Evidence-based answer

Yes, under some circumstances. Patients with type 2 diabetes who aren’t on insulin and perform self-monitoring blood glucose (SMBG) show small but significant reductions in hemoglobin A1c (HbA1c) at 6 months but not at 12 months (SOR: B, systematic reviews and meta-analyses of disease-oriented evidence).

Patients with a baseline HbA1c <8% who self-monitor do not reduce their A1c levels, but patients with a baseline A1c >8% do (SOR: B, systematic reviews and meta-analyses of disease-oriented evidence).

More frequent SMBG—4 to 7 times weekly—does not reduce HbA1c more than less frequent self-monitoring—1 or 2 times a week (SOR: B, a systematic review and meta-analysis of disease-oriented evidence).

Evidence summary

A 2012 Cochrane review and meta-analysis of 9 RCTs found that 1,261 patients who used SMBG showed a small but statistically significant decrease in HbA1c at 6 months compared with 1,063 controls. In 2 other RCTs, patients using SMBG showed a nonsignificant decrease in HbA1c compared with control subjects at 12 months (TABLE 1). A meta-analysis reported similar findings. The study grouped 9 RCTs based on the duration of SMBG and examined the change in HbA1c from baseline. In 5 of the RCTs, SMBG for 6 months was associated with a small decrease in HbA1c, but in the other 4 RCTs, SMBG for >1 year did not significantly change A1c levels.

Baseline HbA1c values make a difference

A meta-analysis of 9 RCTs demonstrated that SMBG was marginally superior to non-SMBG for reducing HbA1c when the baseline value was >8%. SMBG did not lower HbA1c in patients with a baseline A1c <8%. The greatest change in HbA1c occurred in patients with baseline values >10% (TABLE 2).

In another meta-analysis, 12 of 15 RCTs showed that SMBG was better than non-SMBG at reducing HbA1c when the baseline was >8%.
Limitations of studies

Limitations of the studies reviewed included methodological quality, limited patient compliance reporting, heterogeneity of the studies, and small sample size.

More frequent self-monitoring has no effect

A systematic review of 4 RCTs with a total of 637 patients that evaluated whether frequent SMBG reduced HbA1c levels more than less frequent self-monitoring found no difference. Researchers compared patients who self-monitored glucose levels 4 to 7 times a week with patients who self-monitored 1 to 2 times weekly for periods ranging from 3 to 12 months (HbA1c reduction difference between the groups = −0.21; 95% confidence interval, −0.57 to 0.15).

Recommendations

The American Diabetes Association advocates SMBG as a useful guide to successful therapy in patients who use oral or medical nutrition therapies for diabetes. Patients should receive initial instruction in SMBG and routine follow-up evaluation of technique, as well as an assessment of their ability to use data to adjust therapy.

The American Association of Clinical Endocrinology (AACE) advises that SMBG can be initiated at the same time as medical therapy, lifestyle modification, specific diabetes education, or dietary consultation. If HbA1c levels are above target, the AACE recommends more frequent SMBG as follows: preprandially, 2 hours postprandially, occasionally between 2:00 a.m. and 3:00 a.m., during illness, or anytime a low glucose level is suspected.

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From the Editor

The ears of Saturn

...if they had seen what we see, they would have judged as we judge.

—Galileo

Dear EBP Readers,

Ah, the good old days—when a scientist could simply believe the evidence of his (or her) own senses. Galileo lived at a time when a better understanding of the entire universe could be achieved simply by looking into the night sky with a low-powered telescope and making sketches in a notebook.

But now, as then, we have to be a little careful. While Galileo’s notebooks have the moons of Jupiter right, he drew pictures of Saturn that sported lobes resembling ears. In a cheap telescope, that’s pretty much what Saturn looks like. It is not, however, how Saturn really is.

The input of our senses is important, but it is not everything. We need to have some significant humility about our interpretation of what our eyes see.

This was brought home for me recently in a clever little study.1 Investigators sent 16 authors who had published research on a specific clinical question a meta-analysis on that topic (which included their research). These 16 authors were asked to review and interpret the results of the meta-analysis. The sneaky investigators then sent the same meta-analysis to 20 statisticians (unbiased by any research experiences) for their opinions as well. Because the meta-analysis demonstrated significant heterogeneity, this was not an easy meta-analysis to read.

Nevertheless, those authors who had seen an effect in their individual studies tended to (mis)interpret the meta-analysis as also showing effect. In fact, a full 50% of such authors concluded the meta-analysis demonstrated an effect with an odds ratio >1.2. Only 13% of the other authors and only 1 of the 20 statisticians had the same opinion.

What happened? Simply put, if you saw something work in your research study, it was really hard to later believe that your results were a true effect. In fact, a full 50% of such authors concluded the meta-analysis demonstrated an effect with an odds ratio >1.2. Only 13% of the other authors and only 1 of the 20 statisticians had the same opinion.

So go ahead and believe your eyes. But try to be a little humble about any interpretation that Saturn has ears.

Regards,

Jon O. Neher, MD

1. Panagiotou OA, Ioannidis JP. Primary study authors of significant studies are more likely to believe that a strong association exists in a heterogeneous meta-analysis compared with methodologists. J Clin Epidemiol. 2012; 65(7):740-747.
**Diving for PURLs**

### Antibiotics for appendicitis?


This meta-analysis of 4 RCTs compared the safety and efficacy of antibiotics with appendectomy for acute uncomplicated appendicitis. A total of 900 adult patients in these 4 studies were randomized to either appendectomy or 1 of 2 antibiotic regimens: oral amoxicillin plus clavulanic acid or IV cefotaxime plus metronidazole or tinidazole for at least 24 hours, followed by oral antibiotics for another 8 to 10 days.

The primary outcome was complications (wound infection, perforated appendicitis, and peritonitis). Antibiotic treatment was associated with a relative risk reduction of complications by 31% compared with appendectomy (risk ratio 0.69; 95% CI 0.54–0.89). No statistical differences were seen among antibiotic regimens. No differences were seen in length of hospital stay (mean difference 0.34 days; 95%CI, –0.19 to 0.87; \( P = .20 \)) or risk of complicated appendicitis (risk ratio 0.58; 95% CI, 0.18–1.90; \( P = .37 \)). With antibiotics 58% (274 of 470 patients) were treated successfully (no failure of antibiotics or recurrence requiring an appendectomy), while with appendectomy 93% (398 of 430 patients) were treated successfully (no postoperative complication requiring readmission).

**Bottom line:** Based on this meta-analysis, antibiotic treatment is associated with fewer serious complications and no differences in length of hospital stay compared with appendectomy. Unfortunately, the low quality, limited number, and unclear outcome definitions of these studies calls into question the validity of these results.

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### Enoxaparin: a new vulvodynia treatment?


This double-blinded RCT compared the effectiveness of subcutaneous enoxaparin with saline injections in the treatment of severe provoked vulvodynia among 40 Israeli women ages 18 through 50. Participants self-administered their assigned treatment in the abdomen daily for 3 months. Vulvar pain was assessed at 3 months (immediately after therapy) and at 6 months. Women were also given questionnaires about their vulvodynia symptoms before and after treatment, and also had biopsies performed to examine tissue for mast cells and nerve fiber density.

Enoxaparin users experienced a greater reduction of pain during a clinical examination at 6 months (30% reduction in pain for enoxaparin vs 11% for placebo; \( P = .004 \)). However, there were no statistically significant improvements in vulvodynia symptoms according to the questionnaires completed by patients. Three months after completing treatment, 7 women in the enoxaparin group reported almost pain-free intercourse compared with 3 women in the placebo group, but the statistical significance of this difference was not reported.

**Bottom line:** Enoxaparin has some promise as a treatment for provoked vulvodynia. While enoxaparin users experienced improvement in pain provoked during a physician examination, there was no significant improvement in the self-reported symptom.

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### PURLs Criteria

- **Relevant:** Is the topic relevant to family medicine?
- **Valid:** Are the findings scientifically valid?
- **Change in practice:** Would this change practice?
- **Medical care setting:** Is this implementable in clinic, etc?
- **Implementable:** Can we implement this immediately?
- **Clinically meaningful:** Are results clinically meaningful?

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**Review Author and Summary Author:** Sonia Oyola, MD, The University of Chicago, Department of Family Medicine, Chicago, IL

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**Review Author and Summary Author:** Kate Kirley, MD, The University of Chicago, Department of Family Medicine, Chicago, IL
In patients with a history of LEEP, does use of progestin-only contraception increase the risk of cervical stenosis?

Evidence-Based Answer
Use of depot medroxyprogesterone acetate (DMPA) at the time of loop electrosurgical excisional procedure (LEEP) for cervical dysplasia may increase the risk of developing cervical stenosis. The risk seems to be correlated with induction of amenorrhea (SOR: C, single disease-oriented case-series). Other forms of progestin-only contraception (oral, intrauterine, or implantable) have not been specifically studied.

One potential complication of LEEP is stenosis of the cervical os. Use of DMPA has been suggested as a contributing factor to cervical stenosis due to creation of a relatively hypo-estrogenic state.

In 2010, a retrospective case-series was conducted to investigate the effect of DMPA on development of cervical stenosis after LEEP. Of 257 LEEP cases reviewed, 127 had appropriate documentation of data required for analysis. The overall rate of cervical stenosis was 20% (25/127), with 10 cases noted 1 month after LEEP and 15 additional cases noted after 6 months. Among patients using DMPA at some point during the study, 41% (9/22) developed stenosis compared with 15% (16/105) of patients not using DMPA (OR 3.9; 95% CI, 1.4–11; P=.006). Among patients who did not menstruate during the study period, 39% (10/26) developed stenosis compared with 15% (14/93) of patients who did menstruate (OR 0.3; 95% CI, 0.1–0.8; P=.009). The study was limited by a high rate of stenosis compared with other studies and by a 50% follow-up rate.

Another retrospective case-series (N=164) investigated risk factors for development of cervical stenosis after LEEP. The overall incidence of cervical stenosis was 6%. The analysis suggested that 2 factors were associated with stenosis: volume of tissue removed (OR 1.3; 95% CI, 1.1–1.7; P<.001) and history of prior LEEP (OR 17; 95% CI, 2.7–112; P<.001). The incidence of cervical stenosis in women using oral contraceptives (OC) was 4.6% (2/43), less than that seen in women not using OC (6.6%, 8/121), although no comparison statistic was given.

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What are the risks of oral contraceptives in patients with cardiovascular disease risk factors?

Evidence-Based Answer
Women who smoke, have hypertension, hyperlipidemia, or factor V Leiden deficiency and take oral contraception (OC) are at increased risk of myocardial infarction (MI). Third-generation OCs and low-dose OCs are not associated with increased MI risk in women with or without other cardiovascular (CV) risk factors (SOR B, systematic review of cohort studies). OCs are contraindicated in women with preexisting congestive heart failure or CV disease, but may be used in otherwise healthy women with diabetes, hypertension, or hyperlipidemia (SOR C, evidence-based guidelines derived from consensus and expert opinion).

A meta-analysis investigated OC use and the risk of MI in 19 case-controlled studies and 4 retrospective cohort studies. Participants ranged in age from 15 to 55 years of age. Each case-controlled study had 26 to 910 cases and 63 to 3,120 controls. Women currently using OCs had an overall adjusted OR of 2.5 (95% CI, 1.9–3.2; P<.0005) and 3 (95% CI, 1.7–5.3; P<.0005) for MI compared with women who never used OCs or had past OC use, respectively. There was no difference between the overall risks of MI for past OC users compared with women who never used OCs (OR 1.2; 95% CI, 0.98–1.4; P=.096). Researchers also investigated the effect of OC use and CV risk factors compared with women who never used OCs and had no CV risk factors.
The most significant risk factors associated with MI and OC use were hypercholesterolemia, smoking, and hypertension. Additionally, higher estrogen doses were associated with higher risk of MI, with no significant risk seen at doses of 20 mcg.

The American College of Obstetricians and Gynecologists (ACOG) developed evidence-based guidelines for the use of OCs in women with CV risk factors. The Committee on Practice bulletins applied the levels of evidence criteria to independently review and grade the studies. Based on the evidence, ACOG made the recommendations outlined in Table 2.

**TABLE 1**

<table>
<thead>
<tr>
<th>Risk of cardiac event in women who use oral contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC plus 1 additional risk factor vs no risk factor and no OC</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Prothrombin mutation (factor V Leiden or G20210A)</td>
</tr>
</tbody>
</table>

**TABLE 2**

Summary of ACOG recommendations concerning combination oral contraceptives and cardiovascular risk

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th>ACOG recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Combination oral contraceptives should be prescribed with caution, if ever, to women who are older than 35 years and are smokers.</td>
<td>A</td>
</tr>
<tr>
<td>Diabetes</td>
<td>The use of combination contraceptives by women with diabetes should be limited to such women who do not smoke, are younger than 35 years, and are otherwise healthy with no evidence of hypertension, nephropathy, retinopathy, or other vascular disease.</td>
<td>B</td>
</tr>
<tr>
<td>HTN</td>
<td>Women with well-controlled and monitored hypertension who are aged ≤35 years are appropriate candidates for a trial of combination contraceptives, provided they are otherwise healthy, show no evidence of end-organ vascular disease, and do not smoke.</td>
<td>B</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Most women with controlled dyslipidemia can use combination oral contraceptives formulated with ≤35 mcg estrogen. In women with uncontrolled LDL cholesterol &gt;160 mg/dL, a triglyceride level &gt;250 mg/dL, or multiple additional risk factors for coronary artery disease, alternative contraceptives should be considered.</td>
<td>C</td>
</tr>
<tr>
<td>CAD, CHF, CVD</td>
<td>Progestin-only contraceptives may be appropriate for women with coronary artery disease, congestive heart failure, or cerebrovascular disease. However, combination contraceptives are contraindicated in these women.</td>
<td>C</td>
</tr>
</tbody>
</table>

ACOG levels of evidence: A=good and consistent scientific evidence; B=limited or inconsistent evidence; C=consensus and expert opinion.
ACOG=American College of Obstetricians and Gynecologists; HTN=hypertension; LDL=low-density lipoprotein.

Evidence-Based Answer
In patients with a single elevated serum prolactin level (SPL), the test should be confirmed with a repeat morning measurement followed by a clinical evaluation for secondary causes (SOR: C, consensus guidelines). Patients with persistently elevated SPL and no clear cause should undergo gadolinium-enhanced magnetic resonance imaging (MRI) to identify possible pituitary adenomas, regardless of the degree of SPL elevation (SOR: B, retrospective cohort study).

Consensus guidelines by the Endocrine Society and the Pituitary Society Expert Committee recommend that patients with repeatedly elevated, appropriately obtained morning SPL should be evaluated by ruling out secondary causes with a careful history and physical examination; pregnancy test; and kidney, liver, and thyroid function analyses.1,2 Drugs associated with hyperprolactinemia (eg, antipsychotics, neuroleptics, monamine-oxidase inhibitors, selective serotonin reuptake inhibitors, opiates, verapamil, methyldopa, reserpine, metoclopramide, domperidone, H2-blockers, estrogen, etc) should be withdrawn if possible and re-measurement of SPL performed. After excluding possible secondary causes of an elevated SPL, gadolinium-enhanced MRI should be performed to evaluate for pituitary adenoma.

A retrospective cohort study of 104 consecutive female patients (mean age 30 years) with hyperprolactinemia evaluated in a university hospital reproductive endocrinology clinic over a 5-year period sought to establish guidelines for the minimum SPL for which pituitary imaging is indicated.3 Pregnancy, lactation, and medications associated with hyperprolactinemia were exclusion criteria. Initial evaluation included measurements of thyroid-stimulating hormone, estradiol, luteinizing hormone, and follicle-stimulating hormone. SPL measurements were repeated at the endocrinology clinic initial evaluation to confirm persistent elevation (ie, >25 ng/mL). The median SPL was 82.6 ng/mL. A diagnosis of polycystic ovarian syndrome was made in 8 patients, premature ovarian failure in 2, and hypothyroidism in 2. The remaining 86 underwent gadolinium-enhanced MRI testing.

Twenty-three patients (26%) had normal MRI findings, 47 (55%) had microadenomas <10 mm, and 16 (19%) had macroadenomas >10 mm. A SPL level >100 ng/mL was associated with a diagnosis of macroadenoma (OR 7.6; 95% CI, 1.39–55.02; P<.01). For patients with microadenomas, 52% had SPL <100 ng/mL. But 11% of microadenoma patients had SPL levels >200 ng/mL and 44% had a SPL level between 25 and 200 ng/mL. These investigators recommended imaging all patients with persistent elevations of SPL regardless of the value.3

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Should coenzyme Q10 be used to lower blood pressure in asymptomatic patients?

Evidence-Based Answer
Coenzyme Q10 (CoQ10) may lower systolic and diastolic blood pressures in patients with primary hypertension, but is not recommended as an antihypertensive treatment (SOR: C, systematic review of low-quality RCTs using disease-oriented outcomes).

A 2009 systematic review identified 3 RCTs with a total of 96 patients that evaluated the effects of CoQ10 (100–120 mg/d) on heart rate and blood pressure for at least 3 weeks.1 Each study evaluated adult patients with primary hypertension (systolic blood pressure [SBP] >140 mmHg or diastolic blood pressure [DBP] >90 mmHg). In some cases the patients used CoQ10 alone as an antihypertensive treatment, while in others the patient paired CoQ10 with additional antihypertensive treatments. Patients with creatinine levels >1.5 times normal were excluded. All studies had a mandatory washout period of at least 2 weeks before treatment with CoQ10.

CoQ10 lowered SBP by an average of 10 mmHg (95% CI, 7.7–14) and DBP by 6.6 mmHg (95% CI, 5.2–8.1) compared with placebo. In 1 of the reviewed trials (N=58), CoQ10 reduced patients’ heart rate by 12 beats per minute (95% CI, 8.8–15) compared with placebo. The studies did not provide sufficient data to
construct a dose–response curve, nor did they provide data on patients who dropped out.\(^1\)

The authors concluded that because of the inherent bias in each of the reviewed studies, they would not recommend CoQ10 as an antihypertensive agent. The authors were also unable to find any studies that showed that CoQ10 was ineffective, or any head-to-head trials against other hypertensive medications.\(^1\)

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**How does the intensity of therapy to lower HbA1c affect long-term cardiovascular risk in patients with type 2 diabetes mellitus?**

**Evidence-Based Answer**

Intensive glycemic control (glycosylated hemoglobin \([\text{HbA1c}] <6\%\)) is associated with significantly lower rates of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) compared with standard glycemic control; however, there does not appear to be a benefit on all-cause mortality (SOR: \(\text{A}\), meta-analysis of RCTs).

A 2009 meta-analysis of 5 prospective RCTs (UKPDS, ADVANCE, VADT, ACCORD, and PROactive trials) compared the rates of nonfatal MI, CHD, cerebrovascular accident, and all-cause mortality in patients with type 2 diabetes mellitus assigned to intensive glycemic control (HbA1c <6\%) or standard glycemic control (HbA1c 7\%–7.9\%).\(^1\) There were a total of 33,040 participants, with 17,267 participants receiving intensive glycemic control followed over 5 years.

A 17\% reduction (OR 0.83; 95\% CI, 0.73–0.93) in nonfatal MI and a 15\% reduction (OR 0.85; 95\% CI, 0.77–0.93) in CHD events was noted in the intensive glycemic control group. There was no significant change in stroke events (OR 0.93; 95\% CI, 0.81–1.1) or all-cause mortality (OR 0.93; CI, 0.87–1.2).\(^1\)

A subsequent prospective cohort study in the Zwolle region of the Netherlands followed 1,145 patients with type 2 diabetes mellitus in a primary care setting for a median of 5.8 years.\(^2\) The patients achieving a mean HbA1c of <6.5\% did not have a reduction in all-cause mortality (HR 1.1; 95\% CI, 0.71–1.7) or cardiovascular mortality (HR 0.94; 95\% CI, 0.47–1.9).

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**How do you treat perioral dermatitis?**

**Evidence-Based Answer**

Treatment with oral tetracycline and discontinuation of any cosmetics or topical corticosteroids are effective management strategies for perioral dermatitis (POD) (SOR: \(\text{A}\), systematic review). The use of pimecrolimus cream 1\% applied twice daily for up to 4 weeks is also effective (SOR: \(\text{A}\), consistent RCTs).

In a systematic review of 30 RCTs on the treatment of POD, 2 studies (207 patients) were of medium-range quality and the remaining 28 studies (1,261 patients) were of low quality.\(^1\) The authors were unable to combine the data. However, the authors concluded there was “consistent evidence” of effectiveness with oral tetracycline and, to a lesser extent, with the discontinuation of any cosmetics or topical corticosteroids.

Two subsequent RCTs evaluated pimecrolimus for POD. The first study compared pimecrolimus cream 1\% applied twice daily for 1 month with placebo in 40 adults.\(^2\) The disease severity was assessed by the Perioral Dermatitis Severity Index (PODSI) score (the sum of individual scores [0–3] for erythema, papules, and scaling).

The reduction in PODSI score for the pimecrolimus group was significantly greater than that of the placebo group over the entire treatment period (pimecrolimus 4.5 to 1.6; placebo 4.6 to 2.6; \(P=.02\)). Four weeks after completion of therapy, no significant differences were observed between the pimecrolimus group and placebo. The median time until 50\% of patients attained at least a 50\% reduction of PODSI from baseline was 1 week with pimecrolimus treatment and 4 weeks with placebo (\(P=.02\)).\(^2\)

In the second RCT, 124 adult patients with POD were randomized to pimecrolimus 1% twice daily for 1 month or placebo. After treatment, the pimecrolimus group had an average PODSI score of 2.6 versus 3.5 for the placebo group (between-group difference 0.9; 95% CI, 0.4–1.4; \( P = .001 \)). The subgroup of patients (n=35) with topical corticosteroid-associated POD had a mean PODSI score of 5.4 at baseline and 2.3 on day 29 with pimecrolimus. Patients with steroid-associated POD receiving placebo had a PODSI score of 5.4 at baseline and 4.2 on day 29 (between-group difference 1.9; 95% CI, 0.6–3.1; \( P = .007 \)).

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What is the optimum frequency for corticosteroid injections of the knee?

Evidence-Based Answer
The evidence is limited on the optimum frequency of intra-articular corticosteroid (ICS) injections of the knee for treatment of osteoarthritis (OA). Current guidelines recommend ICS injections be performed no more frequently than every 3 months (SOR: C, expert opinion).

A randomized, double-blind, placebo-controlled trial of 66 patients between 40 and 80 years of age with radiologic evidence of OA compared the efficacy (pain) and safety (joint space width) of a scheduled ICS injection with placebo. The ICS group received injections (triamcinolone acetonide, 1 cc of 40 mg/mL) every 3 months over the course of 2 years while the placebo group received saline injections over the same period. Outcomes measured were improvement in subjective pain indices as well as joint space width (JSW) on X-ray.

The radiologic evaluation of JSW performed at study entry (ICS 4.1 mm vs placebo 3.9 mm), year 1 (ICS 4.0 mm vs placebo 3.9 mm), and year 2 (ICS 4.0 mm vs placebo 3.9 mm), revealed no significant differences between treatment groups and no signs of disease progression. At 1 year, the ICS group had significant improvement in range of motion (ICS 4.4° vs placebo 2.7°; \( P < .05 \)). At 2 years the area under the curve analysis for differences in scores on the WOMAC VA 3.0 (visual analog scale, measuring 0–100, with 0 being no pain or stiffness) from baseline to month 24 showed significant differences between groups favoring ICS for night pain (ICS –0.66 vs –0.31 placebo; \( P = .0047 \)) and joint stiffness (ICS –0.636 vs –0.320 placebo; \( P = .05 \)).

A retrospective cohort analysis over a 20-year period studied 65 patients (35 rheumatoid arthritis and 30 OA) receiving ICS injections of varying frequency (interval not less than every 4 weeks) over a period of 4 to 15 years. The total injection count varied from 15 injections in 4 years to 167 injections over 12 years. Post hoc radiographs compared with earlier films did not reveal any correlation between frequency or total injection count and joint deterioration.

A consensus guideline from the American College of Rheumatology states that ICS injections should be given no more than every 3 months per joint for a maximum of 4 per year. This recommendation is based on concerns for steroid and crystal arthropathy, which have been variably reported in the human and animal literature.

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What is the utility of imaging studies in adult patients after a first-time seizure?

Evidence-Based Answer
Neuroimaging with computed tomography (CT) is abnormal in up to half of unselected adult patients with a first-time seizure, resulting in a change in diagnosis in 44%, change in disposition in 26%, and change in acute management in 9%–17%. (SOR: B, systematic reviews of cohorts studies).

An American Academy of Neurology (AAN) subcommittee conducted a systematic review to examine the effects of neuroimaging on the management of the adult emergency patient presenting with a first-time seizure. The authors searched for English-language
studies evaluating patients with a first seizure and found 5 cohort studies with 1,672 patients. Although the studies included mostly adults, 3 included patients as young as 16 years, 1 included patients as young as 15, and the final study included some patients as young as 6 with afebrile seizures.

Up to 56% of patients had abnormal CT scans and in 9% to 17% the scans resulted in changes in acute management after finding traumatic brain injury, subdural hematomas, nontraumatic bleeding, cerebral vascular accidents, tumors, or brain abscesses.1

The Guidelines in Emergency Medicine Network from the United Kingdom completed a systematic review to support a guideline on the management of adults with a first seizure in the emergency department.2 The guideline working group searched multiple databases for studies on an unselected population of adults (≥16 years) presenting with a first generalized seizure.

Seven cohort studies showed 12% to 41% of adults with their first seizure had an abnormal head CT. The authors reported data on the implications of abnormal neuroimaging from a single prospective study showing that abnormal head CT changed diagnosis in 44% of patients and changed disposition in 26% of patients with a first seizure. The specific changes in disposition were not delineated. The guideline did not comment on the size or quality of the included studies or the types of CT abnormalities found.

Another systematic review to support a practice guideline investigated only unprovoked first-time seizures in adults.3 The Quality Standards Subcommittee of the AAN searched multiple databases for studies of adults who had returned to their baseline level of function after a first seizure that was not secondary to cerebral trauma or stroke. Seven cohort studies (1,092 patients) reported significantly abnormal head CT scans in 1% to 47% (average 10%) of adults with an unprovoked first seizure. All of the significant abnormalities were reported to affect management through new diagnosis of brain tumors, vascular lesions, or cerebral cysticercosis.

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What are the indications for lumbar puncture in patients with acute headache?

Evidence-Based Answer
Acute headaches warrant further evaluation with lumbar puncture if there is suspicion for infectious meningitis or encephalitis, subarachnoid hemorrhage (SAH), or idiopathic intracranial hypertension (pseudotumor cerebri) (SOR: C, expert consensus opinion).

The decision to perform a lumbar puncture in the setting of an acute headache depends on the differential diagnosis and clinical presentation. A retrospective study spanning 27 years evaluated 445 adults treated for 493 episodes of acute bacterial meningitis.1 Ninety-five percent of patients presented with fever, 88% with neck stiffness, 88% with altered mental status, and 11% with a petechial rash. Eighty-seven percent of patients had organisms identified by various culture methods. Seventy-five percent of cases had positive cerebrospinal fluid (CSF) culture.

A multicenter prospective cohort study enrolled 592 patients presenting with acute nontraumatic headache to evaluate the accuracy of ruling out a SAH with a negative head CT followed by a negative lumbar puncture (defined as no blood in the last tube collected).2 A CT was performed within 12 hours of headache onset and if the CT was negative, a lumbar puncture was performed. Sixty-one cases of SAH were ultimately identified. Compared with CT with subarachnoid blood seen, xanthochromia in CSF, cerebral angiography, and autopsy (combined as a gold standard), the diagnosis strategy of head CT, followed by lumbar puncture if the head CT was negative for SAH had a sensitivity of 100% and a specificity of 67%, with a negative likelihood ratio (LR–) of 0 and a positive likelihood (LR+) ratio of 3.0.

Idiopathic intracranial hypertension (IIH) may present with headache, pulsatile intracranial noises, diplopia, papilledema, and possibly cranial nerve VI (abducens) palsy. A retrospective study (n=190) analyzed the opening pressures in subjects with acute IIH (n=116), chronic IIH (n=18), and neurologically healthy obese and nonobese patients (n=56).3 All opening pressures were obtained with patients in the lateral decubitus position with legs extended. In acute IIH the mean opening pressure was 344 mm H2O (range 200–550 mm H2O) and 90% of patients had an

opening pressure of more than 250 mm H₂O. In chronic IIH, the mean opening pressure was 253 mm H₂O and 6 of 18 subjects (33%) had an opening pressure of more than 250 mm H₂O. In patients without IIH (obese and nonobese) only 1 of 56 patients (1.8%) had opening pressures exceeding 250 mm H₂O. The authors concluded opening pressures of more than 250 mm H₂O should be considered diagnostic for IIH.

An expert consensus statement by the American Academy of Neurology concludes that lumbar puncture is needed for diagnosis of suspected infectious meningitis and encephalitis. Expert consensus of the American College of Emergency Physicians states that SAH can be safely excluded only with normal head CT and normal lumbar puncture.

What are effective management strategies for impaired fasting glucose and impaired glucose tolerance?

Evidence-Based Answer

To prevent progression to diabetes mellitus (DM), patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are best managed by lifestyle interventions combining dietary modification and moderate-intensity exercise. Medications are less effective. There is no evidence that any of these interventions reduce all-cause mortality or macrovascular outcomes (SOR: A, meta-analyses).

A 2011 meta-analysis of 10 RCTs including 23,152 patients with IFG or IGT (mean age 52 years, 47% male, with at least 1 cardiovascular risk factor or established coronary artery disease) and a mean follow-up of 3.8 years evaluated medications (metformin, acarbose, rosiglitazone, ramipril, valsartan, and nateglinide), lifestyle management, or a combination and their effects on DM incidence, all-cause mortality, cardiovascular death, myocardial infarction (MI), and stroke. Both lifestyle management and pharmacologic interventions reduced progression to overt diabetes compared with controls (combined risk ratio [RR] 0.66; 95% CI, 0.55–0.80). Compared with controls, both drug and nondrug treatments individually reduced progression to diabetes, but lifestyle management, which included diverse approaches to diet and exercise education, was superior (N=3,495; RR 0.52, 95% CI 0.46–0.58) compared with medications (N=20,872; RR 0.70; 95% CI, 0.58–0.85; P<.05 for lifestyle management vs medications). Three studies of monotherapy with pioglitazone, ramipril, or nateglinide did not reduce progression to diabetes. No effect was seen on all-cause mortality (RR 0.96; 95% CI, 0.84–1.10), cardiovascular death (RR 1.04; 95% CI, 0.61–1.78), or MI (RR 0.59; 95% CI, 0.23–1.50) when drug and nondrug therapies were compared with controls. Only 4 trials, all involving medications, examined stroke and showed only a slight reduction compared with placebo controls (RR 0.76; 95% CI, 0.58–0.99). The meta-analysis authors noted that follow-up may have been too brief to reveal macrovascular benefits of the studies.

A 2008 meta-analysis of 8 RCTs including 4,750 participants belonging to any major risk group for development of type 2 diabetes (not all of whom had IGT or IFG) looked at nonpharmacologic prevention. Studies included exercise (average of 150 min/wk of moderate exercise such as brisk walking or cycling) and diet interventions (caloric restriction for overweight patients, low-fat, high-fiber diets) delivered via individual counseling with a physiotherapist, exercise physiologist, or dietician, compared with “standard recommendations” or no intervention. The incidence of new type 2 diabetes was 17% in the exercise and diet group and 27% in the control groups (RR 0.63; 95% CI, 0.49–0.79; NNT=9). Two studies had diet-only and exercise-only arms that did not differ significantly from controls, suggesting the combination of diet and exercise is necessary for preventive benefit.

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What is the best treatment approach to primary nocturnal enuresis in an otherwise healthy adult?

**Evidence-Based Answer**

Desmopressin is effective for the treatment of primary nocturnal enuresis (PNE) in adults (SOR: B, cohort study). While tricyclic antidepressants and enuresis alarms are effective in children (SOR: A, systematic reviews), no information is available on these modalities in adults.

By definition, patients with PNE have never experienced 6 months of dry nights. An observational cohort study examining the effects of desmopressin on PNE evaluated 143 men, of which 86 were naïve to desmopressin. After 2 weeks, patients who did not achieve a “complete response” to desmopressin (defined as <1 wet night monthly) received an additional 0.2 mg. After 3 months, 43% of patients had a complete response to desmopressin. Eleven percent of patients had a partial response to desmopressin 0.4 mg, defined as a 50% to 80% reduction in the number of wet nights monthly. Relapse rates (any recurrence of wet nights) assessed 1 month after treatment discontinuation were higher in patients who had received 0.4 mg compared with those who received 0.2 mg (64% vs 36%; P<.05). This review did not comment on adverse effects.

Other treatment options have been studied primarily in children. A Cochrane meta-analyses of pediatric RCTs (usually <16 years of age) on the efficacy of desmopressin (47 RCTs involving 3,448 patients) and tricyclic antidepressants (TCAs) (58 RCTs involving 3,721 patients) revealed approximately 1 less wet night per week in patients treated pharmacologically compared with placebo (desmopressin: weighted mean difference (WMD) 1.3; 95% CI, –1.6 to –1.1; TCA: WMD 1.2; 95% CI, –1.6 to –0.82). Various TCAs and varying doses were included. More patients became dry (not defined in the meta-analyses) with drug therapy versus placebo (desmopressin: 19% vs 2%; TCAs: 21% vs 5%; P value not reported). Results were not sustained after discontinuation. Evidence comparing the efficacy of desmopressin versus TCAs was unreliable or conflicting; however, TCA use resulted in more adverse effects, including postural hypotension, dry mouth, constipation, perspiration, tachycardia, nausea, lethargy, and insomnia.

A meta-analysis of randomized or quasirandomized trials (56 trials with 3,257 children) studying enuresis alarms demonstrated 65% of patients became dry (RR of failure 0.38; 95% CI, 0.33–0.45), with half (45%) remaining dry after discontinuation of the alarm compared with almost none (1%) after no treatment (RR of failure or relapse 0.56; 95% CI, 0.46–0.68).

Four trials reporting standard deviations demonstrated 3 fewer wet nights per week compared with no treatment (WMD 3.3; 95% CI, –4.1 to –2.6). In the alarm group, the RR of failure (not achieving 14 dry nights) was less compared with no treatment (34% vs 96%; RR 0.38; 95% CI, 0.33–0.45).

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What is the best screening test for diabetic sensory neuropathy?

**Evidence-Based Answer**

Screening methods such as monofilament testing, “on-off” testing with a 128-Hz tuning fork, and superficial pain sensation all detect diabetic sensory neuropathy (DSN), although negative testing does not definitely rule out the diagnosis. Comprehensive scores based on symptoms and physical examination are not as effective (SOR: B, cohort studies).

A cohort study evaluated 478 patients with type 1 or type 2 diabetes for peripheral neuropathy with a standard 10-gram monofilament. The monofilament was applied to the dorsum of the first toe bilaterally 4 times on each foot (scored 0–8 depending if the patient perceived the monofilament). Compared with electromyography (EMG) as the gold standard, an abnormal monofilament test (≥5 attempts not perceived) had a positive likelihood ratio (LR+) of 10.3 and a normal monofilament test (≤1 not perceived) had a negative likelihood ratio (LR–) of 0.34.

The same cohort study of 478 patients with diabetes evaluated both “on-off” and timed responses to a 128-Hz tuning fork versus EMG. Vibration testing
for the “on-off” method was performed by placing the tuning fork on the bony prominence of each great toe. The patient was asked to report the sensation of vibration at the start of vibration and at the cessation on dampening. Each toe was tested twice resulting in a range of scores from 0 to 8 based on the number of times the sensation and dampening of the tuning fork was not felt. An abnormal score (≥5 attempts not perceived) to the “on-off” test had a LR+ of 27, and normal test (≤1 not perceived) had a LR– of 0.51. The timed technique was considered abnormal (a positive test) if the physician perceived the vibration for more than 20 seconds longer than the patient; it generated a LR+ of 16. If the physician perceived the vibration for less time (11–20 seconds), the LR– was 1.1.

The same study evaluated superficial pain sensation with the use of a single sterile neurological exam pin (Neurotip). The pin was applied 4 times to the dorsum of each great toe and an abnormal response occurred when the application of the pin was not perceived by the patient (score 0–8). A score of ≥5 abnormal results had a LR+ of 9.2, and a LR– (≤1 not perceived) of 0.5.

A cohort study of 112 patients with type 2 diabetes evaluated the diagnostic accuracy of the Neurological Symptom Score (NSS) in detecting DSN. The NSS is a patient-administered questionnaire evaluating common neuropathic symptoms. Each of these patients was also tested with an EMG as the gold standard of neuropathy diagnosis. The test produced a nonsignificant LR+ of 1.0 and a LR– of 0.9.

Another cohort study of 176 patients with type 2 diabetes evaluated the validity of the Michigan Neuropathy Screening Instrument (MNSI) for diagnosing peripheral neuropathy. The MNSI uses a combination of a symptom-based questionnaire and a standard physical examination of the feet (inspection, vibration sensation, reflexes, and monofilament testing). An EMG was also performed on each patient for comparison. An abnormal MNSI resulted in a LR+ of neuropathy of 3.8.

Evidence-Based Answer
Corticosteroid injection appears to have a short term benefit (<12 weeks) in treating acute lateral epicondylitis, but does not offer any long-term benefit (SOR: A, meta-analyses).

In a 2010 meta-analysis of 12 RCTs, 1,171 patients with lateral epicondylitis were randomized to corticosteroid injection or noninjection treatment (“wait and see,” NSAIDs, or physiotherapy). The follow-up period was >1 year, and outcomes included measures of pain and function.

Compared with noninjection treatments, injection showed benefit at 12 weeks (given as standard mean difference [SMD], with SMD >0.8 considered a large effect) with pain (SMD 1.4; 95% CI, 1.2–1.7) and function (SMD 1.5; 95% CI, 1.2–1.8). However, at ≥52 weeks, there was no improvement with pain (SMD –0.31; 95% CI, –0.61 to –0.01) or function (SMD –0.32; 95% CI, –0.57 to –0.06).

In 2009, a meta-analysis of 20 RCTs were analyzed to assess the effectiveness of steroid injections on pain and function at weeks 1–3, weeks 4–8, weeks 12–24, and week 48. A total of 744 patients were treated with injections and 987 were treated with “wait and see,” physiotherapy, or NSAIDs; The studies included 618 shoulders and 1,113 elbows with epicondylitis.

Corticosteroid injections were more effective (given as standardized response mean [SRM], with SRM >0.8 considered a large effect) for pain relief at weeks 1–3 (SRM 2.5; 95% CI, 1.1–3.8) and weeks 4–8 (SRM 0.96; 95% CI, 0.63–1.3), compared with standard treatments. At the 48-week follow-up, no benefit was noted in pain reduction with steroid injection (SRM –0.28; 95% CI, –0.53 to –0.03) compared with all alternatives. Steroid injections showed some effectiveness for functional ability in the short term at weeks 1–3 (SRM 0.88; 95% CI, 0.32–1.44) and weeks 4–8 (SRM 1.06; 95% CI, 0.45–1.66). However, by week 48 function SRM was –0.47 (95% CI, –0.72 to –0.22).

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What are the risks of pregnancy after gastric bypass surgery?

**Bottom line**

Pregnancy after gastric bypass surgery is associated with an increased risk of nutritional deficiencies, small-for-gestational-age (SGA) newborns, and postsurgical complications that are not immediately recognized. However, compared with obese women without previous gastric bypass surgery, these women have a decreased risk of hypertensive disorders of pregnancy, gestational diabetes mellitus (GDM), and macrosomia.

**Evidence summary**

The 2 main types of bariatric surgery involve restriction (ie, gastric banding) or malabsorption (Roux-en-Y gastric bypass), each with distinct complications. Because obesity is associated with multiple adverse pregnancy outcomes, bariatric surgery with subsequent weight loss may decrease these risks.¹

Many experts recommend waiting to conceive for at least 1 year after bariatric surgery due to concern of complications from malnutrition, as often the greatest weight loss occurs during this time. However, a retrospective study of 489 pregnancies after surgery (17.8% gastric bypass) found no difference in perinatal outcomes for conception <1 year compared with ≥1 year, including birth weight (3,048 vs 3,123 g; P=.18), congenital malformations (1.9% vs 1.3%; P=.49), prematurity (2.9% vs 3.6%; P=.710), and cesarean section rate (37% vs 30%; P=.23).²

Nutritional deficiencies are common among pregnant women after bariatric surgery, as these procedures often result in volume or specific food intolerances, absorption difficulties from low gastric acid secretion, and nutrients bypassing the duodenum. No specific guidelines exist for pregnant women after bypass surgery. Most experts agree that women should take a prenatal vitamin including 600–1,000 mcg folic acid, calcium citrate 1,200 mg daily, vitamin D at least 800 IU daily, elemental iron 65 mg daily, and vitamin B12 3.5 mg daily.³ Lab monitoring in each trimester is recommended, with more frequent testing for diagnosed deficiencies.⁴

Due to the significant weight loss after gastric bypass surgery, most women have lower incidences of hypertensive disorders of pregnancy and GDM. A retrospective study of insurance claims data in the United States (316 women with bariatric surgery and previous pregnancy, with 89% gastric bypass) found a significant decrease in the incidence of preeclampsia and eclampsia (OR 0.20; 95% CI, 0.09–0.44), chronic hypertension complicating pregnancy (OR 0.39; 95% CI, 0.20–0.74), and gestational hypertension (OR 0.16; 95% CI, 0.07–0.37).⁵ A paired matched case-control study of 144 pregnancies in the same women before and after bariatric surgery also found a significant decrease in hypertensive disorders after surgery (17% vs 32%; P=.004).⁶

The same matched case-control study found a significant decrease in the incidence of GDM after surgery (7.6% vs 21%; P=.001).⁶ A systematic review of case-control studies found that 4 studies (N=1,033 deliveries) showed a decrease in GDM, while 1 study (N=298 deliveries) found an increased risk of GDM in women after bypass surgery.⁷ After surgery, women cannot complete the oral glucose tolerance test to screen for GDM because they are unable to drink the required quantity of fluid. In addition, the amount of glucose may cause dumping syndrome due to the high osmotic load in the small intestine. Alternative screening methods include fasting and 2-hour postprandial glucose levels.⁸

Most studies show a decreased risk of macrosomia in pregnancies after bypass surgery, but there is concern of an increased risk of SGA or intrauterine growth restriction (IUGR) babies. A review of 4 case-control studies of women after bypass surgery (N=787 deliveries) found increased rates of SGA and IUGR, although 3 other studies did not (N=416 deliveries).⁹

Postbariatric surgery complications that may affect pregnancy include adhesions, internal hernias, and small intestine ischemia. Abdominal pain in a pregnant bariatric surgery patient should be considered emergent to allow early recognition and treatment to prevent death.¹⁰

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REFERENCES

1. What is the current standard of care regarding recommended frequency of intra-articular corticosteroid injections for treatment of knee osteoarthritis?
   a. Intra-articular corticosteroid injections can be performed once a year
   b. Injections of corticosteroid can be performed once every 3 months, with a maximum of 4 injections per year
   c. There are presently no recommendations on frequency of intra-articular corticosteroid injection
   d. The current standard of care is an injection once every 4 months, but no more than 2 per year

2. CoQ10 is associated with which of the following effects?
   a. Increased heart rate
   b. Increased diastolic blood pressure
   c. Increased systolic blood pressure
   d. Decreased heart rate

3. In patients with impaired glucose tolerance or impaired fasting glucose, lifestyle modifications including dietary changes, weight loss, and exercise:
   a. Decrease all-cause mortality
   b. Add no benefit to pharmacologic management alone
   c. Delay the onset of diabetes mellitus
   d. Prevent fatal and nonfatal myocardial infarction

4. Which of the following statements is true regarding intensive treatment of patients with type 2 diabetes mellitus?
   a. All-cause mortality is significantly improved with a HbA1c <6%
   b. It decreases nonfatal myocardial infarction
   c. It does not affect the rate of coronary heart disease
   d. It increases the rate of stroke

5. A 55-year-old man has a brief first-time grand mal seizure, but recovers fully. CT scanning in such cases finds
   a. Few abnormalities (<1%)
   b. Few abnormalities that change management (<1%)
   c. Abnormalities fairly commonly (up to 50%)
   d. Abnormalities that usually change management (95% of the time)

6. In which clinical scenario would a lumbar puncture be indicated?
   a. A 24-year-old man with acute onset of headache, fever, chills, and neck stiffness
   b. A 32-year-old woman with headache, double vision, and cranial nerve VI palsy
   c. A 28-year-old man with sudden, severe headache for the past 3 hours unlike any headache he has ever experienced before
   d. All the above scenarios are indications for lumbar puncture

7. Risk of which of the following effects is increased in pregnancy for women after gastric bypass surgery?
   a. Gestational diabetes
   b. Hypertensive disorders of pregnancy
   c. Nutritional deficiencies
   d. Macrosomia

8. A 67-year-old man with diabetes presents to your office for routine diabetes care. Which of the following should not be used to screen for diabetic neuropathy?
   a. 10-gram monofilament
   b. Neurologic Symptom Score
   c. Timed response to a 128-Hz tuning fork
   d. "On-off" response to a 128-Hz tuning fork
FPIN is excited to be building relationships with osteopathic family medicine training programs

- FPIN welcomed Kenneth E. Korber, PA, MHPE, to the FPIN board of directors. Mr. Korber is the Director of Education at the American College of Osteopathic Family Physicians, and will serve as the liaison between FPIN and the ACOFP.

- FPIN will attend the ACOFP residency program directors workshop March 19-20, and Evidence-Based Practice will have a booth at the annual convention March 21-23.

- Faculty and residents of osteopathic family medicine programs will contribute to Evidence-Based Practice in the future.

- In addition, ACGME and AOA are discussing a merge in 2015 to make all AOA programs ACGME-accredited.

To set up a meeting with us at the ACOFP conference, visit www.fpin.org/requestameeting