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# Internal Medicine

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ABSTRACT & COMMENTARY

## Early Hot Flashes Could Signal Increased Risk for Heart Disease

***By Seema Gupta, MD, MSPH***

*Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV*

**Dr. Gupta reports no financial relationships relevant to this field of study.**

SYNOPSIS: Women 42-55 years of age who experience hot flashes are more likely to exhibit poor vascular function.

SOURCE: Thurston RC, Chang Y, Barinas-Mitchell E, et al. Physiologically assessed hot flashes and endothelial function among midlife women. *Menopause* 2017 Jun 19. doi: 10.1097/GME.0000000000000857. [Epub ahead of print].

Vasomotor symptoms (VMS), often referred to commonly as hot flashes and night sweats, are considered by clinicians to be the telltale signs of menopause. In the United States, 75-80% of menopausal women report hot flashes. For about one-third of this group, the reported episodes are described as severe or frequent.[1] Additionally, new data indicate that hot flashes often start earlier than once believed and can persist for a decade or even longer.[2] Although hot flashes can affect quality of life negatively, they may be an indication of emerging vascular dysfunction that can lead to cardiovascular disease (CVD), which is the leading cause of death among women. A fair amount of research has connected menopause with CVD, including several risk factors. A decline in the ovarian estrogen estradiol (E2) may be a factor in CVD increase among post-menopausal women.

Emerging data demonstrate that women with early menopause (42-55 years of age) may exhibit an impairment of endothelial function in the early menopausal years, wherein the carotid intima-media thickness is not yet affected, linking the menopausal symptom of hot flashes to markers of poorer endothelial function.[3] Thus, this endothelial injury

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and dysfunction may be an initiating event in atherosclerosis development among early midlife women.

By evaluating data from 272 nonsmoking women 40-60 years of age reporting either daily hot flashes or no hot flashes and free of clinical cardiovascular disease, Thurston et al tested whether physiologically assessed hot flashes were associated with poorer endothelial function. The study excluded women with neoplasia, hysterectomy and/or bilateral oophorectomy, kidney failure, seizures, Parkinson's disease, Raynaud's phenomenon, or current pregnancy. The researchers also excluded women with a history of recent use of reproductive hormone agents, serotonin reuptake inhibitors, insulin, or cardiovascular drugs.

All women underwent physical examinations, brachial artery flow-mediated dilation (FMD) to assess endothelial function, carotid artery ultrasound, blood draw, and ambulatory hot flash monitoring using an electronic hot flash diary, a wrist actigraph, and a physiologic hot flash monitor. Menopause status was assessed from reported menstrual bleeding patterns. Estradiol levels, glucose, high-density lipoprotein cholesterol, triglycerides, total cholesterol, insulin, C-reactive protein, and interleukin-6 were evaluated.

On average, study participants were 54 years of age, white, college educated, postmenopausal, and demonstrated a relatively favorable CVD risk factor profile. Researchers found that even after controlling for other CVD risk factors, younger women (40-53 years of age) who experienced hot flashes (beta [standard error] = -2.07 [0.79]; $P = 0.01$) and more frequent physiologic hot flashes (for each hot flash: beta [standard error] = -0.10 [0.05]; $P = 0.03$, multivariable) were associated with lower FMD compared to women who did not experience hot flashes, indicating poorer endothelial function. These associations could not be accounted for by estradiol changes and were not observed among the older women (54-60 years of age).

## ■ COMMENTARY

While hot flashes, one of the most common symptoms of menopause, interfere with a woman's overall quality of life, Thurston et al demonstrated that these frequent hot flashes also may signal emerging vascular dysfunction that can lead to CVD, particularly for younger midlife women (40-53 years of age).

The finding that both the reported presence of hot flashes and more frequent physiologically assessed hot flashes were associated with lower flow-mediated dilation among younger midlife women independent of estradiol indicates that impairment in endothelial function may be an initiating event in the atherosclerotic process. Frequent hot flashes may mark emerging vascular dysfunction. Interestingly, associations between hot flashes and FMD were not observed among the older women in the sample.

The important findings of this research point to the potential role of not only hormones, but also hot flashes, in the cardiovascular changes that occur in women undergoing early menopause and highlight the potential role that the endothelium may play in the physiology of early hot flashes and CVD initiation.

Although this work needs further validation, the findings may be an early signal that among early midlife women, frequent hot flashes may herald an emerging vascular dysfunction. Therefore, it is critical that this subgroup not only is treated for hot flashes as a symptom but also be screened more closely for CVD risk factors. ■

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ABSTRACT & COMMENTARY

# Glucose Self-monitoring May Not Be That Useful

*By Seema Gupta, MD, MSPH*

*Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV*

**Dr. Gupta reports no financial relationships relevant to this field of study.**

SYNOPSIS: Researchers could not find any statistically significant differences in glycemic control or health-related quality of life between patients who performed glucose self-monitoring compared with those who did not.

SOURCE: Young LA, Buse JB, Weaver MA, et al. Glucose self-monitoring in non-insulin-treated patients with type 2 diabetes in primary care settings: A randomized trial. *JAMA Intern Med* 2017;177:920-929.

The efficacy of self-monitoring blood glucose (SMBG) for patients with non-insulin-treated type 2 diabetes mellitus (T2DM) has not been proven clearly. Some investigators have found that more frequent self-monitoring of blood glucose levels was associated with clinically and statistically better glycemic control, regardless of diabetes type or therapy. Others have found that neither SMBG testing nor its frequency was associated with glycemic benefit in T2DM patients, regardless of treatment.[1,2] Even meta-analyses of randomized trials have reported conflicting results. Testing such as SMBG actually may promote better awareness of glucose levels for patients, which in turn may lead to improvements in diet, lifestyle, and intensification of pharmacotherapy. However, it is also important to understand that blood glucose monitoring remains a tool, not a therapeutic intervention, which may lead to some collateral consequences, such as adverse effects related to testing, association with higher scores on a depression scale, and higher costs resulting from unnecessary testing.

Young et al aimed to assess whether SMBG is an effective tool for patients with non-insulin-treated T2DM in terms of improving either hemoglobin A1c levels or health-related quality of life (HRQOL). The authors conducted an open-label, randomized trial in 15 primary care practices across central North Carolina. The research involved 450 patients with non-insulin-treated T2DM and with glycemic control (hemoglobin A1c) levels higher than 6.5% but lower than 9.5% within the six months preceding screening. Conducted over a year, the average age of study participants was 61 years, and participants had diabetes for an average of eight years. Interventions included assigning participants into three groups: no SMBG, once-daily SMBG, and once-daily SMBG with enhanced patient feedback, including automatic tailored messages delivered via meter.

Researchers found that there were no significant differences in hemoglobin A1c levels across all three groups ($P$ = 0.74; estimated adjusted mean hemoglobin A1c difference, SMBG with messaging vs. no SMBG, -0.09%; 95% confidence interval [CI], -0.31% to 0.14%; SMBG vs. no SMBG, -0.05%; 95% CI, -0.27% to 0.17%). There also were no significant differences found in HRQOL. There were no notable differences in key adverse events, including hypoglycemia frequency, healthcare use, or insulin initiation. The study authors concluded that in patients with non-insulin-treated T2DM, no clinically or statistically significant differences in glycemic control or HRQOL were observed at one year between patients who performed SMBG compared with those who did not perform SMBG.

## ■ COMMENTARY

The moment a patient is newly diagnosed with T2DM, it is often customary to write a prescription for a glucometer with testing strips, along with recommendations on diet, lifestyle modifications, and perhaps pharmacotherapy. Patients often engage, going to great lengths to manage their glucose logs, believing that proactively following these steps leads to improved outcomes. In fact, data show that approximately 75% of T2DM patients check their blood glucose at least once per day.[3] Incorporating technology into self-management activities often has been recognized as transformative for patients when managing chronic diseases. However, technology infusion must take a common sense approach. Therefore, the findings of this study have significant consequences and suggest that glucose monitoring in patients with non-insulin-treated T2DM should not be routine. These findings seem to support the recommendations of the Society of General Internal Medicine and the Endocrine Society, which discourage frequent blood glucose monitoring among T2DM patients.[4] Once target control is achieved and the results of self-monitoring become quite predictable, there is little gained in most individuals from repeat assessments. Perhaps when it comes to routine SMBG for patients with non-insulin-treated T2DM, it is time we take a "less is more" approach. ■

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ABSTRACT & COMMENTARY

# Possible Benefit from Pharmaceutical-grade Chondroitin on Knee Osteoarthritis

***By David Fiore, MD***

*Professor of Family Medicine, University of Nevada, Reno*

**Dr. Fiore reports no financial relationships relevant to this field of study.**

SYNOPSIS: The authors of a European study found a statistically significant and clinically marginally significant reduction in pain at three and six months in patients taking pharmaceutical-grade chondroitin sulfate for knee osteoarthritis.

SOURCE: Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: The ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis* 2017 May 22. pii: annrheumdis-2016-210860. doi: 10.1136/annrheumdis-2016-210860. [Epub ahead of print].

Symptomatic osteoarthritis (OA) of the knee affects approximately 4.3 million adults in the United States.[1] This can lead to decreased activity, with its concomitant effect of comorbidities such as depression, obesity, and cardiovascular disease. Pharmacologic treatment of knee OA typically starts with acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Unfortunately, acetaminophen has limited efficacy, and NSAIDs may cause renal compromise and gastric bleeding. Patients who have failed first-line treatment may progress to opiate therapy, but there are no data demonstrating a benefit of opiates for chronic pain, and, as we are all aware, there are many problems associated with long-term opiate use.

Current guidelines outline disparate recommendations about treatment, especially regarding what are termed symptomatic slow-acting drugs for osteoarthritis (SYSADOAs).[2,3] In 2012, the American College of Rheumatology conditionally recommended *against* the use of chondroitin for knee OA.[2] On the other hand, the 2016 consensus statement by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) recommended pharmaceutical-grade chondroitin as part of first-step therapy for knee OA, along with paracetamol (acetaminophen).[3] A 2015 Cochrane Review on chondroitin for OA (primarily of the knee) found a likely small benefit compared to placebo, but the authors qualified their endorsement based on low quality and heterogeneity of studies.[4]

In their introduction, the authors of the current study, which was funded by IBSA Institut Biochimique, a manufacturer of pharmaceutical-grade chondroitin, questioned the benefit vs. harm of acetaminophen and NSAIDs, and stressed the inclusion of pharmaceutical-grade chondroitin in the new European guidelines as the basis for their study. The authors randomized 604 patients with symptomatic knee OA into three groups: 800 mg pharmaceutical-grade chondroitin sulfate daily, 200 mg celecoxib daily, and placebo once daily. Baseline characteristics and dropout rates were similar across groups. Subjects were evaluated at baseline and days 30, 91, and 182. The two primary endpoints were well-defined and well-validated: a 100 mm Visual Analog Scale (VAS) and the Lequesne Index.

All three groups demonstrated significant improvement in all measured outcomes at 30, 91, and 182 days. The two active treatment arms demonstrated benefit over placebo in all measures at the end of the study (six months), with both active arms demonstrating a statistically significant improvement in the Lequesne Index at 91 days.

Although the authors stressed the statistically significant difference between both chondroitin and celecoxib when compared to placebo, the magnitude of the difference is small and barely meets criteria for clinical significance according to the 2015 ESCEO guideline on study protocols.[6] To put the benefit in perspective, the chondroitin group exhibited a 9.2 mm greater reduction in pain on the VAS scale compared to placebo, with a minimal clinically significant difference of 5-10 mm,[5,6] but the total reduction in VAS scores were 42.6 mm and 33.4 mm for chondroitin and placebo, respectively. Similar improvements were seen with the other outcome measures.

## ■ COMMENTARY

As a primary care physician with many patients suffering from knee osteoarthritis, I am disappointed that this study doesn't show a greater benefit of pharmaceutical-grade chondroitin compared to placebo. However, I am encouraged that so many patients benefit from placebo, and that there seems to be little harm from chondroitin. I don't believe the minimally positive results from this study are enough to offset the negative results of the GAIT study, which failed to show a benefit of 1,200 mg chondroitin daily compared to placebo.[7] Perhaps there were differences in the quality of the chondroitin, but since we do not have pharmaceutical-grade chondroitin in the United States, we should be cautious before expecting much benefit from chondroitin compared to placebo for knee OA. Therefore, I will continue to recommend non-pharmacologic approaches to first-line knee OA treatment, followed by acetaminophen and/or NSAIDs based on the patient's profile. If I'm asked about using chondroitin and/or glucosamine, I will continue to tell my patients that some patients seem to benefit significantly from these supplements, but that the studies on them are equivocal. ■

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PHARMACOLOGY UPDATE

# Sarilumab Injection (Kevzara)


***By William Elliott, MD, FACP, and James Chan, PharmD, PhD***

*Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco*



**Drs. Elliott and Chan report no financial relationships relevant to this field of study.**


The FDA has approved the second injectable interleukin-6 receptor antagonist (IL-6RA) for the treatment of rheumatoid arthritis (RA), joining tocilizumab. Sarilumab is a human recombinant monoclonal antibody marketed as Kevzara.

### INDICATIONS

Sarilumab is indicated for the treatment of adults with moderately to severely active RA who have demonstrated an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).[1] It may be used alone or in combination with methotrexate or other conventional (non-biological) DMARDs.

### DOSAGE

The recommended dose is 200 mg administered subcutaneously once every two weeks.[1] The dose should be modified because of low neutrophil count, low platelet count, or elevated liver enzyme levels. Sarilumab initiation is not recommended in patients with low absolute neutrophil count < 2,000/mm$^3$, platelet count < 50,000/mm$^3$, or liver enzymes > 1.5 times the upper limit of normal (ULN).[1] Sarilumab should not be used with biological DMARDs.

### POTENTIAL ADVANTAGES

Sarilumab offers another non-tumor necrosis factor (TNF) biologic and the second IL-6RA for the treatment of RA.

### POTENTIAL DISADVANTAGES

Adverse reactions (compared to placebo) include injection site reactions (7% vs. 1%), a decrease in neutrophil count to < 1,000/mm$^3$ (6% vs. 0%), a decrease in platelet count to < 100,000/mm$^3$ (1% vs. 0%), and an elevation of liver enzymes (AST/ALT; between > ULN to three

times ULN; 30-43% vs. 15-25%). The frequency of neutropenia was 10% vs. 0.2% for placebo. Increases in low-density lipoprotein cholesterol and triglyceride levels have been reported with mean increase of 16 mg/dL and 27 mg/dL, respectively. Neutralizing antibodies were detected in 1-1.6% of subjects exposed to sarilumab compared to 0.2% for placebo exposure. Gastrointestinal perforation has been reported (0.11 events per 100 patient-years), primarily as a complication of diverticulosis or concomitant use of nonsteroidal anti-inflammatory drugs or corticosteroids. Sarilumab shares a boxed warning regarding serious infections similar to that of other biological DMARDs.

## COMMENTS

IL-6 is a proinflammatory cytokine produced by various cells, including synovial and endothelial cells.[1] Elevated levels have been reported in serum and synovial fluids of RA patients. Sarilumab binds to both soluble and membrane-bound IL-6 receptors, thereby inhibiting IL-6 signaling. The efficacy and safety of sarilumab were assessed in two randomized, double-blind, placebo-controlled studies in adult subjects with moderately to severely active RA.[1-4] The first study included subjects with inadequate response to methotrexate (n = 1,197), and the second study included those who demonstrated an inadequate response to or were intolerant of one or more TNF-alpha antagonists. Patients were randomized to sarilumab 150 mg or 200 mg every two weeks or placebo. The primary endpoint was a 20% improvement in the American College of Rheumatology Criteria (ACR20) at week 24. Other endpoints were physical function (Health Assessment Questionnaire Disability Index at week 16 in the first study and week 12 in the second study). Change from baseline in van der Heijde-modified Total Sharp Score (mTSS) was assessed at week 52 in the first study. Major clinical response also was assessed in the first study, which was defined as a 70% improvement (ACR70) for at least 24 consecutive weeks during the 52-week period. ACR20 at week 24 for the first study was 58% for the 150 mg group, 66.4% for the 200 mg group, and 33.4% for the placebo group. For the second study, the results were 55.8%, 60.9%, and 33.7%, respectively. Both doses in each study were statistically significant at $P <$ 0.0001 compared to placebo. There were significant improvements in patient-reported outcomes.[1,4,5] The treatment benefit was maintained through week 52 in the first study.[1,2] There also was significantly less radiographic progression of structural damage compared to placebo. Major clinical response was 12.8% and 14.8% for the two doses of sarilumab, compared to 3% for placebo. Currently, there are no published comparative trials with the first approved IL-6RA, tocilizumab. In an indirect comparison of the drugs in a similar study with moderately to severely active RA, in patients who demonstrated inadequate response to methotrexate, the addition of sarilumab 200 mg or tocilizumab 8 mg/kg every four weeks to methotrexate produced similar ACR20 responses at week 24.[1,6] The adverse reaction profiles for tocilizumab and sarilumab also appear similar as they are regarded as class effects. Both drugs have been reported to be more effective than adalimumab as monotherapy in active RA patients who should not continue with methotrexate because of intolerance or inadequate response.[7,8] However, the IL-6RAs were more likely to cause reduced neutrophil and platelet counts and increase liver enzymes.

## CLINICAL IMPLICATIONS

Currently, there are two classes of biologics to treat RA: TNF inhibitors (TNFi) and non-TNF biologics. The majority target TNF-alpha (etanercept, adalimumab, infliximab, certolizumab, and golimumab). Non-TNF drugs are anakinra, which targets IL-1RA; tocilizumab, which targets IL-6; and rituximab, which targets B lymphocytes. Sarilumab is the second IL-6RA approved for moderately to severely active RA. The American College of Rheumatology recommends the addition of a TNFi or non-TNF biologic with methotrexate as options in patients with established RA who have failed DMARD monotherapy.[9] The cost of sarilumab is $3,000 for a four-week supply, compared to $1,796-$3,592 depending on body weight and clinical response for tocilizumab. ■

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# Clinical Briefs

By Louis Kuritzky, MD

## Desmopressin Nasal Spray for Treatment of Nocturia: Proceed with Caution

SOURCE: Fralick M, Kesselheim AS. *JAMA* 2017;317:2059-2060.

Nocturia is a symptom than can reflect a variety of underlying pathologies, including heart failure, diabetes, and benign prostatic hyperplasia. Although it might be tempting to go directly to pharmacologic treatment, with the recent approval of an agent designed to treat such symptoms, caution is in order. The indication for the recently approved desmopressin nasal spray (Noctiva) is specified for "treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void." Fralick and Kesselheim reinforced the FDA labeling, indicating that the use of desmopressin should be preceded by elimination of underlying serious pathology (e.g., bladder cancer, pituitary pathology) as well as confirmation of polyuria with a 24-hour urine collection.

Adverse effects of desmopressin include hyponatremia, which can be severe. Although clinical trial data demonstrated severe hyponatremia (≤ 125 mmol/L), only rare (0.7% of desmopressin recipients vs. 0.3% of placebo subjects), moderate hyponatremia (126-129 mmol/L) is substantially more common (2.2% of desmopressin subjects vs. no placebo subjects). Finally, the mean change in nocturia episodes decreased from about 3.3 episodes per night to about 1.9/night with desmopressin treatment, which many of us might consider only a modest symptomatic improvement.

Because desmopressin can result in serious adverse events, it is important that clinicians become fully familiar with FDA labeling of the new product and be confident that no underlying serious pathology is present before prescribing. ■

## Efficacy of Cephalexin Monotherapy for Cellulitis

SOURCE: Moran GJ, Krishnadasan A, Mower WR, et al. *JAMA* 2017;317:2088-2096.

The past decade has seen methicillin-resistant *Staphylococcus aureus* (MRSA) maintain sufficient prevalence in cases of acute cutaneous abscesses that treatment oriented to that pathogen, typically trimethoprim-sulfamethoxazole or doxycycline, has become routine adjunctive treatment to incision and drainage. The pathogen responsible for cellulitis without abscess often has been assumed to involve MRSA frequently, leading to similar treatment regimens. Although nailing down with certainty the etiologic agent of cellulitis presents greater difficulty than an abscess, the currently predominant cellulitis pathogen is believed to be beta-hemolytic strep. In typical clinical settings, the pathogen usually is not identified prior to treatment initiation. If MRSA is not a major player in simple cellulitis (without abscess), might agents to address MRSA be omitted safely?

A randomized, clinical trial of cellulitis patients (n = 500) without evidence of abscess compared cephalexin + trimethoprim-sulfamethoxazole to cephalexin monotherapy. The primary outcome was clinical cure.

There was no statistically significant difference in the primary outcomes for the two groups, with a higher than 80% success rate in both treatment arms. In the absence of evidence of purulent infection, these data support the use of cephalexin treatment (500 mg four times daily for seven days) as a simpler, less expensive antimicrobial regimen. ■

## Combination Treatment for Patients Hospitalized with Influenza

SOURCE: Hung IFN, To KKW, Chan JFW, et al. *Chest* 2017;15:1069-1080.

Was I the only clinician who was unaware that either clarithromycin or naproxen possess antiviral activity? In their opening discussion of the topic, Hung et al commented, "In vitro and animal studies have shown that ... clarithromycin and naproxen ... both possess antiviral activity. ... In addition, macrolides have effects on the host response to influenza virus infection." Who knew?

In the United States, thousands of people die each year from influenza. The effect of "traditional" antiviral therapy, most commonly neuraminidase inhibitors, often is limited by the fact that patients are admitted more than 48 hours after symptom onset, rendering neuraminidase inhibitors less effective.

Patients admitted to the hospital (n = 217) with confirmed influenza A (H3N2) were randomized to five days of treatment with oseltamivir 75 mg twice daily, plus either clarithromycin 500 mg + naproxen 200 mg twice daily for the first two days or placebo.

There was a dramatic, statistically significant effect of the combination therapy on mortality. Of the 10 deaths in the 30-day follow-up, nine were in the neuraminidase monotherapy group. Confirming that this is unlikely to be related to the antibacterial effects of clarithromycin, the authors indicated that < 5% of these patients had confirmation of bacterial coinfection at presentation. Clinicians may want to consider such a regimen for hospitalized influenza pneumonia patients. ■

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log on to **AHCMedia.com** and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on their mailing label, invoice, or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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## CME QUESTIONS

1. **Based on the study by Thurston et al, which group of women experiencing hot flashes was associated with poorer endothelial function as a marker for cardiovascular disease?**
   a. Those who were 32-39 years of age.
   b. Those who were 40-53 years of age.
   c. Those who were 54-60 years of age.
   d. Those who were > 60 years of age.

2. **Based on the study by Young et al, in patients with non-insulin-treated type 2 diabetes mellitus, researchers found which of the following to be true regarding self-monitoring of blood glucose (SMBG) as an effective tool for patients:**
   a. The once-daily SMBG monitoring group exhibited improved hemoglobin A1c levels.
   b. The once-daily SMBG with enhanced patient feedback group improved hemoglobin A1c levels.
   c. No SMBG group demonstrated improved hemoglobin A1c levels.
   d. No significant differences were found in hemoglobin A1c levels or health-related quality of life across all three groups.

3. **In patients suffering from knee osteoarthritis, compared to placebo:**
   a. pharmaceutical-grade chondroitin sulfate was superior in pain reduction.
   b. herbal supplement chondroitin sulfate was superior in pain reduction.
   c. celecoxib was superior in pain reduction.
   d. None of the above

## CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

## [IN FUTURE ISSUES]

Glycemic Measures May Vary Depending on Race

Risk of Death Among Users of Proton Pump Inhibitors