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INSIDE

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Should We Use Colchicine for Acute Gout, and If So, How Much?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

Dr. Scherger reports no financial relationship to this field of study.

Synopsis: *A randomized controlled trial showed that low-dose colchicine, 1.2 mg initially followed by 0.6 mg at 1 hour, was equally effective with fewer side effects as high-dose colchicine, eight 0.6 mg pills over 6 hours. The < 40% response rate with 23% getting diarrhea in the low-dose group calls into question whether colchicine is the superior choice over NSAIDs for acute gout.*

Source: Terkeltaub RA, et al. High versus low dosing of oral colchicine for early acute gout flare. *Arthritis Rheum* 2010;62:1060-1068.

COLCHICINE IS A NATURAL PRODUCT FROM THE PLANT, *COLCHICUM AUTUMNALE* or meadow saffron. It is a toxic substance that has been used for medicinal purposes generically for 200 years. Its best known use has been for acute attacks of gout, but it also has been used as a cathartic and emetic, and for Familial Mediterranean Fever and pericarditis.[1] Like other natural products not well studied for their uses, such as quinine, the FDA removed the generics from the market and gave exclusive rights to a major drug company to study and develop a brand name product. URL Pharma now has Colcrys in the same 0.6 mg pill, with a cost many times higher than the generics.

In a controlled multicenter trial based at the University of California San Diego and the San Diego VA Medical Center, 184 patients were randomized to receive low-dose colchicine (1.2 mg initially followed by 0.6 mg at 1 hour), high-dose colchicine (1.2 mg initially followed by 0.6 mg every hour for 6 hours), or placebo. The response was measured as ≥ 50% reduction in pain; 37.8% (28 of 74 patients) in the low-dose group responded, 32.7% (17 of 52 patients) in the high-dose group

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responded, and 15.5% (9 of 58 patients) in the placebo group responded. The most common side effect was diarrhea and 23% of the low-dose patients developed diarrhea compared with 76.9% of the high-dose patients. More than 17% (17.3%) of the high-dose patients had severe diarrhea compared with none in the low-dose group.

About one-third of the patients in both treatment groups took a "rescue" medication because of recurrence of symptoms, usually indomethacin. Half of the placebo group patients required the rescue medication. The authors conclude that low-dose colchicine gave comparable results in treating acute gout to high-dose therapy with many fewer side effects, especially diarrhea.

■ COMMENTARY

Over my 35 years of medical practice, I have avoided colchicine and used high-dose NSAIDs to treat acute attacks of gout. While colchicine gave some diagnostic value, that seemed a large price to pay for the high side-effect profile. The NSAIDs ibuprofen and naproxen were released during my years of medical education in the 1970s and I welcomed them as a preferred treatment for acute gout.

Now that a major drug company has a new brand name colchicine product, we are likely to see more studies like this supported by the industry. Most NSAIDs are generic and much less expensive than Colcrys for treating acute gout. The side effect profile of colchicine is such that there are plaintiff attorneys specializing in colchicine cases, although most of these are from IV use. This study tries to convince us that only 3 pills are needed, but more than 20% of the patients still got diarrhea, and one-third of patients had to take an NSAID anyway as a rescue medication. Some patients cannot tolerate NSAIDs and the low-dose treatment with colchicine would be helpful in these cases. I suspect that I will use some number of pills between the low dose and high dose in this study for more severe cases of acute gout. ■

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Where There's a Wheel, There's a Way

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureaus for Resmed and Respironics.

Synopsis: *The more bike riding a premenopausal women does, the less likely she is to gain weight.*

Source: Lusk AC, et al. Bicycle riding, walking, and weight gain in premenopausal women. *Arch Intern Med* 2010;170:1050-1056.

This report comes from the Nurses' Health Study II (NHSII), which is an ongoing study of more than 100,000 U.S. female nurses who were 25-42 years in 1989. Participants have completed questionnaires about their medical history and lifestyle every other year since then. The overall response rate has been approximately 90% over the nearly 20 years of follow-up.

For purposes of this analysis, the investigators used data from women who were still premenopausal in 2005. They excluded those who had recently been pregnant, those from whom data about weight or physical activity were missing, those who reported extreme weight values or weight changes, those who had physical conditions preventing exercise, those who reported exercising more than 4 hours a day, and those who had had myocardial infarction, stroke, angina, cancer, or diabetes. They were left with 18,414 healthy premenopausal women for analysis.

Data about the amount and kind of physical activity were collected in detail in 1989 and in 2005. The respondents were asked about walking or hiking outdoors, jogging, running, bicycling (including on a stationary machine), calisthenics/aerobics/aerobic dance/rowing machine, tennis/squash/racquetball, lap swimming, or other

aerobic activity (e.g., lawn mowing and stair climbing). Women categorized each physical activity by duration per week. Bicycling in 1989 and 2005 was categorized into 4 groups (0, ≤ 5, 5-15, and > 15 min/day).

Sedentary behavior was assessed by the following questions: "How many hours per week do you spend: 1) Sitting at home while watching TV/VCR?" 2) "Other sitting at home (e.g., reading, meal times, and at desk)?" The main outcome was the weight change between 1989 and 2005. A secondary outcome was gaining more than 5% of weight from baseline in 1989 by 2005. Eating behavior known to predict weight gain (intakes of sugar-sweetened beverages, energy-adjusted *trans* fats, and energy-adjusted dietary fiber) was included in the analysis, as were alcohol consumption at baseline, smoking, oral contraceptive use, parity, and antidepressant intake.

Nearly half (48%) of the women reported they spent some time bicycling in 2005 (this could include stationary biking), but the average time they bicycled was only 2.5 min/day. Of the bicyclists, only 13% bicycled for at least 10 min/day. Participants reported spending much more time walking briskly than biking (average about 16 min/day), and overweight women reported walking more slowly than normal weight women. The mean time spent sitting at home was about 5 times (about 2.5 hours/day) more than the time spent doing any kind of physical activity (about 0.5 hour/day), and overweight women spent the most time sitting at home.

Over the 16 years of follow-up, the group of women gained an average of 9.3 kg (20.5 lbs) Women who were not overweight to begin with (BMI < 25 kg/m^2) gained much less weight (8.4 kg vs 12.6 kg). Over the 16 years of study, the women as a group decreased the mean time they spent doing physical activity by about 8.5 min/day. Not surprisingly, those women who increased their total daily physical activity over the course of the study gained less weight; similarly, increased time sitting at home was associated with greater weight gain. In terms of biking, very few women (1.2%) actually increased bicycling over the course of the study, but for those who did, protection from weight gain was substantial. For women who did not bike at all in 1989 but who had started bicycling by 2005, even 5 min/day of biking was associated with statistically significantly smaller weight gain; the more a woman biked, the less weight she gained, controlling for many confounders. The mean weight gain was the smallest (5.5 kg) in women who engaged in 4 hours/wk or more of bicycling compared with women who bicycled for less time. Of note, the benefits of brisk walking, bicycling, and other physical activities were significantly greater among overweight and obese women (BMI ≥ 25 kg/m^2) than for normal weight women. Of the physical activities assessed, only slow walking (< 2 mph) showed no benefit in preventing weight gain.

■ COMMENTARY

Among the most notable findings of this study were how few women actually increased their biking by 30 min/day (about 1%), and that the study is all about reducing the amount of weight gain, not reducing the amount of weight. It was not possible for me to determine from the data provided how many women actually lost weight or what the correlates of that were, but it is clear that very few women lost, or even maintained their weight.

Nevertheless, the odds of doing so were enhanced by any kind of physical activity except for slow walking. In their excellent discussion, the authors undertake some sensible and gentle advocacy, pointing out that, "Unlike discretionary gym time, bicycling could replace time spent in a car for necessary travel … for activities of daily living. Bicycling could then be an unconscious form of exercise because the trip's destination, and not the exercise, could be the goal." They review several studies of bicycling and weight in men, and point out that little work has been done to assess the effect of bicycling and weight gain in women. They also discussed the emphasis on walking, as opposed to biking, in the United States, and the lack of appropriate bike paths, particularly for women, in the United States. It turns out that the bike paths that exist in the United States were designed primarily by and for men, and that women prefer different kinds of bike paths than men do; women want the paths to be separated from motorized vehicular traffic.[1,2] The authors speculate that this could result in exercise-minded women choosing to walk, rather than bike, for transportation. In support of this notion is the contrast between the United States and the Netherlands with regard to commuting. In the Netherlands (and much of Europe), specifications for bike paths recommend separate cycle tracks parallel to road with high speed limits, for example. Perhaps as a result, 22% of the population walks and 27% commutes by bicycle.[3] In the United States, 9% of the population walks for commuting, whereas only 0.5% commutes by bicycle.[4]

Another implication of this study is that walking may not confer the benefit some walkers expect. Slow walking was not associated with reduced weight gain, and overweight women were much more likely to be slow walkers. ■

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Effects of Fibrates on Cardiovascular Outcomes

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Fibrates can reduce the risk of major cardiovascular events predominantly by prevention of coronary events, and might have a role in treating individuals who are at especially high risk of cardiovascular events and in those with combined dyslipidemia.*

Source: Jun M, et al. Effects of fibrates on cardiovascular outcomes. *Lancet* 2010;375:1875-1884.

As is well known, cardiovascular (CV) disease is the leading cause of premature morbidity and mortality worldwide.[1] For many years it had been clearly proven that lipids have a significant effect on the causation of coronary artery disease (CHD) and, therefore, pharmacotherapy with statin drugs,[2,3] which primarily target LDL cholesterol, has proven to be a particularly effective intervention strategy, substantially reducing the risks of CHD, stroke, and mortality. However, an extremely high residual risk for these illnesses persists, drawing attention to the need for additional effective preventive therapies. Several studies have demonstrated associations of low HDL cholesterol and/or high triglyceride concentrations with increased vascular risk, and numerous studies beneficially altering HDL and triglyceride levels have proven to be of great value.[4,5] Fibrates have been demonstrated to significantly raise HDL, lower triglycerides, and reduce LDL;[6] however, the ACCORD study suggested no overall benefit for fenofibrate,[7] raising a significant question as to the clinical benefit of this class of drugs.

Jun and colleagues attempted to determine the overall efficacy of fibrates on CV risk and outcomes by systematically searching multiple databases published between 1950 and March 2010. They identified and analyzed 18 prospective, randomized, controlled trials providing data on 45,058 participants. Outcomes analyzed included major CV events, coronary events, stroke, heart failure, coronary revascularization, all-cause mortality, CV death, nonvascular death, sudden death, new-onset albuminuria, and drug-related adverse events. Fibrate therapy reduced the risk of CV disease by reducing the number of coronary events; however, the magnitude of this effect was only moderate. Meaningful reductions in outcome risk, however, were achieved particularly in high-risk individuals and in those with combined dyslipidemia. Also, fibrate therapy appears safe and well tolerated in the modern era.

■ COMMENTARY

There is an increasing awareness that even after achieving beneficial results with statin therapy, CV risk remains high, especially in patients with diabetes and even in those receiving optimum statin therapy resulting in excellent control of the LDL cholesterol values. Fibrates have consistently been demonstrated to be efficacious, but appear to be most useful in patients with combined dyslipidemia. The analysis by Jun et al demonstrated no increase in adverse events (including rhabdomyolysis) with fibrate therapy, which is very reassuring in view of the previously reported severe drug-drug interaction of gemfibrozil with statins, which precipitated several reports of life-threatening myopathy. They concluded that there's reason to suspect that fibrate therapy would have an added benefit in patients with CHD and they attributed the negative results in the ACCORD trial to the limited power of that study.[7]

In summary, it appears that the new generation of fibrate drugs will be useful in managing certain groups of patients with CV disease, providing safety is maintained. The greatest benefit of fibrate therapy appears to be in the 20% of diabetic patients who have high triglyceride and low HDL cholesterol levels. A carefully controlled, randomized study in this subset of patients at high CV risk and with combined dyslipidemia is the next step needed to permit what appears to be appropriate application of targeted therapy. The results of such a study will possibly provide the data needed to formulate therapy for those patients at high residual risk of CHD and other CV events after effective statin therapy and even in patients who have been "successfully" treated with statin therapy alone. ■

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Two Streams Merge into One Mighty River?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Combining extended physical therapy and high-dose cholecalciferol can reduce two different complications of hip fracture: falls and hospital readmission.*

Source: Bischoff-Ferrari HA, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture. *Arch Intern Med* 2010;170:813-820.

Previous research has shown that supplementation with cholecalciferol (vitamin D3) can reduce falls[1] and prevent first non-vertebral fractures in the elderly,[2] but perhaps not provide secondary prevention.[3] Physical therapy, aimed at muscle strengthening and balance retraining, is also effective in preventing falls.[1] These researchers wondered what the effect of combining the two interventions would be. In this 2 × 2 factorial design, they randomized patients who had suffered a hip fracture to one of two doses of vitamin D3, 800 IU or 2000 IU per day, and to extended physical therapy (EPT) or standard physical therapy (SPT). Patients received SPT during the acute hospitalization for 30 minutes a day. EPT added an additional 30 minutes of home program instruction each day and encouragement at discharge to continue therapy at home for 30 minutes a day. The drug randomization was double-blind; physical therapy randomization was single-blind. Inclusion criteria were acute hip fracture, age ≥ 65 years, no dementia, no history of ipsilateral hip fracture, no metastatic cancer or chemotherapy in the last year, no hearing or visual impairment, adequate kidney function, ability to walk before the hip fracture, and no contraindication to vitamin D3 or calcium use. The study ran throughout 2005, during which 667 patients were prescreened. After applying the inclusion criteria and eliminating patients who refused to participate, 173 remained.

All patients took a combination of cholecalciferol 400 IU and elemental calcium 500 mg twice daily. The intervention group received an additional capsule of cholecalciferol 1200 IU daily. The patients were seen at 6 and 12 months, at which time the patients were interviewed and functionally assessed, and blood was drawn for 25-hydroxyvitamin D [25(OH)D]. They were phoned monthly and kept diaries to record falls and injuries. The outcomes of interest were falls, fall-related injuries, and hospital readmissions. Analysis was by intention-to-treat. The subjects were evenly matched at baseline. They averaged 84 years of age, were predominantly female (79%), were not obese, and were living at home. All but two individuals in both groups were vitamin D3-deficient with 25(OH)D levels averaging < 13 ng/mL.

Forty-five (45) patients dropped out, 20 of them dying. The patients in both groups reported > 90% medication adherence. At 6-month follow-up, the average 25(OH)D level in the 800 IU/d group was 37.7 ng/mL, and in the 2000 IU/d, 45.4 ng/mL. At 12-month follow-up, the values were 35.4 ng/mL and 44.7 ng/mL, respectively. The increases at both times were statistically significant. There was a total of 212 falls and 74 hospital readmissions. The rate of falls was slightly higher in the 2000 IU/d group (1.63 vs 1.25 falls per observed patient-year), but this did not reach statistical significance. Comparing the EPT and SPT groups, the rate of falls was significantly lower in the EPT group (1.21 vs 1.66). The rate of hospital readmission was significantly lower in the 2000 IU/d group than the 800 IU/d group (0.40 vs 0.59 readmissions per observed patient-year). This was driven by fewer fall-related injuries and fewer infections. The rate was also lower in the EPT group, but not significantly so (0.50 vs 0.51). Adverse reactions were limited to 3 cases of mild hypercalcemia. The two interventions did not affect the rates of death or of new nursing home admission.

■ COMMENTARY

I was really hoping to see that the combination of these two easy interventions reduced mortality. Hip fractures cause excess mortality,[4] so perhaps the damage had already been done, and I should not be surprised that the interventions had no effect on death rates. The study lasted only 12 months, so maybe we'll see an effect on mortality if they follow the patients a while longer. The good news is that the interventions reduced falls and hospital readmissions. What I found strange was that the authors did not compare the group of patients who received both therapies to the group that received neither.

Vitamin D deficiency is common in the elderly, and the usual supplementary dose (400 IU/d) is inadequate to reverse it.[5,6] The American Geriatrics Society and the British Geriatrics Society updated their *Clinical Practice Guideline: Prevention of Falls in Older Persons* earlier this year.[7] It has more than 40 recommendations, including "Vitamin D supplements of at least 800 IU per day should be provided to older persons with proven vitamin D deficiency ... [and] should be considered for people with suspected vitamin D deficiency or who are otherwise at increased risk

for falls." The intervention dose used in this study (2000 IU daily) is considerably higher than that in the guideline, but, as this study showed, it is safe and effective, if you do not prescribe it to patients with a recent history of kidney stones, hypercalcemia, primary hyperparathyroidism, and sarcoidosis. However, once-a-year dosing of 500,000 IU results in increased falls and fractures.[8] My experience as a nursing home director was that many patients who had suffered hip fractures arrived at our sub-acute unit without any vitamin D, calcium, or antiresorptive drug prescription. This experience has been confirmed in the literature.[9] Just as Goldilocks, avoid too much and too little. Somewhere in the middle is just right. ■

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Correction

In the May 15 issue of *Internal Medicine Alert*, there was an error in CME question #19. The question asked for the incorrect response and all of the answers were correct. We apologize for any confusion this may have caused. ■

Pharmacology Update

Everolimus Tablets (Zortress®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

EVEROLIMUS, A DERIVATIVE OF SIROLIMUS, IS A MAMMALIan target of rapamycin (mTOR) inhibitor. The drug has been approved by the FDA for prophylaxis of organ rejection after kidney transplantation. It was originally approved for the treatment of advanced renal cell carcinoma and marketed as Afinitor®. For the new indication, everolimus is marketed by Novartis as Zortress® and at a much lower dose. Everolimus has been approved for renal and heart transplantation by the European Agency for the Evaluation of Medicinal Products since 2004.

Indications

Everolimus is indicated for prophylaxis of organ rejection in adults at low-moderate immunologic risk who are receiving a kidney transplant.[1] It is given in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids.

Dosage

The initial dose is 0.75 mg orally twice daily in combination with reduced-dose cyclosporine started as soon as possible after transplantation. Everolimus may be taken without regard to meals and at the same time as cyclosporine. The recommended whole blood therapeutic range is 3-8 ng/mL. Routine monitoring is recommended and dose adjustments can be made at 4-5 day intervals. Adjustments are based on blood level, tolerability, individual response, concomitant drugs, and clinical situation.[1] Oral prednisone should be started as soon as oral medications are tolerated and may be tapered based on the clinical status of the patient and function of the graft.[1]

Everolimus (Zortress) is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets.

Potential Advantages

Everolimus with a reduced calcineurin inhibitor provides an effective alternative antigraft rejection regimen.[1,2]

Potential Disadvantages

Moderate to strong inhibitors and inducers of CYP3A may affect the blood levels of everolimus and dose adjustment may be required.[1] Non-infectious pneumonitis, angioedema, risk for delayed wound healing, and graft thrombosis have been associated with everolimus. Proteinuria, hyperlipidemia, and hyperglycemia can occur; therefore, monitoring is recommended. Male infertility has also been associated with everolimus. The combination of everolimus and cyclosporine may increase the risk of thrombotic, microangiopathy/thrombotic thrombocytopenia purpura/hemolytic uremic syndrome.

Comments

Everolimus is a derivative of sirolimus with greater water solubility, shorter elimination half-life, and better bioavailability.[2] The mechanism of action is based on mTOR inhibition, leading to an antiproliferative effect of T and B lymphocytes. Everolimus potentiates cyclosporine-associated nephrotoxicity and is used with reduced-dose cyclosporine.

The approval was based on a 24-month, multinational, open-label, randomized trial comparing everolimus with mycophenolate.[1] Study participants were 18-70 years of age, undergoing their first transplant with low-to-moderate immunologic risk. This was defined as an ABO blood type-compatible first organ or tissue transplant with anti-HLA Class I PRA < 20% by a complement-dependent cytotoxicity-based assay, or < 50% by a flow cytometry or ELISA-based assay, and with a negative T-cell crossmatch. All participants received basiliximab induction and were randomized to everolimus 1.5 mg per day (n = 279), everolimus 3 mg per day (n = 277), or mycophenolate (Myfortic®) 1.44 g per day (n = 277). Everolimus was given with reduced doses of cyclosporine and corticosteroids, and mycophenolate with standard doses of cyclosporine and corticosteroids. The primary endpoint was treatment failure defined as a composite of biopsy-proven acute rejection, death, graft loss, or loss to follow-up. The percent failures were 25.3% for everolimus 1.5 mg and 24.2% for mycophenolate. Data presented to the FDA suggest everolimus may be less effective in female patients.[4] The incidences of adverse events were similar although psychiatric disorders (33% vs 26%), peripheral edema (45% vs 40%), wound healing-related reactions (33% vs 26%), and dyslipidemia (15% vs 9%) were higher with everolimus.[1] Incidence of viral infections (CVM and BK) were lower with everolimus (10% vs 21%). The discontinuation rate in the 3 mg study arm was 34%; therefore, that dose is not recommended. Data on another mTOR inhibitor, sirolimus, suggest that conversion from calcineurin inhibitors may reduce the risk of post-transplant cancer.[5,6] Recent data suggest that everolimus may be dosed once-daily.[7]

Clinical Implications

Everolimus provides an alternative antigraft rejection regimen with a reduced dose of calcineurin inhibitor (e.g., cyclosporine). It is currently being evaluated in addition to calcineurin inhibitor reduction or discontinuation for the maintenance of renal transplant recipients.[8] ■

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CME Questions

33. Which of the following fits a low-dose protocol for treating an acute episode of gout?
a. 0.6 mg every hour for 4 hours
b. 1.2 mg initially and 0.6 mg every hour for 4 hours
c. 1.2 mg initially and 0.6 mg every hour for 3 hours
d. 1.2 mg initially and 0.6 mg given at 1 hour

34. For premenopausal women, bicycle riding:
a. has no effect on weight gain.
b. can prevent weight gain only in women who were of normal weight to begin with.
c. is not as effective as slow walking in prevention weight gain.
d. can prevent weight gain.

35. Fibrate therapy:
a. is of no value in reducing the risk of major CV events.
b. may be used with impunity in patients receiving statin therapy.
c. can reduce the risk of major CV events, especially in individuals at high risk of these events and in those with combined dyslipidemia.
d. is especially valuable in the reduction of LDL cholesterol.

Answers: 33. d, 34. d, 35. c.

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Female sexual dysfunction in diabetes

Source: Esposito K, et al. *Int J Impot Research* 2010;22:179-184.

Male sexual dysfunction is well recognized as a consequence of diabetes. Currently, there are no approved medications for treatment of female sexual dysfunction (FSD), though epidemiologic surveys suggest that the population prevalence of FSD rivals that of male sexual dysfunction. FSD is typically categorized as either disorders of desire, arousal, orgasm, or pain. Of course, FSD subcategories are commonly comorbid.

This study recruited adult type 2 diabetic women (mean age, 58 years) attending a clinic in Italy for routine care of diabetes to complete the Female Sexual Function Index, a validated instrument for assessing FSD.

Overall, the prevalence of FSD in the entire population was 53%. This is similar to, but greater than, the prevalence reported in 2 large population surveys (both with broader age range, and not limited to diabetics), which indicated an FSD prevalence of 43%. FSD was 30% more frequent in postmenopausal women than premenopausal women and was associated with depression. The only recognized protective factor was physical activity.

The etiology of FSD in diabetes is unclear, and may include vascular, neurologic, and endocrinologic factors. The high prevalence of FSD in diabetic women should motivate clinicians to be more proactive in its identification. ■

Exenatide + rosiglitazone added to metformin

Source: DeFronzo RA, et al. *Diabetes Care* 2010;33:951-957.

It is widely recognized that approximately half of beta-cell function (BCF) has been lost by the time type 2 diabetes (DM2) is diagnosed. Additionally, it appears that despite vigorous treatment, loss of BCF continues inexorably.

The most recently published treatment algorithm for DM2 management by the ADA suggests that initial therapy should be lifestyle with metformin, unless a specific contraindication to metformin exists. Over time, however, most patients will require augmentation of treatment.

Exenatide (EXE) and rosiglitazone (ROS) are effective therapies for glucose control and work by complementary mechanisms of action. Additionally, sometimes thiazolidinedione therapy is compromised by weight gain, but since EXE consistently provides weight loss, their combination is clinically sensible.

DM2 subjects already on treatment with lifestyle + metformin (n = 101) were randomly assigned to add-on therapy with EXE alone, ROS alone, or EXE + ROS, and followed for 20 weeks. BCF was measured by the glucose disposition index.

In addition to the anticipated reduction in A1c by polypharmacy, EXE + ROS provided significant improvements in insulin secretion and overall BCF. Long-term studies are necessary to discern whether these favorable effects can be sustained and translated into risk reduction for macro- and/or microvascular outcomes. ■

Dietary added sugar and lipids

Source: Welsh JA, et al. *JAMA* 2010; 303:1490-1497.

Processed foods often contain added sucrose or high-fructose corn syrup to enhance palatability. Such added sugars (aSUG) may comprise as much as 16% of Americans' caloric intake. The Institute of Medicine suggests a 25% maximum of daily calories from aSUG and the American Heart Association suggests a 5% maximum. The incidence of obesity, diabetes, and dental caries is associated with increased aSUG, but the relationship between aSUG and lipids is less well-defined.

Welsh et al studied the relationship between aSUG and lipids in NHANES participants (n = 6113). Overall, approximately 16% of calories daily were supplied by aSUG in this population of adults. Excluded from analysis were persons with dietary reports that appeared unreliable (e.g., < 600 calories/day), marked triglyceride elevation, BMI > 65 kg/m^2, and those taking cholesterol-lowering medications.

There was a statistically significant association between progressively higher levels of aSUG and lower HDL. Similarly, LDL and triglyceride levels were linearly related to aSUG, although the LDL results were not statistically significant in men.

The mechanism(s) by which aSUG consumption is related to lipid levels is incompletely understood, although it is recognized that fructose may stimulate hepatic lipid production and reduce peripheral lipid clearance. Although not demonstrated in a clinical trial, conceptually, reductions in aSUG on a population-wide basis could have important public health benefits. ■