin D content of a patient's multivitamins is also important to avoid added expense.

Use of calcium citrate should be recommended for the elderly and those with achlorhydria, as acid is necessary to absorb the less expensive calcium carbonate. There is no evidence at this time suggesting a need to recommend other calcium salts.

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Do glucosamine or chondroitin cause regeneration of cartilage in osteoarthritis?

■ EVIDENCE-BASED ANSWER

No direct evidence suggests glucosamine or chondroitin cause regeneration of cartilage in osteoarthritis. Use of glucosamine sulfate in knee osteoarthritis prevents joint space narrowing on radiographs (strength of recommendation [SOR]: **B**, based on 1 randomized controlled trial).

Intramuscular chondroitin polysulfate prevents radiographic progression of finger osteoarthritis (SOR: **B**, based on 1 randomized controlled trial).

Both chondroitin sulfate and glucosamine sulfate stimulate chondrocyte growth in vitro and in animal models (SOR: **D**, based on several bench research studies).

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■ EVIDENCE SUMMARY

A systematic review of glucosamine sulfate use for osteoarthritis, based on early research (1956–1991), found that it has anti-inflammatory properties and rebuilds damaged cartilage.¹ These studies evaluated chondrocytes grown in culture and animal models.^{1,2} Chondroitin sulfate also stimulates chondrocyte biosynthesis in both animal and in vitro studies. There is insufficient evidence to demonstrate glucosamine sulfate or chondroitin sulfate stimulates chondrocyte growth in humans with osteoarthritis.^{2,3}

Joint space narrowing on radiographs suggests progression of osteoarthritis. This narrowing is thought to imply cartilage destruction or loss due to osteoarthritis. A double-blinded randomized controlled trial studied the effect of glucosamine sulfate on tibial-femoral compartment joint space narrowing in 212 patients older than 50 with mild to moderate knee osteoarthritis.⁴ Patients took either 1500 mg/day of glucosamine sulfate or placebo over 3 years. Knee radiographs in a standing anterior-posterior view, using visual and digital analysis, were used to assess joint space narrowing.⁵ The average mean joint space loss was 0.31 mm in the placebo group and 0.07 mm in the treatment group ($P < .05$; 95% confidence interval, 0.13–0.48).

The clinical relevance of knee joint space narrowing is undetermined. Radiographic evaluation of a weight-bearing joint space may not be an accurate or reproducible technique. A study of 15 patients with mild to moderate knee osteoarthritis used standing and semi-flexed radiographic views after an analgesic and nonsteroid anti-inflammatory drug washout period, and 1 to 12 weeks after resumption of analgesic therapy (mean 6.0 weeks).⁶ Knee pain significantly decreased radiographic joint space in the standing anterior-posterior position, but not in the semiflexed position. Using the standing anterior-posterior method may confound accurate interpretation of joint space narrowing and changes in articular cartilage since glucosamine may have an anti-inflammatory effect.⁶

One double-blinded randomized controlled trial, comparing chondroitin sulfate with placebo, evaluated joint space in patients with symptomatic hand osteoarthritis.⁷ One hundred sixty-five Caucasian patients, aged 40 to 70 years, were randomized to receive either a 50-mg intramuscular injection of chondroitin polysulfate, twice weekly, for 8 weeks, every 4 months, versus placebo, or 400 mg of oral chondroitin sulfate, 3 times a day, versus placebo.

Osteoarthritis progression in the metacarpal-phalangeal and interphalangeal joints was assessed with radiographs over 3 years. Evaluators used the Anatomic Lesion Progression Scale to assess the development of osteophytes and joint space narrowing, with or without subchondral bone changes, to determine osteoarthritis progression. This scale makes it very difficult to determine whether improvements are clinically significant.

Chondroitin sulfate and polysulfate did not prevent osteoarthritis from occurring in previously normal joints. In joints already affected, intramuscular chondroitin polysulfate significantly reduced progression of distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joint space narrowing ($P < .013$), using the progression scale. Oral chondroitin sulfate did not prevent progression.⁷

■ RECOMMENDATIONS FROM OTHERS

The American College of Rheumatology stated in 2000 that recommending glucosamine sulfate or chondroitin sulfate for osteoarthritis might be premature due to the methodology, lack of standardization, and insufficient information on study designs. More research was recommended.⁸

These products are sold as supplements in the United States. Their purity is often questionable and thus may affect study results. When studying glucosamine, the National Institutes of Health was forced to manufacture the drug itself due to lack of a reliable amount present in commercial products.⁹

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■ CLINICAL COMMENTARY

Most family physicians see many patients with osteoarthritis, which can be difficult to treat. My patients typically want improvement in their symptoms, function, and disease progression. Although there is good evidence that the use of glucosamine sulphate (but not chondroitin sulphate) can improve the common symptoms and functional problems of osteoarthritis, this review states it is unclear whether these substances can alter disease progression through regeneration of cartilage.

I tell my patients with osteoarthritis that glucosamine sulfate can help problems like joint pain and function, but that we do not have a safe and reliable treatment for reversing the disease or the joint damage resulting from it.

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THE JOURNAL OF FAMILY PRACTICE

Evidence-based medicine terms

The Journal of Family Practice uses a simplified rating system derived from the Oxford Centre for Evidence-based Medicine. More detailed definitions may be found at its website: <http://minerva.minervation.com/cebml/>.

Level of Evidence characterizes the validity of a study while making no specific practice recommendation

- 1a Systematic review of randomized controlled trials
- 1b Individual randomized controlled trial with narrow confidence interval
- 1c All or none—all patients died before therapy was available, but now some survive; or, some patients died before therapy was available, but now all survive
- 2a Systematic review of cohort studies
- 2b Individual cohort study, or low-quality randomized controlled trial
- 2c “Outcomes” research
- 3a Systematic review of case-control studies
- 3b Individual case-control study
- 4 Case series, or poor quality cohort or case-control studies
- 5 Expert opinion

Strength of Recommendation translates a given level of evidence into a practice recommendation

- A Includes 1a–c levels of evidence
- B Includes levels 2a–c and 3a, b
- C Includes levels 4 and 5

Strength-of-recommendation ratings do not always reflect a direct one-to-one correspondence with levels of evidence, as depicted above, but may take into account such variables as intervention cost, ease of use, and impact of the disease in the population.