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INSIDE

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A Lot More Physical Activity Needed to Prevent Weight Gain

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

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Synopsis: *A prospective study found that women gained weight at similar rates even though their physical activity levels varied substantially. Only women with normal BMI at baseline and higher levels of activity who maintained that activity level also maintained normal BMI.*

Source: Lee IM, et al. Physical activity and weight gain prevention. *JAMA* 2010;303:1173-1179.

The Women's Health Study was a prospective cohort study involving almost 40,000 women. The women completed health questionnaires from 1992 to 2004. When that study ended, more than 33,000 women continued in an observational follow-up study until 2007. Detailed data on physical activity were collected, which allowed calculation of energy expenditure per week. These calculations allowed women to be classified into three groups based on energy expenditure: < 7.5, 7.5-21, or > 21 metabolic equivalent (MET) hours per week. These are equivalent to < 150 min/week, 150-420 min/week, and > 420 min/week of moderate-intensity physical activity.

The women reported their body weight in the questionnaires along with several potential confounders of activity and weight: race, educational attainment, height, smoking status, menopausal status, postmenopausal hormone use, diabetes, hypertension, alcohol intake, and diet. Statistical analyses were carried out on physical activity and weight trends. Repeated measures linear regression was used to test correlations. All of the confounders were examined statistically.

At baseline, the average age of the women was 54.2 years. The mean follow-up time in the study was 13.1 years. Data for this

Table. Calories used per hour in common physical activities.

Moderate Physical Activity	Approximate Calories/30 Min for a 154 lb Person*	Approximate Calories/Hr for a 154 lb Person*
Hiking	185	370
Light gardening/yard work	165	330
Dancing	165	330
Golf (walking and carrying clubs)	165	330
Bicycling (< 10 mph)	145	290
Walking (< 3.5 mph)	140	280
Weight lifting (general light workout)	110	220
Stretching	90	180
Vigorous Physical Activity	**Approximate Calories/30 Min For a 154 lb Person***	**Approximate Calories/Hr For a 154 lb Person***
Running/jogging (5 mph)	295	590
Bicycling (> 10 mph)	295	590
Swimming (slow freestyle laps)	255	510
Aerobics	240	480
Walking (4.5 mph)	230	460
Heavy yard work (chopping wood)	220	440
Weight lifting (vigorous effort)	220	440
Basketball (vigorous)	220	440

* Calories burned per hour will be higher for persons who weigh more than 154 lbs (70 kg) and lower for persons who weigh less.

Source: Adapted from Dietary Guidelines for Americans, 2005.

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study was analyzed at intervals of approximately 3 years. At baseline, the distribution of women between the least, intermediate, and most active groups was 49.5%, 28.8%, and 21.7%. After 14 years, the proportions were 34.2%, 30.3%, and 35.5%. On average, women gained weight during the study, with the average weight increasing from 70.2 kg at baseline to 72.8 kg at the end. All three groups showed similar weight gain patterns. Those in the least active group gained 0.12 kg more weight per three-year interval compared to those in the most active group ($P = 0.002$). The intermediate activity level group had 0.11 kg more weight gain per three-year interval compared to those in the most active group ($P = 0.003$). The weight gain in the least and intermediate activity groups did not differ significantly. The two less active groups were significantly more likely to have meaningful weight gain in each three-year interval. Meaningful weight gain was defined as 2.3 kg (5 lb).

The overall association between activity and weight gain was significantly correlated to age and BMI, but not smoking status or menopausal status. When these

Preventing Weight Gain

If you're currently at a healthy weight, you're already one step ahead of the game. To stay at a healthy weight, it's worth doing a little planning now.

Or maybe you are overweight but aren't ready to lose weight yet. If this is the case, preventing further weight gain is a worthy goal.

As people age, their body composition gradually shifts — the proportion of muscle decreases and the proportion of fat increases. This shift slows their metabolism, making it easier to gain weight. In addition, some people become less physically active as they get older, increasing the risk of weight gain.

The good news is that weight gain can be prevented by choosing a lifestyle that includes good eating habits and daily physical activity. By avoiding weight gain, you avoid higher risks of many chronic diseases, such as heart disease, stroke, type 2 diabetes, high blood pressure, osteoarthritis, and some forms of cancer.

Choosing an Eating Plan to Prevent Weight Gain

So, how do you choose a healthful eating plan that will enable you to maintain your current weight? The goal is to make a habit out of choosing foods that are nutritious and healthful. To learn more, visit Healthy Eating for a Healthy Weight (www.cdc.gov/healthyweight/healthy_eating/index.html).

If your goal is to prevent weight gain, then you'll want to choose foods that supply you with the appropriate number of calories to maintain your weight. This number varies from person to person. It depends on many factors, including your height, weight, age, sex, and activity level.

Get Moving!

In addition to a healthy eating plan, an active lifestyle will help you maintain your weight. By choosing to add more physical activity to your day, you'll increase the amount of calories your body burns. This makes it more likely you'll maintain your weight.

Although physical activity is an integral part of weight management, it's also a vital part of health in general. Regular physical activity can reduce your risk for many chronic diseases and it can help keep your body healthy and strong. To learn more about how physical activity can help you maintain a healthy weight, visit Physical Activity for Healthy Weight (www.cdc.gov/healthyweight/physical_activity/index.html).

Self-monitoring

You may also find it helpful to weigh yourself on a regular basis. If you see a few pounds creeping on, take the time to examine your lifestyle. With these strategies, you make it more likely that you'll catch small weight gains more quickly.

Ask yourself —

- Has my activity level changed?
- Am I eating more than usual? You may find it helpful to keep a food diary for a few days to make you more aware of your eating choices.

If you find that you've decreased your activity level or made some poor food choices, make a commitment to yourself to get back on track. Set some reasonable goals to help you get more physical activity and make better food choices. ■

Source: Centers for Disease Control and Prevention. Available at: www.cdc.gov/healthyweight/prevention/index.html. Accessed April 18, 2010.

associations were examined by activity groups, only BMI was significant. Only women who started the study with a BMI of 25 or less (normal) were unlikely to have meaningful weight gain of 2.3 kg ($P < 0.001$). No other group showed this correlation. Approximately 4,500 women started the study with a normal BMI and remained at normal BMI throughout the study without gaining 2.3 kg weight. The mean activity level of these women over the duration of the study was 21.5 MET hours per week, or 60 minutes per day of moderate-intensity activity.

The authors draw two main conclusions from their data. The first is that once people are overweight, physical activity at the level carried out by these participants was not associated with less weight gain. Prevention of overweight is crucial and requires much further research. The second conclusion is that 60 minutes per day of moderate-intensity physical activity is necessary to maintain normal BMI and prevent weight gain.

■ COMMENTARY

Nothing further needs to be said about the growing problem with obesity and the challenges of helping people lose weight. Each new weight loss strategy runs into problems with the difficulties many people have maintaining a healthy weight. With all of the attention these issues are receiving, relatively little research has examined weight gain prevention strategies. The old adage that "an ounce of prevention is worth a pound of cure" would appear to be remarkably apt in this area. Yet much remains unclear about how much physical activity is needed to prevent weight gain.

For example, the most recent guidelines suggest people need at least 150 min/week of moderate-intensity exercise for health benefits.[1,2] Whether this helps prevent weight gain is unclear. The Institute of Medicine recommends 420 min/week (an hour per day) of moderate exercise to prevent becoming overweight.[3]

Moderate-intensity physical activity is defined in various ways as it varies by individual. Common rules of thumb are moderate activities allow someone to carry on a conversation, or the heart rate reaches 50%-70% of resting. According to the Centers for Disease Control and Prevention, moderate-intensity activities include walking briskly, bicycling (slower than 10 mph), water aerobics, doubles tennis, ballroom dancing, and general gardening.[4] Jogging, running, faster bicycling, hiking uphill, and singles tennis are categorized as vigorous activities *(see page 50)*.

This prospective study adds important insight to help people understand what is necessary to maintain healthy weight over many years. Although the overall weight gain found in this study may appear small, averaging 2.6 kg over 13 years, this can have significant health impact. The study's findings point to the importance of preventing weight gain in the first place. They also point to the not-insignificant quantity of physical activity necessary to prevent weight gain. An hour per day of moderate-intensity activity will appear challenging to many people, although the benefits are increasingly being shown to be very significant.

The study has some important limitations. The average age of the women was older (54.1 years, with a standard deviation of 6.8 years). The findings may not be directly applicable to women of all ages, nor to men. The women were consuming "a usual U.S. diet," and thus factors related to special diets were not taken into account. The study used self-reported physical activity and weight, which have limitations, although these are often the only methods available in large, long-term studies.

The findings suggest that an important caveat must be added to recent guidelines on physical activities. These recommend 150 min/week of moderate activity for health benefits.[1,2] While this is important for overall health, prevention of weight gain requires more physical activity, on the order of 420 min/week (or an hour a day). Given the failure of many weight-loss strategies to achieve long-term weight-loss maintenance, preventing weight gain in the first place is crucial. This supports giving high priority to the physical activity levels of children and adolescents and instilling healthy habits early in life. ■

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"D-feat D Flu?" Vitamin D and Pediatric Influenza

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *The promising results of this study suggest that timely supplementation with vitamin D3 may help prevent seasonal influenza A, though not influenza B, in school-aged children. A side finding was that children with asthma taking vitamin D3 experienced fewer exacerbations, though not a lesser rate of influenza A infection. I hope this trial will be replicated, and with measurement of 25-OH D levels, in both children and adults, to help tease out the role of vitamin D in flu prevention.*

Source: Urashima M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010 Mar 10; doi:10.3945/ajcn.2009.29094.

The authors of this Japanese multicenter (12 hospitals and 8 outside physicians), randomized, double-blind, placebo-controlled, parallel-group trial investigated whether vitamin D supplements might impact the incidence of influenza A in school children during winter and early spring. Children aged 6-15 years (mean age 10.2 years, with 65% having started nursery school or kindergarten at 3 years or older) were enrolled from November to early December in 2008 and then asked to begin taking their study drugs within the first 2 weeks of December. Subjects were randomized to receive daily divided doses of either 1,200 IU of vitamin D3 or placebo from December 2008 through March 2009. Parents were provided with eight numbered bottles, each containing 90 tablets of either 200 IU vitamin D or placebo identical in appearance. The children were to take 3 tablets twice

daily. Pre-study questionnaires collected demographic data and medical history, while the post-study questionnaire focused on answers to questions about compliance with study protocol, outdoor activities, specific food intake, and illnesses that may have occurred. Daily logs were also completed. Compliance was measured in part by direct viewing of the supplement bottles on clinic visits. Primary outcome of interest was the incidence of influenza A, diagnosed by outpatient rapid influenza antigen testing using a nasopharyngeal swab specimen.

A total of 430 schoolchildren/parent pairs were randomized but there was significant study attrition, with 50 and 46 children being lost to follow-up in the active and placebo groups, respectively (intention-to-treat analysis was used). Compliance with the study medication was very high (96%). Influenza A occurred in 18/167 (10.8%) of children in the vitamin D group compared with 31/167 (18.6%) in the placebo group (relative risk [RR] = 0.58), with peak incidence occurring from middle to late January. Between days 31 and 60, influenza A occurred significantly less often in the vitamin D group than in the placebo group (5.4% vs. 13.2%; RR = 0.41), but there was no difference in the development of influenza A between the two groups early or late in the trial. In subgroup analysis it was shown that a reduction in occurrence in influenza A was more prominent in children who previously had not been taking vitamin D and in those who had started nursery school after age 3 years (starting nursery school before age 3 years may increase the chances of exposure to influenza and of obtaining immunity). In children with a previous history of asthma, exacerbations occurred in 2 children taking vitamin D3 vs. 12 children in the placebo group (RR = 0.17). The incidence of influenza B and antigen-testing negative flu-like illness was not different between the two groups. No serious adverse effects were identified, including urinary stones.

The authors concluded that vitamin D3 supplementation during the winter and early spring may have a preventive effect against the development of childhood influenza A infection.

■ COMMENTARY

This is a very interesting study. As the authors note, one hypothesis regarding the seasonal pattern of influenza infections reflects the seasonal oscillation of vitamin D levels as a reflection of sun exposure. It is known both that vitamin D up-regulates innate immunity and that serum levels of vitamin D decrease during the winter months when people spend more time indoors. Vitamin D may also function to lessen inflammation in the body, and some data suggest a protective effect of vitamin D against uncomplicated upper respiratory tract infection.

Some might think the dose of vitamin D employed in this study was high, but vitamin D supplementation in the range of 200-2,000 IU in schoolchildren over the course of a year has been shown to be safe.[1]

There are limitations to the data (aren't there always?). Unfortunately, but understandably considering the patient population, 25-hydroxyvitamin D levels were not obtained, so a threshold level for any preventive activity remains unknown. The sample size was small, a significant number of children were lost to follow-up, and an unspecified number of children apparently began taking vitamin D supplements in addition to the study medication after randomization (why was this not prohibited?).

It is notable that vitamin D did not have an impact against influenza B, nor did it lessen the risk of influenza A in children with asthma (although it appeared to lessen the risk of asthma attacks). In addition, a consideration is the number of pills that children were asked to consume every day, though this could be easily remedied.

Limitations aside, the results of this trial are intriguing. Could adequate repletion of vitamin D together with appropriate vaccination help lessen the incidence of seasonal influenza A? Maybe. This type of trial should be replicated both in children and in adults. ■

Reference

1. Maalouf J, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *J Clin Endocrinol Metab* 2008;93:2693-2701.

Hot or Not? 5-HTP for Hot Flashes

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *The single author of this small pilot study concludes that 50 mg of 5-HTP taken three times a day for 4 weeks is ineffective against menopausal hot flashes. The paper is disappointing in many ways, however, and readers might question whether the actual reason behind the trial was indeed to test 5-HTP.*

Source: Freedman R. Treatment of menopausal hot flashes with 5-hydroxytryptophan. *Maturitas* 2010;65:383-385.

THE LONE RESEARCHER BEHIND THIS STUDY EMPLOYED double-blind, placebo-controlled methodology to evaluate the effects of 5-hydroxytryptophan (5-HTP) on

hot flashes in 24 postmenopausal women who reported at least 6 hot flashes per day. Subjects were recruited through local newspaper advertisements, received $300 for participating, and were randomized to receive either 5-HTP or placebo. Treatment outcome was measured using a miniature electronic hot flash recorder that measures chest wall humidity, defining a hot flash as a change in relative humidity of at least 3%/min. At study initiation subjects were to wear the recorder continuously for one week, removing it only when bathing, and then return it at which time they were given bottles of either 5-HTP (50 mg) or placebo to be taken three times a day for 3 weeks. At the start of the fourth week subjects again donned the recorder continuously for 7 days, this time while also taking their assigned pills. Pre- and post-treatment hot flash recorder readings were then compared. Of note, subjects were not asked about hot flash frequency.

The author reports no significant effects of 5-HTP on hot flash incidence compared with placebo. Pre- and post-treatment 24-hour hot flash frequency was 23.8/18.5 in the active group and 22.8/22.6 in the placebo group, respectively. No *P* values were noted, though a power analysis statement was made.

The author concludes that 50 mg of 5-HTP provided three times daily over 4 weeks does not reduce menopausal hot flashes significantly as measured objectively with an electronic recorder.

■ COMMENTARY

At face value, one might assume this article adds salient information to the discourse on appropriate management of hot flashes, but a thorough review makes that stance at least debatable. The problems go beyond those methodological in nature, which include the small sample size (again, it was a pilot trial), short duration of intervention, and lack of control for differences in ambient temperature or levels of physical activity. The oft-cited recommended dosage range for 5-HTP of 150-300 mg/day comes with a paucity of supportive data. Looming large, however, are persistent questions regarding the safety of 5-HTP that linger in the aftermath of now remote case reports on the associated development of eosinophilia myalgia syndrome, though many experts believe these episodes were probably due to the presence of contaminants.[1,2]

In an interesting twist, hot flash occurrence was determined objectively with the use of a recorder that was reportedly validated in a small 2007 study. Therein lies a potential rub, however. The lone researcher and author of this trial is also the president and CEO of the company making the monitor, and a patent is pending. To be sure, objective methods of hot flash measurement could add important information, since data are likely lost when subjects are simply queried on hot flash frequency or asked to record such occurrences in a diary (still, it would have been interesting in this trial to see what the subjects had to say about their response to the given agents). In addition, the placebo effect might be lessened, although objective indications of a hot flash might not always be indicative of a bothersome subjective sensation of one.

Hot flashes are the most common symptom associated with menopause and can negatively impact quality of life in significant ways. Extrapolation of animal data led to the conclusion that increasing brain serotonin levels might help ameliorate menopausal hot flashes, and some studies using SSRIs support this approach. Tryptophan is a precursor of serotonin, so exploring the use of 5-HTP in this setting makes sense. But the current study does not answer the question of its potential utility.

Not a small amount of space in the article is devoted to the recorder itself, and concerns of bias cannot be comfortably dispelled. Was this trial designed to test the safety and effectiveness of 5-HTP against menopausal hot flashes or to help validate the usefulness of the author's invention? One might offer the benefit of the doubt to the former, but the latter issue gnaws. The results of this trial do little to answer the question of the place of 5-HTP, if any, in the treatment of menopausal hot flashes. ■

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Vitamin B6 and Connections to Colorectal Cancer Risk

ABSTRACT AND COMMENTARY

By David Kiefer, MD

Dr. Kiefer is Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson; and Adjunct Faculty, Bastyr University, Seattle; he reports no financial relationship to this field of study.

Synopsis: *The authors reviewed 12 articles representing 13 prospective studies searching for a link between vitamin B6 consumption or blood pyridoxal 5-phos-*

phate (PLP, the main active coenzyme form of B6) and lower rates of colorectal cancer, finding a linear inverse relationship (relative risk 0.52) between blood PLP and colorectal cancer risk.

Source: Larsson SC, et al. Vitamin B6 and risk of colorectal cancer: A meta-analysis of prospective studies. *JAMA* 2010;303:1077-1083.

THE AUTHORS OF THIS STUDY DID A COMPREHENSIVE SEARCH using MEDLINE and EMBASE for vitamin B6 (pyridoxine), PLP, and colon, rectal, or colorectal cancer studies, including any studies mentioned in the reference sections. The authors' focus was on studies of a prospective design, and ones that involved vitamin B6 intake or PLP blood levels and the aforementioned cancers, as well as those that reported relative risk (RR) values. The search started with 123 articles and was weaned down to 12 articles after all exclusions were applied. Of the 12 articles included in the meta-analysis, eight articles representing nine studies examined vitamin B6 intake, while four examined blood PLP levels.

The nine studies on vitamin B6 intake involved 6,064 cases, and were of a lower quality (6-7 on a 10-point rating system, usually because physical activity was not adjusted for) than the four studies on blood PLP levels, which included 883 cases and 1,424 controls and had an average research quality of 8-9. The overall relative risk of colorectal cancer for the highest vs. lowest quintiles of vitamin B6 intake was 0.90 (95% confidence interval [CI], 0.75-1.07), indicating, essentially, no effect; closer examination of the individual studies showed both positive and inverse relationships that averaged out to no effect when combined together. On the other hand, all four trials on blood PLP levels showed an inverse relationship that was statistically significant in three of four trials, yielding a RR of 0.52 (95% CI, 0.38-0.71).

Other salient points from this meta-analysis include the heterogeneity analysis, the dose-response meta-analysis, and subgroup analyses. Only the vitamin B6 intake studies had statistically significant heterogeneity (P = 0.01), most of which could be accounted for by a large cohort study in the Netherlands[1] that used a very small difference in highest to lowest quintiles of vitamin B6 intake compared to the other studies. Interestingly, when this study was removed, the highest vs. lowest vitamin B6 intake RR was 0.80 (95% CI, 0.69-0.92). No differences in dietary vs. total vitamin B6, or geographic region were found, but in the five studies that were age-adjusted, the RR across the quintiles of vitamin B6 intake was 0.79 (95% CI, 0.70-0.90). The dose response for blood PLP appeared linear, with a 100 pmol/mL amount (approximately 2 standard deviations) conferring a RR benefit of 0.51 (95%CI, 0.38-0.69).

■ COMMENTARY

It would be nice to know that as a result of this study, we could now definitively tell patients to take vitamin B6 supplements to prevent colon cancer. However, that is not what the study is all about. This meta-analysis brings together a few pieces of the vitamin-cancer puzzle, its prospective design focus avoiding a major pitfall of retrospective analyses ("I'm pretty sure I ate that vitamin B6-enriched food last week…"), while adding an interesting, and hard-to-dispute, laboratory side with the PLP levels.

Vitamin B6 should work, as we know from the proposed mechanism of action outlined in prior work, via the 1-carbon metabolic pathway where it helps to transfer 1-carbon groups during DNA synthesis and methylation. This process is impaired in animals that are vitamin B6-deficient: DNA changes, and increased risk of cancer, would follow. Other research shows that dietary B6 may decrease cell proliferation, oxidative stress, nitric oxide, and angiogenesis, all of which should decrease the development of colorectal cancer.[2]

The results of this meta-analysis hint at a connection between blood PLP and colorectal cancer, though not vitamin B6 intake, but a few issues complicate any final interpretation of the results. The authors point out three main issues: possible confounders, a potential misclassification problem, and the ever-present problem with pooling studies that have different methodologies. With respect to confounders, most, but not all, of the individual trials controlled for other known risk factors, such as physical activity, smoking, and alcohol and folate intake, though lingering effects from these or unknown confounders are theoretically still a problem. Also, six of the vitamin B6 intake studies only assessed the diet at baseline, whereas serial dietary estimates would have more accurately classified study participants into the correct quintiles. Finally, the heterogeneity resulting from methodological differences of the individual trials, a particular problem for the vitamin B6 intake studies, could have affected the final results.

The authors call for, and rightfully so, a well-designed randomized controlled trial (RCT) to settle the above questions. Yes, in conversations about many aspects of integrative health we've heard that request before. Until that RCT happens, however, this meta-analysis provides some food for thought and a few extra data points in a very important topic on the minds of practitioners and patients alike: Do these vitamins really help? We're still not completely sure. ■

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Dietary Fat Consumption and Risk of Endometriosis

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Dr. Jensen is the Leon Speroff Professor of Obstetrics and Gynecology, Vice Chair for Research, Oregon Health & Sciences University, Portland; he receives research support from, is a consultant to, and serves on the speakers bureau of Bayer Healthcare/Bayer Schering, and receives research support from Wyeth and Warner-Chilcott. This article originally appeared in the May issue of OB/GYN Clinical Alert. *At that time it was reviewed by Catherine LeClair, MD, Associate Professor, Department of OB/GYN, Oregon Health & Sciences University, Portland; Dr. LeClair reports no financial relationship to this field of study.*

Synopsis: *Consumption of* trans *fats increases the risk of endometriosis, while long-chain omega-3 fats are protective.*

Source: Missmer SA, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod* 2010 March 23; Epub ahead of print.

To investigate the relationship between dietary fat intake and the risk of endometriosis, these authors analyzed 12 years of prospective data from the Nurses' Health Study II that began in 1989. Dietary fat intake was assessed via validated food-frequency questionnaire in 1991, 1995, and 1999 and averaged over the three diet questionnaires. The risk of a new diagnosis of laparoscopically confirmed endometriosis was assessed using a Cox proportional hazards models after adjustment for total energy intake, parity, race, and body mass index at age 18. The cohort included 586,153 woman-years of follow-up and 1199 cases of laparoscopically confirmed endometriosis. While there was no association with total fat consumption and endometriosis risk, those women in the highest fifth of long-chain omega-3 fatty acid consumption were 22% less likely (risk rate [RR], 0.78; 95% confidence interval [CI], 0.62-0.99) and those consuming at the highest quintile of *trans* unsaturated fat intake were 48% more likely (RR, 1.48; 95% CI, 1.17-1.88) to be diagnosed with endometriosis compared with those with the lowest fifths of intake, respectively. Furthermore, the tests for trends were positive for increasing consumption in both groups. These data support findings from other animal and observational studies that *trans* fat is associated with an increased risk or progression of confirmed endometriosis.

■ COMMENTARY

This large prospective study of diet and endometriosis demonstrates once again the impact of diet on overall health. If there were not enough reasons to avoid *trans* fats already (associated with increased risks of obesity, cardiovascular disease, stroke, Parkinson's), we can now add endometriosis. Endometriosis is a highly prevalent condition that is the third leading cause of gynecologic hospitalization. Endometriosis is also associated with pelvic pain and infertility, two important health concerns of women. Therefore, identification of a modifiable risk factor that could reduce the risk of operative intervention for endometriosis represents an important contribution that warrants careful scrutiny.

The Nurses' Health Study (NHS) was established in 1976 with funding from the National Institutes of Health to investigate the potential long-term consequences of the use of oral contraceptives, but has yielded important health information in many other areas. The selection of nurses for this long-term prospective cohort study was a deliberate design feature; their nursing education would motivate them to participate in a long-term study and yield high-quality responses to technically worded questionnaires. The initial cohort consisted of approximately 122,000 married registered nurses ages 30-55. This group has received follow-up questionnaires every 2 years with an impressive 90% response rate. To address the interaction of diet and disease, food-frequency and diet questions were added in 1980. Questions related to quality-of-life were added in 1992. The Nurses' Health Study II cohort was established in 1989 to study these same associations in a younger (ages 25-42) population. A total of 116,686 women were enrolled in NHS II, and response rates have been the same (90%) as the original cohort. The data from the current report come from this younger population of nurses that would be expected to develop gynecologic problems. While a cohort study always suffers from potential bias, the large number of participants, excellent follow-up, multivariant adjustment of confounders, and careful independent validation of self-reported outcomes renders extremely high-quality data. Furthermore, only those women with laparoscopically diagnosed endometriosis were included as cases. Since asymptomatic endometriosis may have been discovered incidentally in women with infertility undergoing laparoscopy, this group was considered separately.

The consumption of *trans* fats correlates with high plasma lipid levels, inflammation, and arterial calcifi-

cation, known risk factors for coronary heart disease.[1] They also inhibit cyclooxygenase, an enzyme required for the conversion of arachidonic acid to prostacyclin, necessary for the regulation of blood flow. Epidemiological data suggest that when *trans* fat percentages go up, death rates rise, and when *trans* fats go down, death rates go down.[1] Just as governments justify increasing taxes on cigarettes and alcohol to recover health care costs, perhaps we should consider taxes on *trans* fat-containing food to finance our new expansion of health insurance.

Although the FDA ruled that the amount of *trans* fat in a food item must be stated on the label after Jan. 1, 2006, the exact wording contains loopholes that permit many *trans* fat-containing foods to be sold without this warning. In contrast, omega-3 fatty acids (derived from fish oil) reduce inflammation and cardiovascular risk. Dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events.[2] Even more importantly, substitution of omega-3 and polyunsaturated fats tends to reduce the overall consumption of *trans* fat.

It is important to point out that there was no association with overall fat consumption and endometriosis. This reduced the confounding influence of proportion of fat calories. What emerged from the data was a consistent story: As *trans* fat consumption increased, so did the risk of endometriosis, and as omega-3 fat consumption increased, the risk diminished. In other words, as women shifted their diet away from pro-inflammatory *trans* fats to anti-inflammatory omega-3 fats, their risk of endometriosis decreased.

Clinicians have previously had little information to offer guidance to women who present with a significant family history of endometriosis. Compared with other modifiable risks, diet is an attractive lifestyle intervention to stress during general counseling. "You are what you eat" is more than a cliché. Over 20% of women in the cohort that reported consuming total dietary fat at the highest quintile were overweight and 18% obese, compared to only 14.8% overweight and 7.2% obese in the group reporting the lowest total fat consumption.

So we can feel even more comfortable encouraging a healthy diet in our general counseling of young women (that Big Mac might lead to a laparoscopy for endometriosis). With the HPV vaccine and new schedules for less frequent pap tests, we need to rethink the annual exam. Get back to the basics and focus on preventive measures: a healthy diet low in *trans* fat and high in omega-3 fat, smoking cessation, regular exercise, safe sexual practices, and effective contraception are all low-cost interventions with great benefits to patients. ■

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Got Milk!

ABSTRACT & COMMENTARY

By Ralph R. Hall, MD, FACP, FACSM

Dr. Hall is Professor of Medicine Emeritus, University of Missouri-Kansas City; he reports no financial relationship to this field of study. This article originally appeared in the April 15, 2010 issue of Internal Medicine Alert. *At that time it was reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY; Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *An increase in dairy food intake produces significant and substantial suppression of oxidative and inflammatory stress associated with overweight and obesity.*

Source: Zemel MB, et al. Effects of dairy compared with soy on oxidative and inflammatory stress in overweight and obese subjects. *Am J Clin Nutr* 2010;91:16-22.

The objective of this study was to evaluate the acute effects of a dairy-rich diet on oxidative and inflammatory stress in overweight and obese subjects in the absence of changes in adiposity. Previous studies performed by the authors had demonstrated that dairy-rich products had markedly reduced inflammatory markers in obese mice.

Twenty subjects (10 obese and 10 overweight) participated in a blinded, randomized, crossover study of dairy compared with soy-supplemented eucaloric diets. Two 28-day dietary periods were separated by a 28-day washout period. Inflammatory and oxidative stress biomarkers were measured on days 0, 7, and 28 of each dietary period.

The dairy-supplemented diet resulted in significant suppression of oxidative stress (plasma malondialdehyde, 22%; 8-isoprotane-F alpha,12%; $P < 0.0005$). Inflammatory markers decreased as shown in the Table *(see page 58)*.

Soy exerted no significant effect. There were no signif-

icant differences in response to treatment in overweight and obese subjects.

Other findings of note were a decrease in C-reactive protein (57%) in the dairy-treated subjects, and a significant decrease in LDL cholesterol (-8.9 mg/dL with the dairy supplement compared with +2.9 mg/dL with the soy supplement.)

The authors concluded that an increase in dairy food intake produced significant and substantial suppression of oxidative and inflammatory stress associated with overweight and obesity.

■ COMMENTARY

This is an interesting and timely report. There is a concern that some women are likely to replace their dairy products with soy, in view of the recent reports from China that diets high in soy are associated with a decrease in breast cancer.[1]

The two diets (dairy and soy) in the form of smoothies were administered three times per day throughout each 28-day treatment period. Each smoothie contained 170 Kcal, 10 g protein, 1 g of fat, and 30 g carbohydrate. The dairy smoothies were milk-based, with non-fat milk as the protein source.

The authors note that it is well established that excess adiposity results in an increase in both reactive oxygen species and inflammatory cytokine production and a corresponding suppression of anti-inflammatory cytokine production. This phenomenon is regulated, in part, by calcitriol. The authors have previously reported that a reduction in calcitriol reduces oxidative and inflammatory stress in mice fed with high-calcium diets compared with low-calcium diets. They also demonstrated that non-fat dry milk elicited a significantly greater response than calcium carbonate.[2]

Findings in studies using low-fat dairy products continue to stimulate research about their nutritional effects.

Table. Effect of dairy on inflammatory markers.

Tumor necrosis factor-alpha	-15%	$P < 0.002$
Interleukin-6	-13%	$P < 0.01$
Monocyte chemoattractant protein-1	-10%	$P < 0.0006$
Adoponectin*	+20%	$P < 0.002$

* Higher adoponectin levels are associated with increased insulin sensitivity and are decreased in overweight individuals.

Low-fat dairy products are an important constituent in the Dietary Approach to Stop Hypertension (DASH) diet.[3] A recent study from the University of Minnesota examining beverage habits and other dietary parameters in a 5-year prospective analysis of 2294 adolescents showed no association between sugar-sweetened beverage consumption and adolescent weight gain. However, adolescents who consumed little or no white milk gained significantly more weight than their peers who consumed white milk.[4]

The authors point out that it is not possible to determine which effects were mediated by calcium or other components of the milk. For instance, milk contains angiotensin-converting enzyme-inhibiting peptides, whereas adipose tissue expresses all components of the renin-angiotensin system. Pharmacologic antagonism of this system suppresses oxidative stress.[5]

In addition, the authors have previously shown that leucine in milk may contribute to the reduction in the oxidative and inflammatory stress.[6] Leucine stimulates muscle protein synthesis and inhibits protein degradation and suppresses energy storage in adipose tissue.

This work was supported by The National Dairy Council. However, the authors previous effort in this field and

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

the rigorous documentation and presentation of their data support the importance of this study. ■

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CME Questions

17. In the observational follow-up study conducted by Lee et al, all of the following are true about women who maintained their weight *except*:
- a. They reported normal BMI at baseline.
- b. They engaged in 150 minutes of high-intensity exercise each week.
- c. They engaged in 420 minutes of moderate-intensity exercise each week.
- d. They consumed a "usual" U.S. diet.

18. Lower risks of colorectal cancer seem to be related to which of the following?
- a. Increased dietary vitamin B6 intake
- b. Increased vitamin B6 from supplements
- c. Blood levels of pyridoxal 5'-phosphate (PLP, the main active coenzyme form of B6)
- d. None of the above; the data are not convincing for any connection between vitamin B6 and/or its metabolites and colorectal cancer

19. Which of the following statement about milk products in this study is *true*?
- a. Dairy products raised the serum cholesterol to a greater extent than soy.
- b. Dairy products did not lower C-reactive protein levels.
- c. Calcium carbonate was as effective as dairy products in lowering inflammatory proteins.
- d. Leucine in dairy products has been reported to suppress energy storage in adipose tissue.

Answers: 17. b, 18. c, 19. d.

Helping Hands: Osteopathic Treatment for LBP of Pregnancy

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Osteopathic manipulative treatment (OMT) is one of a number of CAM therapies often considered for the treatment of third trimester lower back pain (LBP). Results of this small trial suggest that manual therapy during late pregnancy may help improve back-specific functioning but has little impact on back pain. While OMT may be appropriate for some pregnant women experiencing LBP, unless the obstetrician is a DO such care requires additional appointments, and ultimately still may not offer significant pain relief.*

Source: Licciardone JC, et al. Osteopathic manipulative treatment of back pain and related symptoms during pregnancy: A randomized controlled trial. *Am J Obstet Gynecol* 2010; 202:43.e1-8.

THIS PHASE II RANDOMIZED, PLACEBO-CONTROLLED INTERVENtion trial was conducted through The Osteopathic Research Center at the University of North Texas Health Science Center. The researchers were interested in examining the effects of osteopathic manipulative treatment (OMT) on back pain occurring in the third trimester of pregnancy, as well as associated symptoms and related physical functioning.

Obstetric clinic patients were screened up to the 30th week of pregnancy for eligibility and willingness to participate in the study, with all subjects enrolled between the 28th and 30th weeks gestation. Subjects were then randomized to one of three treatment groups: conventional prenatal care with OMT (C+OMT); conventional prenatal care with sham ultrasound treatment (C+SUT); or conventional prenatal care only (C). Participants were stratified by age and gravid status into four groups: age ≤ 24 years and primigravida, age ≤ 24 years and multigravida, age ≥ 25 years and primigravida, age ≥ 25 years and multigravida. Blocks of 6 subjects were used to randomly assign two subjects to each of the three treatment groups within each age- and gravid-specific stratum. Treatments of 30 minutes' duration were to be administered at seven successive visits by licensed faculty (weeks 30, 32, 34, 36, 37, 38, and 39). A standardized OMT protocol was used that permitted identification and treatment of specific areas of somatic dysfunction. Any

of the following treatment modalities could be employed: soft tissue, myofascial release, muscle energy, and range-of-motion mobilization.

Data were collected by research personnel blind to therapy and included information on back pain measured using an 11-point scale, and back-specific functioning as measured by the Roland-Morris Disability Questionnaire (RMDQ). Intention-to-treat analysis was employed.

A total of 49, 48, and 49 subjects were randomly assigned to the three groups, respectively. Two subjects were lost to follow-up, both prior to first visit, so the intention-to-treat analysis included data on 144 women. Completion percentages from highest to lowest were: C > C+OMT > C+SUT. Four women missed more than 50% of their scheduled appointments, two each in the C+OMT and C+SUT groups. Before visit 7 a total of 67 subjects were either withdrawn from the study (development of high-risk condition, n = 7) or censored due to delivery (n = 60).

Pain levels between the groups were similar at the outset. By study's end, however, non-statistically significant differences were evident between the groups, with mean pain levels dropping in the C+OMT group, remaining stable in the C+SUT group, and increasing in the C group. RMDQ scores increased significantly over time, representing decreased back-related functionality, but less so in the C+OMT group than in the other two groups. No adverse effects of treatment were noted. The authors concluded that OMT as a complement to conventional obstetric care slows or halts the worsening of back-specific functioning during the third trimester of pregnancy.

■ COMMENTARY

The development of LBP during the late stages of pregnancy remains a significant health issue that impacts an estimated 25% of all expectant mothers. Physicians and patients alike are reticent to use pain medication for obvious reasons so conservative approaches are the norm, but they are not always fully effective. This reality prompts many women to explore complementary approaches such as acupuncture, massage therapy, mind/body interventions, and pregnancy yoga. OMT is a form of manual therapy that often comes up in such discussions not only because of its perceived potential clinical benefit, but also because it is offered by licensed physicians.

Osteopaths focus not only on the structural body changes inherent in pregnancy, such as an increased pelvic tilt, but also fluid and hormonal shifts. For example, the increased ligamentous laxity typically seen during pregnancy usually precludes use of high velocity, low amplitude manipulative techniques (think "cracking") due to theoretical risks.

In the current study the treating physicians followed a standardized OMT protocol or applied sham ultrasound therapy, the latter using machines modified to provide convincing sights and sounds associated with fully operational ultrasound equipment. By the end of the trial it was shown that back-specific functioning appeared to improve most when OMT was added to conventional care, but there was not a statistically significant associated improvement in back pain with OMT. This finding could be related to the small sample size or to faulty randomization as noted by the authors, but it weakens the argument for OMT in this setting. Another concern is the need for multiple additional medical appointments to meet with an osteopath, much the same if a patient were to seek massage therapy or acupuncture, unless the woman is fortunate enough to have a DO as her obstetrician. This paper underscores the possibility that OMT may help in the treatment of LBP in late pregnancy, but it also points out potentially significant limitations of OMT in this setting. ■

In Future Issues: **Magnesium Supplementation and Asthma Control**

Health Care Reform Update

What Health Care Reform Means to You A supplement to *Alternative Medicine Alert*

Increased provider access tops list of what clinicians will like about HC bill

Changes will take a few years

HEALTH CARE CLINICIANS AND ORGANIZATIONS LIKELY will find that the new health care reform bill's positive features outweigh its drawbacks, experts say.

The Patient Protection and Affordable Health Care Act, signed into law on March 23, 2010, by President Barack Obama, provides a series of changes to take place to health care insurance coverage, Medicare, Medicaid, prescription drugs, quality improvement initiatives, medical malpractice, and other items. These are to be implemented from 2010 to 2014.

"The thing that is so big is the coverage for tens of millions of people who don't have health insurance now," says **Cecil Wilson**, MD, an internist in Winter Park, FL, and the president-elect of the American Medical Association in Chicago, IL.

People no longer will have to worry about losing health care coverage for existing diseases if they lose their jobs, and increasing numbers of people will have access to preventive care, primary care, and disease management, Wilson adds.

"Those are the big things that make this such a sea change in my opinion," he says. "For physicians, this is good because they won't have to worry about their patients' insurance being cut off, and thus putting their patients at risk."

Hospitals will find that significantly more patients will have health care coverage, resulting in a decline in uncompensated care, says **Caroline Steinberg**, vice president for trends analysis for the American Hospital Association of Washington, DC.

"We also would expect that demand for care from formerly uninsured patients will increase," Steinberg says. "Hopefully, we'll see some increases in primary care so by the time they hit the hospital they won't have some of the same kinds of problems they've had before."

The new bill provides billions of dollars in funding for clinics that provide primary care to uninsured, indigent, and immigrant patients. In 2014, it also expands Medicaid to all non-Medicare eligible individuals who have incomes up to 133% of the federal poverty level. These initiatives could help send more people to primary care services and keep them from using the emergency room for non-emergency care, Steinberg adds.

"We may [identify] more people with conditions that require specialty care because once people have access to coverage they tend to use more health care across all levels of the system," Steinberg says. "So that could go either way."

Plus, hospitals should expect the next few years to continue to be rough fiscally since most of the more significant provisions in the bill will not be fully implemented until 2014.

"Our hospitals are telling us that uncompensated care is going up because of job losses and loss of insurance, and these people show up in hospitals," Steinberg says.

There won't be much improvement in the immediate future until the economy recovers and the government provides more funding for Medicaid, she notes.

More oncology patients will have access to care, as a result of the bill's prohibition of lifetime limits on the dollar value of coverage, which begins Jan. 1, 2014. There is a temporary national high-risk pool to provide health care coverage to people with pre-existing medical conditions, which will be in place between June 2010 and 2014.

"Many cancer patients who need repeated courses of treatment can easily exceed their caps and find themselves unable to afford needed treatment and medication," says **Allen S. Lichter**, MD, chief executive officer of the American Society of Clinical Oncology (ASCO), in a statement issued after the bill was signed.

By this fall, insurers will not be able to exclude children with pre-existing conditions from being covered by their family policy, and this also is a positive move, Lichter says.

The bill's focus on prevention and wellness will benefit infectious disease and public health initiatives.

"There are a few things in the bill that we're pleased to see stay in the final version," says **Michael Ochs**, government relations associate with the Infectious Diseases Society of America (IDSA) in Arlington, VA.

The bill's emphasis on wellness and disease prevention with billions of additional federal dollars for these is one example, Ochs says.

The bill's impact on physician and other provider payments is a more mixed bag, however. *(See story on*

physician payments, below.)

"There's a 10% incentive pay for primary care and general surgery," says **Jason A. Scull**, program officer for clinical affairs at IDSA.

"They're focusing on primary care in a lot of these new innovative payment models, but I think primary care does need to be incentivized," Scull says.

But the drawback is that cognitive specialists, like infectious disease specialists, cardiologists, and neurologists, could be shortchanged as the pie is cut differently, but not expanded.

"There will be unintended consequences," Scull notes. "Already last year the Centers for Medicare & Medicaid Services [CMS] eliminated payments for consultation codes that cognitive specialties use to give them money to distribute elsewhere in the fee schedule and to send more to primary care physicians."

This redistribution of payments might result in fewer medical students choosing to spend extra years of training beyond their general internal medicine residency, he adds.

While the sweeping health care reform provides some specifics on how changes will occur in the industry, no one knows precisely how things will change until the regulatory details emerge, the experts say.

"There are a lot of moving pieces to this," Scull says. "I think it's anybody's guess to where all of this ends up." ■

Doctors will be more closely scrutinized with bill's provisions

Experts talk about bill's negatives

PAY ATTENTION TO THE NEW HEALTH CARE BILL'S REGulatory details, experts warn providers.

There are some items in the sweeping legislation that could result in more documentation, work, and risk for physicians and other providers.

For instance, the new bill makes it clear that the government wants doctors to be doctors and not own hospitals, says **LaDale K. George**, JD, a partner with Neal, Gerber, Eisenberg in Chicago, IL.

The bill puts a moratorium on any physician-owned hospitals in non-rural settings that were not Medicare providers as of December 2010.

"The new law says that the practice of physicians owning hospitals no longer is allowed," he explains. "If a physician owns or has a financial interest in a hospital and refers patients to that hospital then every service the patient receives at the hospital is a Stark violation of $25,000 per incident."

Also, the anti-kickback law has been changed by the new bill.

"The way the new act changes it is that it appears to eliminate the need to have actual knowledge or specific intent to violate the statute," George says. "It moves in the direction of where the Stark law is where if you do not meet the safe harbors in which providers can refer to one another and engage in commercial practices together then you will be viewed as being guilty."

From physicians' perspectives, some of the other requirements will be more onerous, particularly as far as documentation and accounting are concerned.

For instance, the bill's Physician Payment Sunshine Provision requires physicians to disclose every payment they receive from pharmaceutical and biotech companies in excess of $100, and this includes drug samples. This could prove to be an accounting problem for physician investigators and others.

This likely will be a headache to physicians, who will have to keep track of every sample they receive and every payment that flows through to them for research, George says.

The new health care bill also appears to give physicians incentives and/or penalties depending on their compliance with reporting data as part of the physician quality reporting initiative (PQRI), which was established with the 2006 Tax Relief and Health Care Act.

"What's clear is that Congress is moving into the direction of mandating physicians to participate in PQRI and also moving in the direction of mandating physician resource use reporting," says **Jason A. Scull**, program officer for clinical affairs at the Infectious Diseases Society of America.

"These are somehow merged into a value modifier that also will adjust payment based on the quality of care they provide," Scull says.

About one of six eligible physicians now makes the reports, and about half of these receive incentive payments, he adds. ■

Alternative Medicine Alert

2010 Reader Survey

In an effort to learn more about the professionals who read *AMA*, we are conducting this reader survey. The results will be used to enhance the content and format of *AMA*.

Instructions: Fill in the appropriate answers. Please write in answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2010.**

1. Are the articles in *Alternative Medicine Alert* written about issues of importance to you?

- O A. Always
- O B. Most of the time
- O C. Some of the time
- O D. Rarely
- O E. Never

In future issues of *AMA*, would you like to see more or less coverage of the following topics?

A. more coverage B. less coverage C. about the same amount

2. Acupuncture	O A	O B	O C
3. Biofeedback	O A	O B	O C
4. Chiropractic	O A	O B	O C
5. Dietary supplements	O A	O B	O C
6. Energy medicine	O A	O B	O C
7. Exercise	O A	O B	O C
8. Herbal therapies	O A	O B	O C
9. Massage therapy	O A	O B	O C
10. Meditation	O A	O B	O C
11. Nutrition	O A	O B	O C
12. Vitamins, minerals, amino acids	O A	O B	O C
13. Yoga/tai chi	O A	O B	O C

Please rate your level of satisfaction with the following.

A. excellent B. good C. fair D. poor

14. Quality of newsletter	O A	O B	O C	O D
15. Article selections	O A	O B	O C	O D
16. Timeliness	O A	O B	O C	O D
17. Length of newsletter	O A	O B	O C	O D
18. Overall value	O A	O B	O C	O D
19. Customer service	O A	O B	O C	O D
20. Quality of supplements	O A	O B	O C	O D

22. How would you describe your satisfaction with your subscription to *AMA*?

- O A. Very satisfied
- O B. Somewhat satisfied
- O C. Somewhat dissatisfied
- O D. Very dissatisfied

23. What is your specialty?

- O A. Family medicine
- O B. Internal medicine
- O C. Obstetrics/gynecology
- O D. Alternative medicine
- O E. Other _____

24. What degree do you hold?

- O A. Medical doctor/Doctor of osteopathy
- O B. Pharmacy degree
- O C. Doctor of naturopathy
- O D. Nursing degree
- O E. Other _____

25. On average, how much time do you spend reading each issue of *AMA*?

- O A. less than 10 minutes
- O B. 10-20 minutes
- O C. 21-30 minutes
- O D. 31-60 minutes
- O E. more than an hour

26. On average, how many articles do you find useful in *AMA* each month?

- O A. None
- O B. 1
- O C. 2
- O D. 3
- O E. All articles and clinical briefs

21. Do you plan to renew your subscription to *AMA*? O A. yes O B. no

If not, why? _____

27. To which other publications or information sources about complementary medicine do you subscribe?

28. Which publication or information source do you find most useful, and why?

29. Please list the top three challenges you face in your job today.

30. What do you like most about *AMA* newsletter?

31. What do you like least about *AMA* newsletter?

32. What issues would you like to see addressed in *AMA* newsletter?

33. Has reading *Alternative Medicine Alert* changed your clinical practice? If yes, how?

Contact information

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VOLUME 15, NUMBER 5 PAGES 9-10 MAY 2010

Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375: 735-742.

THERE IS LITTLE DISPUTE REGARDING THE beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increase incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events.

Maximize benefits of metform in DM2

Source: Brown JB, et al. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010;33:501-506.

TO DATE, CONTROLLED TRIALS INDICATE THAT no matter what pharmacotherapy is used to control glucose in type 2 diabetes (DM2), one can anticpate a progressive loss of control over time. Loss of efficacy is termed secondary failure: An initially effective medication later becomes insufficient to maintain control. It seems to me that this is too harsh an indictment of pharmacotherapy, since even if the medication continues with similar action over long time periods, confounders such as weight gain, inherent disease progression, and addition of confounding comorbidities might make it appear as if the medication is failing, when in reality, counterbalancing forces are increasing.

In any case, Brown et al performed an observational cohort study of DM2 subjects (n = 1799) initially treated with metformin monotherapy successfully (i.e., able to maintain an A1c < 7.0 without adding a second agent). Secondary failure was defined as either the addition of a second agent, or an increase of A1c above 7.0 while still on monotherapy. Subjects who required additional therapy within the first 6 months of metformin treatment were regarded as primary failure, and were excluded from this analysis.

In subjects able to maintain good control with initial metformin monotherapy, secondary failure occurred at a rate of 17% per year. Predictors of higher failure rates included longer duration of diabetes before treatment and higher baseline A1c at initiation of treatment. These data suggest that early initiation of treatment, especially when A1c is not yet markedly elevated, results in greater durability of metformin efficacy.

Prediabetes therapy and beta-cell function

Source: Hanley AJ, et al. Effect of rosiglitazone and ramipril on {beta}-cell function in people with impaired glucose tolerance or impaired fasting glucose. *Diabetes Care* 2010;33:608-613.

PREDIABETES (PDM) IS DEFINED AS EITHER impaired fasting glucose (FBG = 100-125 mg/dL), impaired glucose tolerance (IGT; 2-hour post-load glucose = 140-199 mg/dL), or supranormal but not diabetic A1c (A1c = 5.7-6.4). Untreated pDM predictably progresses to frank DM at a rate of about 7%-10% per year. Numerous interventions have been shown to alter the progression from pDM to diabetes, including diet, exercise, metformin, acarbose, orlistat, and thiazolidinediones; this year, nateglinide, an insulin secretagogue, was not confirmed to delay progression from pDM to diabetes.

Hopefully, treatments to prevent diabetes will also impact beta-cell function favorably, rather than simply compensate for progressive metabolic decline. The DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) randomized 5269 pDM subjects to ramipril and/or rosigliatoze. A substudy of DREAM (n = 982) had measurements of beta-cell function at baseline and periodically during the 3-year (median) follow-up, as well as measurements of progression from pDM to DM.

Subjects randomized to ramipril did not experience any meaningful change

in beta-cell function. In contrast, rosiglitazone-treated subjects enjoyed substantial improvements in beta-cell function. Benefits were less in pDM subjects who only manifest IFG compared with IGT or both.

In addition to reducing beta cells induced by glucotoxicity, thiazolidinediones lower free fatty acid levels, which may favorably affect beta-cell apoptosis.

Onychomycosis: Long-term follow-up

Source: Piraccini BM, et al. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010;62:411-414.

Although onychomycosis (ONCM) is often considered a cosmetic problem, some patients suffer significant disability due to foot pain, and difficulty wearing shoes. The treatment course for toenail ONCM is lengthy and costly. There are few data on long-term follow-up to ascertain recurrence rates, although prevailing opinion suggests recurrence is common.

Praccini et al performed a prospective study of ONCM patients (n = 73) who had been treated with pulse therapy (treatment 1 week/month for 6 months) with terbinafine or itraconazole. After clinical cure, subjects were prospectively followed for 7 years. Cure was defined as normalized clinical appearance and negative fungus culture.

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Patients were seen every 6 months during follow-up. Overall, recurrence developed in 16.4% of subjects. Each case of recurrence involved the same organism identified in the original infection. However, the recurrence rate for itraconazole was 3-fold greater than terbinafine. Terbinafine is widely regarded as the treatment of choice for toenail ONCM; this trial suggests superior durability of cure for terbinafine when compared with itraconazole.

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctible and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid homone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.