How should a DEXA scan be used to evaluate bisphosphonate therapy for osteoporosis?

■ EVIDENCE-BASED ANSWER

If bone density is evaluated after initiating bisphosphonate drug therapy, it should be tested no earlier than 2 years (strength of recommendation [SOR]: **B,** based on case series of dual energy x-ray absorptiometry [DEXA] scanning precision and bisphosphonate efficacy). Currently no prospective, randomized trials investigate the impact of bone density follow-up testing on osteoporotic patients receiving bisphosphonate therapy.

■ EVIDENCE SUMMARY

Testing the effectiveness of therapy for osteoporosis by measuring changes in bone mineral density (BMD) is difficult because changes are often small and occur slowly, and a decrease in BMD does not necessarily mean treatment failure. Testing patients after starting bisphosphonate therapy has been part of many drug trials to assess the effectiveness of therapy. Follow-up testing in clinical practice has not been the focus of a prospective trial and therefore remains controversial.[1]

DEXA is considered the gold standard because it is the most extensively validated test for predicting fracture outcomes.[2] Understanding the rate of bone density response to therapy, and the precision error of DEXA, helps to determine monitoring intervals. The larger the responses in BMD to therapy and the more precise the DEXA scan result, the shorter the period between testing in which clinically relevant differences can be found. Precision error rates are estimated at <1% for the anterior-posterior spine and 1% to 2% for

the hip.[3] The BMD change after the initiation of treatment must escape the precision error of the testing device or exceed the least significant change (LSC) value.[4] The LSC—roughly analogous to a 95% confidence interval—is 2.8 times the precision error of the test on a specific machine and site of measurement. If the precision error for DEXA of the femoral neck BMD is 2%, then the LSC is 5.6%.[5] Changes in BMD of <2%–4% in the vertebrae and 3% to 6% at the hip could be due to inherent measurement error.[6]

A clinician must also understand the anticipated response to the prescribed therapy. It is not

FIGURE

Bone mineral density in osteoporosis

**DEXA scanning is useful
if its limitations are understood**

Imprecision is a reality with the DEXA scan. Clinical experience has shown that, for patients receiving biphosphonate therapy to increase bone mineral density (BMD) in the femoral neck, any change in BMD of less than 5.6% may be due to measurement error and should not necessarily prompt a change in treatment. BMD response to bisphosphonates vacillates in the first few years of use but can be expected to increase femoral neck BMD by 3% to 6% over 3 years. If serial DEXA scanning is made part of the management plan, it should be considered no sooner than 2 to 3 years following the start of therapy.

clinically useful to retest BMD before a therapy would have time to affect bone turnover. Alendronate and risedronate increase lumbar spine BMD by 5% to 7% and hip BMD by 3% to 6% when used for approximately 3 years.[7,8] These increases in BMD are associated with 30% to 50% reductions in vertebral and hip fractures.[6] Alendronate continues to increase BMD: following 10 years of treatment, it increased BMD by 13.7% in the lumbar spine, 6.7% in the total hip, and 5.4 % in the femoral neck.[9]

Frequent testing, as seen in bisphosphonate clinical trials, demonstrates the phenomenon of regression to the mean. One analysis of the FIT trial, which compared alendronate with placebo in postmenopausal women with low BMD and at least 1 vertebral fracture, focused on the early evaluation of BMD. The study found a high degree of variability in BMD when tested after 1 year of treatment. This wide variety of response

in the first year normalized in the second year.[10] A second analysis showed that when women were divided into 8 groups, the group with the greatest increase in BMD in the first year (10.4%) also had the greatest decrease (1.0%) in year 2. In addition, the group with the greatest decrease in year 1 (6.6%) had the greatest increase in year 2 (4.8%). The variability in response among the 8 groups was approximately 17% (+10.4% and −6.6%) in year 1 and narrowed to a 6% difference in year 2 This regression to the mean leads to a normalization of bone density results.[11,12] This patient variability in BMD response to the prescribed therapy should be considered when deciding to retest.

In summary, limitations in DEXA precision mean any changes in BMD of less than 5.6% at the femoral neck may be due to measurement error, and BMD response to bisphosphonates vacillates in the first few years of use but can be

	TABLE

Recommendations on monitoring the clinical response to DEXA in osteoporosis therapy

Organization	Method used to formulate responses recommendation	Recommendations for monitoring treatment to anti-resorptive therapy
AHRQ Evidence Report (*Osteoporosis in Postmenopausal Women*)[14]	Systematic review	Advises against repeating bone density tests within the first year of treatment. Insufficient evidence to determine whether repeating tests 2 years after starting therapy is useful
American Association of Clinical Endocrinologists[13]	Rating scheme (Statement not rated)	Yearly for 2 years and if bone mass has stabilized, follow-up measurements are recommended every 2 years
Canadian Panel of Int'l Society for Clinical Densitometry[15]	Not stated	Repeat scan should be considered after 1 to 3 years if concerned about progressive bone loss or with new intervention
Institute for Clinical Systems Improvement[1]	Not stated	Controversy exists as to whether follow-up testing is necessary in all patients, but if performed, it should be done after 1 to 2 years of therapy
National Institute of Health[16] change	Expert consensus	Monitoring has not been shown to improve compliance. Physicians should not stop or therapies because of modest bone density loss
National Osteoporosis Foundation[6]	Expert consensus	Recommended 1 to 2 years following initiation of therapy
North American Menopause Society[17]	Expert consensus	Monitoring before 2 years of treatment would not be useful
Osteoporosis Society of Canada[18]	Not stated	Suggests at least 1 follow-up measurement is necessary. Central bone densitometry 1 to 2 years following initiation of bisphosphonate therapy. For patients receiving hormone therapy, repeat BMD is recommended at 2 to 4 years
University of Michigan[19]	Evidence rating scheme	For most persons an interval of >2 years between DEXAs provides the most meaningful information

expected to increase femoral neck BMD 3% to 6% over 3 years. Therefore, if serial DEXA scanning is preformed on patients prescribed bisphosphonate therapy, it should be considered no earlier than 2 to 3 years after therapy begins. When monitoring osteoporosis therapy, a BMD change within the LSC should be interpreted as "no change" and should not lead to changes in patient management. If the BMD has decreased beyond the LSC there is cause for concern and reevaluation of diagnosis and treatment are warranted.[4]

■ **RECOMMENDATIONS FROM OTHERS**

Guidelines on monitoring the clinical response to osteoporosis therapy with DEXA are available from numerous groups (**Table**). In clinical practice, it is common for a BMD difference of 3% to 5% at the spine or 4% to 6 % at the hip to be considered clinically significant.[13]

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■ CLINICAL COMMENTARY

If follow-up is needed, rescan in 2 to 3 years

Rates of vertebral and hip fractures are significantly reduced by alendronate and risedronate, making them important in the prevention and treatment of osteoporosis. Despite controversies over the timing and necessity of monitoring bisphosphonate therapy with DEXA scans, they may be useful clinically if their limitations are recognized. It is necessary to wait 2 to 3 years to repeat the DEXA after initiating therapy to account for the slow rate of change of bone density and compensate for the regression-to-the-mean phenomenon seen in clinical trials.

If after 2 or 3 years the bone density remains stable or has increased, reassurance can be given that fracture risk has decreased. If bone density has decreased more than the LSC, consider the following questions. Is the medicine is being taken first thing in the morning on an empty stomach? Is weight-bearing exercise performed routinely, tobacco avoided, and caffeine limited? Is the patient continuing adequate calcium and vitamin D supplements? The physician should also consider secondary causes of osteoporosis, such as hyperthyroidism and hyperparathyroidism.

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What is the addiction risk associated with tramadol?

■ EVIDENCE-BASED ANSWER

Tramadol (Ultram, generic and with acetaminophen in Ultracet) carries a risk of substance abuse (strength of recommendation [SOR]: **B**, based on case report surveillance programs). While it appears that tramadol's risk of substance abuse is low (SOR: **B**, based on case report surveillance programs), tramadol is associated with a withdrawal syndrome usually typical of opioid withdrawal (SOR: **B**, based on case report surveillance programs, and a prospective descriptive study).

■ EVIDENCE SUMMARY

Tramadol is a novel, central-acting synthetic opioid with weak mu-opioid activity, and is approved for treatment of moderate to moderately severe pain in adults. Anecdotally, some clinicians have assumed this popular analgesic's nonscheduled status under the Controlled Substance Act (CSA) means tramadol has no substance abuse potential. (The term "abuse" herein denotes substance abuse or dependence.)

Evidence of tramadol abuse in the US comes primarily from federally operated programs collecting adverse drug event (ADE) data. The MedWatch program of the Food and Drug Administration (FDA) provides a central depository for receiving and compiling postmarketing voluntary case reports. While passive reporting systems can significantly underestimate serious ADE numbers, these reports are often the first evidence of an ADE after a new drug's release into the market.[1] MedWatch has received 766 case reports of abuse associated with tramadol, as well as 482 cases of withdrawal associated with tramadol from the drug's initial US marketing in 1995 through September 2004.[2,3]

The Drug Abuse Warning Network (DAWN) is a federally operated, national surveillance system that monitors trends in drug-related emergency department visits. Over the period from 1995 to 2002, DAWN reported drug-related emergency department visits mentioning tramadol in more than 12,000 cases. Tramadol case numbers significantly increased 165% during this time. For perspective, during the same period, DAWN found nalbuphine (Nubain, also not CSA scheduled) in 118 cases, propoxyphene drug combinations (CSA Class IV) in more than 45,000 cases, codeine drug combinations (CSA Classes III & V) in about 50,000 cases, and hydrocodone drug combinations (CSA Class III) in around 128,000 cases.[4]

Using data from observational postmarketing studies, investigators have extrapolated a tramadol abuse rate for the general tramadol-exposed population.[5,6] Ortho-McNeil, Ultram's manufacturer, funded a surveillance program that compiled tramadol abuse and withdrawal case reports from 2 sources: (1) periodic surveys for tramadol abuse case reports from a group of 255 substance abuse experts studying and caring for addiction communities, and (2) voluntary ADE case reports from health care professionals and consumers received by Ortho-McNeil. Over 3 years of surveillance, the program received 454 case reports classified as tramadol abuse. Over 5 years of surveillance, 422 cases of substance withdrawal, with primarily opioid withdrawal symptoms, were reported. There are significant threats to the validity and generalizability of the investigators' estimated abuse rate of 1 to 3 cases per 100,000 tramadol-exposed patients. The abuse cases were collected in nonrepresentative samples of the tramadol-exposed population. Tramadol exposure is likely suppressed in addiction communities with access to preferred, more potent or euphoriant opioids than tramadol. Voluntary case reports of tramadol abuse significantly underestimate the actual number of abuse cases in the tramadol-exposed population. In addition, the low survey return rate (49%) further decreases the accuracy of any estimation of tramadol abuse rates.

Prospective studies among patients with known abuse, or at high risk of abuse, reported a tramadol abuse rate, as well as subjective experiences of tramadol withdrawal. A 3-year post-mar-

keting cohort study measured tramadol's nonmedical misuse rates using urine drug testing for tramadol among 1601 participants in 4 US state monitoring programs for impaired healthcare professionals.[7] Tramadol exposure occurred in 140 (8.7%) participants. Thirty-nine (28%) were classified as extensive experimentation or abuse of tramadol. Overall, the rate of extensive experimentation or abuse was 18 cases per thousand person-years. The Hawthorne effect, where awareness of being monitored alters a subject's behavior, may threaten these measured frequency rates' generalizability. Another prospective study assessed the subjective tramadol withdrawal experience in 219 patients with a diagnosis of "Tramadol misuse" who were attending 6 drug detoxification centers in China.[8] Validated drug dependence symptom scales found that while the degree of physical dependence reported was uniformly mild, the majority of patients reported the psychic dependence symptom of tramadol craving.

The FDA's Drug Abuse Advisory Committee performed a formal review of the tramadol abuse evidence in 1998, including the data from Ortho-McNeil's surveillance studies and federal case reporting/surveillance programs. The FDA did not recommend changing tramadol's unscheduled status.[9] The FDA's considered decision to not schedule tramadol as a controlled substance implies its abuse risk to the general population is *low* in comparison to its novel analgesic benefit.

■ RECOMMENDATIONS FROM OTHERS

Ortho-McNeil's revised 2001 product package insert for Ultram states, "Tramadol may induce psychic and physical dependence of the morphine type (mu-opioid). *Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence*" (italics in original, emphasizing 2001 addition). The risk for patients with a history of substance abuse has been observed to be higher.[10]

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■ CLINICAL COMMENTARY
Though it may not have high abuse potential, prescribe tramadol cautiously

Although tramadol appears to have a low potential for abuse, the literature does reveal evidence of abuse, addiction, and withdrawal, even in patients without a history of such problems. We do not know if tramadol is less addictive than other narcotics in high-risk patients. For patients at risk for dependence, tramadol is a reasonable alternative to other opioids, but abuse appears more likely in these patients. Tramadol may be most appropriate for treatment of acute painful conditions, but it can be administered chronically under a watchful eye. Providers should prescribe it cautiously, particularly in patients with a history of abuse or addiction, at least until more definitive evidence surfaces.

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What are the indications for evaluating a patient with cough for pertussis?

■ EVIDENCE-BASED ANSWER

Pertussis should be considered in infants with apnea or severe coughing illnesses of any duration, and in older children or adults with prolonged cough (eg, longer than 2 weeks), especially if accompanied by inspiratory whoop or household exposure to a prolonged cough illness (strength of recommendation [SOR]: **B**, based on consecutive cohort studies with poor reference standards). Coughing paroxysms, posttussive vomiting, and absence of fever, while typical of pertussis, are of little help in distinguishing it from other causes of prolonged coughing illnesses (SOR: **B**, based on consecutive cohort studies with poor reference standards).

■ EVIDENCE SUMMARY

Pertussis is an important cause of cough in all age groups. Ten prevalence studies of adolescents and adults seeking medical attention for a prolonged cough (defined variously as >1–4 weeks) found acute pertussis in 12% to 32%.[1]

While cough longer than 2 weeks, inspiratory whoop, posttussive vomiting, coughing paroxysms, and absence of fever are commonly associated with pertussis, relatively few studies have assessed the sensitivities and specificities of these symptoms. The **Table** summarizes results from 5 cohort series of children and adults with laboratory-confirmed pertussis. Comparison groups were variously defined by negative pertussis cultures, negative pertussis serology, or serologic confirmation of other respiratory infections. Likelihood ratios (LR) were calculated from the data presented in each paper.

The magnitude and variability of these likelihood ratios suggest that individual symptoms may be of limited help in distinguishing pertussis from other causes of prolonged cough. Combinations of symptoms may be slightly more helpful. In a study comparing 10 patients with culture-confirmed pertussis with 10 patients with serologically confirmed mycoplasma pneumonia, the combination of cough >14 days and whoop had a sensitivity of 80%, a positive LR (LR+) of 8 and a negative LR (LR–) of 0.22.[2] A cohort series of children aged <5 years with suspected pertussis compared 33 with positive cultures to 55 with negative cultures. The constellation of spasmodic cough and lymphocytosis (>10,000) had a sensitivity of 83%, a LR+ of 2.5, and a LR– of 0.25. Cough >14 days with whoop and vomiting had a sensitivity of 67%, a LR+ of 3.2, and LR– of 0.42.[3]

Infants aged <6 months with pertussis are at particular risk for atypical presentations and serious complications. In a US series of 18,500 infants with pertussis, apnea was seen in 64% of infants under 1 month and in 44% between 6 and 11 months. Forty percent of the 6- to 11-month-olds had received at least 3 doses of pertussis vaccine.[4] A British study of 126 infants aged <5 months admitted to the pediatric intensive care unit with apnea, bradycardia, or respiratory failure found that 20% had pertussis. Apnea as a predictor of pertussis had a sensitivity of 68% and a specificity of 60%.[5]

Pertussis should be considered early in the evaluation of young infants with cough. In a case-control study comparing 15 fatal cases of pertussis with 32 who survived (infants aged <6 months), the mean number of days from symptom onset to hospital admission were 5.3 (fatal) and 8.6 (survivors). Rates of apnea on admission were 40% and 52%.[6] A case series of 9 infants aged <7 weeks requiring admission to an intensive care unit for pertussis found that 8 had been sick for less than 4 days at the time of admission. All 9 presented with poor feeding and cough, and 5 had experienced apnea.[7]

■ RECOMMENDATIONS FROM

TABLE	**Clinical features of pertussis**			
History	**Sensitivity**	**Specificity**	**LR+**	**LR–**
Cough >2 weeks[3,12]	84%–100%	35%–36%	1.3–1.5	0–0.44
Cough >3 weeks[3,12]	75%–97%	51%–59%	1.8–2.0	0.06–0.42
Whoop[3,10–12]	37%–90%	49%–96%	1.6–9.2	0.18–0.66
Posttussive vomiting[3,10,11,13]	28%–84%	45%–84%	0.9–2.2	0.36–1.0
Paroxysms[3,12,13]	68%–94%	15%–45%	1.1–1.4	0.29–0.71
Household exposure[11,13]	20%–50%	73%–91%	1.9–2.2	0.68–0.88
Afebrile (temp <38ºC)[11–13]	62%–96%	12%–54%	0.8–1.1	0–1.7
Lymphocytosis[3]	88%	57%	2.0	0.21

LR+ = positive likelihood ratio: sensitivity/(1–specificity); † LR– = negative likelihood ratio: (1–sensitivity)/specificity.

OTHERS

The Centers for Disease Control and Prevention and the World Health Organization describe the clinical case definition for pertussis as a cough illness lasting at least 2 weeks with at least 1 of the following: paroxysms of coughing, inspiratory whoop, or posttussive vomiting, without other apparent cause. Laboratory criteria for diagnosis include a positive *Bordetella pertussis* culture or a positive polymerase chain reaction (PCR) for *B pertussis*.[8,9]

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■ CLINICAL COMMENTARY

Infants may have complications; evaluate if there is apnea or significant cough

Immunity to pertussis wanes following vaccination, leaving many adolescents and adults susceptible to infection. In older children and adults, there is often little in the clinical presentation that distinguishes chronic cough due to pertussis from that associated with other causes. Clinicians should consider evaluating for pertussis in older children and adults with chronic cough (>2 weeks) if there is reason to suspect they have been exposed, if the cough is associated with inspiratory whoop, or if the individual has household or frequent contact with infants.

Infants may suffer severe complications from pertussis, and should receive evaluation when presenting with apnea or significant cough of any duration. In current practice, evaluation usually includes obtaining a nasopharyngeal swab for culture and PCR, though these tests may be insensitive, especially in later phases of illness. The usefulness of single, quantitative immunoglobulin G titers with comparison to pop-

impact the epidemiology of pertussis in the US.

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Does quinine reduce leg cramps for young athletes?

■ EVIDENCE-BASED ANSWER

Very little evidence exists regarding the use of quinine for cramps in young adult athletes. Quinine may be an effective treatment for heat cramps in athletes (strength of recommendation [SOR]: **C**, 1 case series involving 2 patients). Quinine is better established as an effective treatment for nocturnal leg cramps in the general adult population (SOR: **A**, 1 meta-analysis and 2 randomized controlled trials).

■ EVIDENCE SUMMARY

Leg cramps (heat cramps) in athletes are defined as painful involuntary muscle contractions, usually in the large muscle groups of the legs, which occur during or in the hours following exercise. Oral quinine is sometimes used to treat nocturnal leg cramps in the general adult and elderly populations. However, its use is controversial secondary to concerns regarding efficacy and safety.

Efficacy of quinine in young athletes has not been well studied. A case series reported on 2 athletes: 1 college basketball player and 1 professional football player.[1] The basketball player experienced heat cramps during games that were resistant to hydration and dietary treatment. A regimen of 60 mg oral quinine sulfate taken 1 hour before game time and again at halftime eliminated cramps during the first game and the subsequent 15 games. The football player's heat cramps were only partially improved with oral electrolyte repletion and oral hydration. However, he suffered no further cramps after initiating a regimen of 120 mg oral quinine sulfate

before games and 60 mg oral quinine during games for an undisclosed period of time. Both players had normal blood chemistries before starting quinine. No side effects were mentioned.

Several trials involving the general adult population exist. A meta-analysis of 4 published and 3 unpublished reports of randomized, double-blind controlled crossover trials (n=409) showed that adult patients had significantly fewer nocturnal cramps when taking quinine compared with placebo.[2] The absolute reduction in number of leg cramps was 3.6 (95% confidence interval [CI], 2.15–5.05) over a 4-week period, and the relative risk reduction was 0.21 (95% CI, 0.12–0.30).

Two randomized controlled trials were not included in the meta-analysis discussed above. One double-blind, randomized, controlled parallel group trial of 98 adult patients with a mean age of 50 years demonstrated that a regimen of daily quinine sulfate therapy of 200 mg with the evening meal and 200 mg at bedtime significantly reduced the number of nocturnal muscle cramps compared with placebo.[3] Over a 2-week treatment period the quinine group experienced a median of 8 fewer cramps (95% CI, 7–10), while the placebo group experienced a median of 6 fewer cramps (95% CI, 3–7). However, patient evaluation of global efficacy of treatment was not statistically significant between the quinine and placebo groups.

A second double-blind, randomized, controlled parallel group trial of 102 adult patients, mean age approximately 50 years, showed that a 2-week treatment period of hydroquinine (not available in the US) also produced a significant reduction in day- and nighttime muscle cramps compared with placebo.[4] This study used a regimen of two 100-mg hydroquinine or placebo tablets with the evening meal and one 100-mg tablet or placebo at bedtime. The median difference in the number of cramps between the treatment and control groups was 5 (95% CI, 2–8).

It should be noted that during the 2 weeks immediately following the treatment period, numbers of cramps were still low compared with the pretreatment period and no significant difference was seen in number of cramps between groups. This raises suspicion that the improvement in both groups was due to the self-limited nature of cramps and represented the regression-to-the-mean phenomenon rather than a true treatment effect of hydroquinine. In addition, extrapolating results from studies of nocturnal cramps to heat cramps is problematic, as it is unknown whether these differ in physiology or cause.

Use of quinine for common cramps in nonathletes has been controversial. In 1994 the Food and Drug Administration (FDA) issued a statement banning over-the-counter sale of quinine for nocturnal leg cramps, citing lack of adequate data to establish efficacy and concern for potential toxicity.[5] Between 1969 and 1990 the FDA received 26 adverse reaction reports in which quinine was concluded to be the causative agent. The 3 studies discussed above consistently mention only tinnitus as likely related to quinine use. However, the descriptions and inference testing of side effects were inadequate in each study.

Of note, quinine is a category X drug and should not be used during pregnancy.[6]

■ RECOMMENDATIONS FROM OTHERS

No specific recommendations exist regarding the use of quinine in athletes. The American Medical Society of Sports Medicine recommends rest, stretching, and oral hydration for simple heat cramps, and intravenous fluids for very severe cases.[7] Several texts also recommend rehydration with an oral electrolyte solution, as well as rest, stretching, and massage.[8–10]

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> Hydration before, during, and after activity remains the cornerstone to approaching cramping in athletes

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■ CLINICAL COMMENTARY

Hydration and salt intake best approach for cramping in athletes

The use of quinine for the treatment or prevention of leg cramps in young adult athletes is not well studied. Safety and efficacy issues make it an unappealing option in the treatment of cramps and consequently it is not recommended for use in athletes. Hydration before, during, and after activity remains the cornerstone to approaching cramping in athletes. Appropriate salt intake for those who lose high concentrations of salt in their sweat may also be useful in prophylaxis. Once cramps occur, rehydration, stretching, massage, and rest work best.

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Can type 2 diabetes be prevented through diet and exercise?

■ EVIDENCE-BASED ANSWER

Diets that result in long-term weight loss of 5% to 7%, along with moderate-intensity exercise for more than 150 minutes per week, reduce the incidence of type 2 diabetes for patients with impaired glucose tolerance (IGT) (strength of recommendation [SOR]: **A,** based on multiple randomized controlled trials [RCTs]). Each of the trials demonstrating this finding included fairly intensive counseling as part of the successful intervention. Diet and exercise reduce the incidence of diabetes in both lean (body mass index [BMI] <25) and overweight patients with IGT (SOR: **B,** based on a single, large RCT).

■ EVIDENCE SUMMARY

Three large prospective RCTs evaluated the effect of dietary and exercise interventions in populations at risk for developing diabetes.

The **Diabetes Prevention Program Research Group**[1] randomized 3234 patients age >24 years without diabetes but with IGT and a BMI >24 to 1 of 3 groups: intensive lifestyle modification, metformin, or control; they then compared the incidence of diabetes over 3 years. Patients were men and women from primary care populations and represented diverse ethnic backgrounds. Investigators defined IGT as plasma glucose of 140 to 200 mg/dL 2 hours after a 75-g glucose bolus when the fasting glucose was <140 mg/dL. Intensive lifestyle intervention comprised individual training sessions on a

TABLE

Incidence of diabetes among patients with impaired glucose tolerance participating in diet and exercise programs

Study population	Mean BMI	Intervention	Diabetes incidence*	RRR	NNT
Diabetes Prevention Program[1] (3234 primary care patients, men and women, mixed ethnic backgrounds, various ages)	34	Control	11.0	Baseline	Baseline
		Metformin	7.8	31%	14 (over 7 years)
		Intensive lifestyle modification	4.8	58%	7 (over 7 years)
Finnish Diabetes Prevention Study[2] (522 patients)	31	Control	23	Baseline	Baseline
		Intensive lifestyle modification	11	58%	5 (over 5 years)
Da Qing IGT and Diabetes Study[3] (577 primary care patients, men and women aged >25 years)	25.8	Control	15	Baseline	Baseline (all over 6 years)
		Diet	10	31%	17
		Exercise	8	46%	14
		Diet and exercise	9.5	42%	16

*Incidence of diabetes per 100 person-years.
IGT, intensive glucose control; BMI, body mass index; RRR, relative risk reduction; NNT, number needed to treat.

low-calorie, low-fat diet, aerobic exercise (such as brisk walking), and behavior modification. Case managers met with each participant for at least 16 sessions during the first 24 weeks and at least monthly thereafter. The control group received lifestyle change recommendations without individualized attention.

After 24 weeks, 50% of the lifestyle group met the 7% weight loss goal and 74% were exercising at least 150 minutes per week. At the final visit, 38% maintained their target weight and 58% met their exercise goal. Lifestyle intervention produced greater weight reduction and increased activity compared with the metformin and control groups, with a corresponding decreased incidence of diabetes (**Table**). Subgroup analysis found that lifestyle intervention produced the greatest reduction in diabetes (71%) for patients aged >60 years.

The **Finnish Diabetes Prevention Study**[2] similarly randomized 522 patients, aged 40 to 65 years, with IGT and obesity (mean BMI=31) to either intensive lifestyle intervention or control and followed them for 3.2 years. The lifestyle intervention included moderate exercise for at least 150 minutes per week and weight loss of at least 5%. Patients were offered an individualized exercise plan with supervised aerobic exercise plus circuit-type resistance sessions 3 times a week. Nutritionists met with patients 7 times in the first year and every 3 months after that. Patients were counseled to increase fiber intake, reduce total fat below 30% of total calories, and reduce saturated fat below 10%. The control group was given general information on diet and exercise without individualized programs. Most patients (86%) in the intervention group met their exercise goal, and 25% met the fiber requirement.

Compared with the control group, the intervention group had greater success rate for each category. Intensive lifestyle intervention reduced the incidence of diabetes by 58% (number needed to treat=5 for 5 years; see **Table**).

The **Da Qing IGT and Diabetes Study**[3] divided

> Exercise was more effective in reducing diabetes in lean patients, but overweight patients also benefited

577 patients with IGT into 1 control and 3 intervention groups: diet, aerobic exercise, and combined diet plus aerobic exercise. Patients in this study had the lowest average BMI (25.8) of the 3 studies. The intervention group received individual and group counseling sessions at weekly intervals for 1 month, then monthly for 3 months, and then every 3 months. The control group received generalized information on IGT and diabetes but individual or group instruction was not included.

At the 6-year follow-up, the quantity of exercise was significantly higher in the exercise intervention groups, but no significant difference in caloric intake was seen among all 4 groups. The incidence of diabetes in the exercise intervention group was approximately half that in the control group overall (**Table 1**). Exercise was more effective in reducing diabetes in lean patients (BMI <25), but both lean and overweight patients benefited. The combination of diet plus exercise and diet changes also significantly reduced diabetes, although to a lesser degree.

■ RECOMMENDATIONS FROM OTHERS

The American Diabetes Association recommends structured programs that emphasize lifestyle changes, including education, reduced fat and energy intake, regular physical activity, and regular participant contact. These changes can produce long-term weight loss of 5% to 7% of starting weight and reduce the risk for developing diabetes.[4] They also stress the importance of promoting exercise as a vital component of the prevention as well as management of type 2 diabetes. The benefit of exercise in improving the metabolic abnormalities of type 2 diabetes is probably greatest when it is used early in its progression from insulin resistance to impaired glucose tolerance to overt hyperglycemia.[5] The World Health Organization states that increased physical activity and maintaining a healthy weight play critical roles in the prevention and treatment of diabetes.[6]

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■ CLINICAL COMMENTARY

Encourage patients to exercise and eat well, and see a dietician if they are willing

Diet and exercise are important components in the management of patients at risk for diabetes; the challenge revolves around the time and money commitment necessary for these interventions. A physician in a typical office setting has limited time to implement the interventions used in these trials. Referral to other health professionals (dietician, exercise

physiatrist, etc) for counseling or individual guidance may be prohibitively costly, as these services are often not covered by insurance, and patients may not be willing to pay.

Bottom line—at every office visit, encourage patients to increase their exercise and watch what they eat as part of prevention. If they are willing to see a dietician, by all means send them.

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Does neonatal circumcision decrease morbidity?

■ EVIDENCE-BASED ANSWER

Evidence suggests that neonatal circumcision decreases the incidence of childhood urinary tract infections, phimosis, paraphimosis, balanitis and other genital dermatoses, invasive penile cancer, and the sexually transmitted diseases human papilloma virus (HPV) and HIV (strength of recommendation [SOR]: **B**, based on case control and cohort studies). The benefits of decreased incidence of HPV and HIV infections go beyond the index patient and have public health implications on the transmission of these diseases (SOR: **B**). Further, a decrease in HPV incidence and transmission may lead to a lower incidence of cervical cancer (SOR: **B**).

While there appears to be some evidence for reduced morbidity with routine circumcision, decisions regarding routine neonatal circumcision requires balancing risks and benefits of the procedure with the alternatives in the context of social, familial, and religious beliefs.

■ EVIDENCE SUMMARY

Observational studies have shown at least a 10- to 12-fold increase in urinary tract infections (UTIs) in uncircumcised male infants compared with their circumcised counterparts.[1] The number of male infants that need to be circumcised to prevent 1 UTI is estimated to be between 44 and 100.[2,3] The only randomized controlled trial of circumcision for UTI prevention was not during the neonatal period (average age was 30 months) and focused on secondary prevention.[4] It demonstrated a statistically significant decrease in the rate of bacteriuria. The long-term effect on UTI incidence, renal scarring, and subsequent complications such as hypertension and end-stage renal disease is unknown.

Evidence from case series supports the protective effect of circumcision on the rates of penile cancer. A review of 592 cases of penile cancer revealed that none of those affected had been circumcised in infancy.[5] In another series of 89 men with penile cancer, only 2 had been circumcised in infancy, while 87 were uncircumcised.[6] Since HPV is thought to be a major etiologic agent in both penile cancer and cervical cancer, investigators studied the link between circumcision status and cervical cancer. In a meta-analysis of 7 case-control studies, penile HPV was detected 2.7 times more often in uncircumcised men after controlling for confounders.[7] In this same meta-analysis, monogamous female partners of high-risk circumcised men (men with more than 6 lifetime partners) had a lower risk of cervical cancer than women whose high-risk partner was uncircumcised (adjusted odds ratio=0.42; 95% confidence interval [CI], 0.23–0.79).[7]

The evidence that circumcision prevents most sexually transmitted diseases is not very strong, with the exception of HIV and genital ulcer disease. Most of these studies are from sub-Saharan Africa, where rates of HIV infection are extremely high. A meta-analysis of 15 observational studies in Africa, with adjustment for potential confounding factors, found that circumcision decreased the risk of acquiring HIV by more than half (relative risk [RR]=0.42; 95% CI, 0.34–0.54).[8] A more recent prospective study from India showed a strong protective effect of circumcision against HIV infection (RR=0.15; 95% CI, 0.04–0.62).[9] This study found no protective effect of circumcision against herpes, syphilis, or gonorrhea, suggesting a biological rather than a behavioral explanation for the pro-

tective effect of circumcision against HIV.

A conservative estimate of the post-neonatal childhood circumcision rate for purely medical reasons is 2% to 5%; estimates go as high as 7% to 10%.[10] The most common medical indication for circumcision is phimosis, followed by recurrent balanitis and paraphimosis. Circumcision may also be protective against genital dermatoses; a case-control study found an age-adjusted odds ratio of 3.2 (95% CI, 2.3–4.6) for penile skin diseases in uncircumcised men compared with circumcised men.[11]

■ RECOMMENDATIONS FROM OTHERS

Circumcision rates vary widely worldwide, with strong cultural and religious preferences. Most major organizations have cautiously neutral opinions on circumcision, stating that medical benefits are not large enough to justify routine neonatal circumcision. The American Academy of Pediatrics Task Force on Circumcision recommends parents "should be given accurate and unbiased information" and that "parents should determine what is in the best interest of the child."[12] The American Medical Association, American College of Obstetrics and Gynecology, and the American Academy of Family Physicians all use similar statements.[13–15]

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■ CLINICAL COMMENTARY

Explain risks and benefits of circumcision to parents so they make informed decisions

A dilemma exists in the practice of recommending circumcision to parents of newborn males. Although the evidence shows that morbidity is decreased in circumcised males, the occurrence of complications (such as UTI or balanitis) is believed to be preventable through good hygiene, and the incidence of the preventable disease (such as penile cancer) is so low in the general population as to not justify the procedure. The challenge is there because the procedure is not without pain or risk of complications.

This is the basis for the American Academy of Pediatrics not recommending routine neonatal circumcision. The consensus was that the evidence was not sufficient to support it. Since then, many studies have been published on HPV and HIV transmission, the incidence of phimosis and paraphimosis, UTI, and balanitis, and how circumcision reduces the incidence of these diseases. Again, these are believed to be preventable through hygiene and condom use. In practice, it is difficult to persuade parents because these complications usually occur much later in life.

Most patients made their decisions on circumcision based on religious or cultural experiences. My practice has a large Hispanic immigrant pop-