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INSIDE

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To D or Not to D?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

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

Synopsis: *The American Geriatrics Society has published guidelines on the use of vitamin D supplementation for the prevention of falls in the elderly, but some researchers are not on board with this.*

Source: American Geriatrics Society workgroup on vitamin D supplementation for older adults. Recommendations abstracted from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences. *J Am Geriatr Soc* 2013; Dec. 18. doi: 10.1111/jgs.12631. [Epub ahead of print].

THIS SUMMARY CONDENSES THE EFFORTS OF THE AMERICAN GERIATRICS Society (AGS) workgroup on vitamin D supplementation for the elderly into what the workgroup imagined would be bite-size, digestible nuggets for primary care providers (PCPs). It is a very dense report. The entire 38-page document is available for sale.[1] [*Disclaimer: I am a member of AGS, but did not have a hand in the development of these guidelines.*]

The recommendations begin with a brief review of how vitamin D is made. It is synthesized in the skin by way of exposure of cholesterol to ultraviolet B light, hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D], and then hydroxylated again to 1,25-dihydroxyvitamin D (D3). We get our vitamin D through sun exposure, by way of supplements, and through eating foods that are fortified with vitamin D.

The overall goal of the recommendations is to reduce injuries from falls attributable to low serum vitamin D levels. To achieve that goal, the workgroup reviewed the literature through 2010 and formulated six objectives:

• Develop clinical guidelines that address vitamin D intake from all sources.

• Set goals for 25(OH)D levels that correlate with reduced risk of falls and injuries, while avoiding toxicity.

• Strategize on how to obtain those levels.

• Develop clear guidelines for PCPs.

• Define at-risk groups of the elderly.

• Rate the various ways vitamin D levels are measured.

The recommendations are as follows: Every community dwelling senior (i.e., ≥ 65 years) and institutionalized older adults should be supplemented with at least 1000 international units (IU) daily. This should *always* be coupled with calcium (Ca++) supplementation; however, the workgroup did not specify an amount of Ca++. It did note that vitamin D doses < 600 IU do not prevent falls, and Ca++ doses in the studies reviewed were commonly 1000-1200 mg daily. Supplementation of an institutionalized older adult should be with a dose of vitamin D ≥ 1000 IU/d, plus Ca++.

Serum 25(OH)D levels should be > 30 ng/mL (75 nmol/L). The best way to achieve this is by reviewing all sources of vitamin D and keeping the total at 4000 IU. The authors include a table for individualizing the dose based on food intake, multivitamin use, unprotected sun exposure, obesity, and skin pigmentation. Individuals taking medications that bind vitamin D or increase its metabolism or have malabsorption syndromes may need their doses tweaked.

Routine measurement of 25(OH)D serum levels isn't necessary before beginning supplementation, nor after for monitoring, unless you are outside the recommended dose. If you decide to monitor anyway, wait until 4 months and measure at the midpoint between doses. You might want to monitor the people who show up in the table.

Vitamin D is available as ergocalciferol (D2) by prescription and cholecalciferol (D3) over-the-counter, and either form may be used. Vitamin D3 is derived from animal sources, possibly a problem for vegetarians. They differ in their pharmacokinetics; the maximal dosing interval for vitamin D2 is 2 weeks and vitamin D3 is 4 months. Because of its long dosing interval, vitamin D3 can be given daily, weekly, or monthly.

There were a number of warnings and "don't do this" statements. Don't prescribe once-yearly doses of either to get a patient through the winter. Don't use combination vitamin D/Ca++ tablets as the primary source of vitamin D, because the doses of vitamin D are too small and the tablets need to be dosed daily. The combination of a daily vitamin D/Ca++ tablet and a monthly vitamin D capsule may be a good compromise. Don't rely on cod liver oil, because of the risk of vitamin A toxicity at the dose needed for adequate vitamin D. Taking vitamin D with meals that contain oil is good; taking vitamin D with cholestyramine and high-fiber foods or supplements is not.

■ COMMENTARY

One thing I like about these recommendations is that the goal was outcome-based (preventing injuries), rather than biochemically-based. However, before adopting these guidelines, please read the following.

Things got a little murky in late 2013 and last month with the publication of four systematic reviews/meta-analyses and one study. Powe and colleagues' study noted the paradox of black Americans consistently having lower levels of total 25(OH)D than whites, while having higher bone mineral density (BMD) and a lower risk of fragility fractures.[2] These researchers measured levels of total 25(OH)D, vitamin D-binding protein, the parathyroid hormone, and BMD. They discovered that the average levels of both total 25(OH)D and vitamin D-binding protein were lower in blacks than in whites and concluded that

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the bioavailable vitamin D are similar. This study was followed by a systematic review of articles that measured the effect of 25(OH)D concentrations on non-skeletal health outcomes in adults.[3] The authors concluded, "Supplementation in elderly people (mainly women) with 20 µg [note: equivalent to 800 IU] vitamin D per day seemed to slightly reduce all-cause mortality," and speculated that low levels of vitamin D were not the cause of illness, but the result of inflammatory processes and a marker of illness.

Then, in April, came three articles. In the first two, published in *BMJ* on April 1, both systematic reviews and meta-analyses, Chowdhury et al concluded that vitamin D3 (but not vitamin D2, which may make things worse) supplementation "significantly reduces overall mortality among older adults," but cautioned against widespread supplementation.[4] Theodoratou et al concluded that there is no highly convincing evidence of a clear role of vitamin D for any outcome.[5] I do not think that *BMJ* publishes an April Fools' edition. You could argue that these two meta-analyses took on the very broad effects of vitamin D on health in general, and the AGS guidelines are focused on preventing falls in the elderly. You could argue that, except for the most recent April article, a trial sequential analysis by Bolland et al[6] which asserts that vitamin D does not reduce falls by 15% or more (the risk reduction threshold they set before they conducted the analysis) and thus, there is little reason to prescribe vitamin D.

This is exasperating! My advice? First, do no harm. If you want to prescribe vitamin D, follow the AGS's guidelines and avoid poisoning your patients. Use vitamin D3 because it's cheap, it may be safer than vitamin D2, and you can space out the doses. If you don't want to, you have several meta-analyses to back you up. ■

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Value of the Physical Examination in Heart Failure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the April 2014 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that physical examination signs of congestion are important prognostic indicators in the modern therapeutic milieu of congestive heart failure.*

Source: Caldentey G, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: Insights from the AF-CHF Trial (Atrial Fibrillation and Chronic Heart Failure). *JACC Heart Fail* 2014;2:15-23.

These investigators from the Montreal Heart Institute asked the question whether the physical examination was still of value in the modern era of heart failure management that includes the use of biomarkers and echocardiography. They employed the patient population in a trial of heart failure and non-permanent atrial fibrillation (AF) randomized to a rhythm control vs rate control strategies. The study showed no differences in outcome between the two groups. The physical examination findings were evaluated retrospectively and four signs were studied: peripheral edema, jugular venous distention (JVD), third heart sound, and pulmonary rales. The patients were followed for up to 6 years and the primary outcome was cardiovascular (CV) mortality. Secondary outcomes included all-cause mortality, heart failure-related mortality, sudden death, and heart failure hospitalizations. Of the 1376 patients enrolled, all but seven had data on all four of the physical exam findings. At enrollment, 31% had peripheral edema, 22% had JVD, 15% a third sound, and 13% had rales. Over a mean follow-up of 37 months, 32% died and 25% had at least one heart failure hospitalization. In the univariate analysis, all four of the physical findings were associated with increased CV mortality (hazard ratios [HRs], 1.5-1.9; all $P < 0.004$). On multivariate analysis up against laboratory tests and echocardiographic parameters, peripheral edema (HR, 1.25;

95% confidence interval [CI], 1.00-1.57; $P < 0.05$) and rales (HR, 1.4; 95% CI, 1.08-1.86; $P < 0.02$) remained predictive of CV mortality. Peripheral edema was independently associated with all-cause mortality and heart failure-related death. Rales were independently associated with heart failure-related death and hospitalization. JVD or a third heart sound were not independently associated with any CV outcome. The authors concluded that physical examination signs of congestion are important prognostic indicators in the modern therapeutic milieu of congestive heart failure.

■ **COMMENTARY**

In the current era where the serial use of echocardiography, brain natriuretic peptide levels, and measures of renal function are often the drivers of therapeutic decisions in heart failure management, it is interesting to see that signs of congestive heart failure on physical examination are still useful predictors of outcome. This study involved patients with left ventricular ejection fractions < 35% and heart failure symptoms within 6 months of enrollment. They were on modern therapy: 86% on angiotensin-converting enzyme inhibitors, 79% on beta-blockers, and 45% on aldosterone antagonists. However, it is not known how many had ventricular pacing. Also, the patients all had a history of non-permanent atrial fibrillation and some were on antiarrhythmic drugs such as amiodarone. Whether the results would apply to other less sick or less well treated populations is unknown, but previous studies would suggest that they would.

The major limitation of this study is that it is observational and cannot be adjusted for unknown confounders. For example, rales can be caused by lung disease; a third sound may be due to marked mitral regurgitation; and edema can be due to venous insufficiency. Also, this is a retrospective analysis of a study designed for another purpose, so it is difficult to know how well the physical examination was conducted. Unless each patient is put in the left lateral position and the bell of the stethoscope used, third heart sounds can be missed. In addition, JVD is notoriously hard to determine. Perhaps this is why rales and edema were more predictive than the third sound and JVD.

The new Accreditation Council for Graduate Medical Education mandated resident evaluation system emphasizes the attainment of milestones. At my institution, we are including the mastery of identifying these four physical findings as milestones that the residents should achieve. ■

Changes in Diabetes-Related Complications in the United States

ABSTRACT & COMMENTARY

By Jeff Unger, MD, ABFP, FACE

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Synopsis: *In diabetes-related complications in the United States from 1990-2010, the incidence of myocardial infarctions and death has decreased by 68%, stroke and amputation has declined by 50%, while end-stage renal disease has declined by 28%.*

Source: Gregg EW, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 2014; 370:1514-1523.

The authors used several population-based data sets to determine the incidence of lower-extremity amputation, end-stage renal disease, acute myocardial infarction (MI), stroke, and death from hyperglycemic crisis from 1990-2000. The data for the diabetes cohort were compared with age-matched controls within the non-diabetic population. The incident rates of all five complications declined from 1990-2010 in the diabetes population with the largest risk reduction observed in MI (-67.8%). Death from hyperglycemic crisis decreased -64.4%, while stroke and amputation declined -52.7% and -51.4%, respectively. End-stage renal disease decreased -28%. Interestingly, the rates of reduction for these comorbidities were significantly greater in the diabetes cohort than among adults without diabetes. Despite the observed improvement in long-term diabetes complications incidence, a large burden for clinicians persists. During the study period, the number diagnosed with diabetes tripled from 6.5 million to 20.7 million.

■ **COMMENTARY**

Let the celebration begin! Finally, patients with diabetes have cause to rejoice. Maybe, just maybe they can

live their lives without having to worry about losing a toe or having an acute MI while attending their grandchild's 2nd birthday party at the pizza parlor. Before we put away those blood glucose meters, we should ask ourselves a few insightful questions related to the future of diabetes care.

First, who is responsible for the improvement in long-term outcomes? The American Association of Clinical Endocrinologists (AACE) were quick to confirm to their members that this paper validated its own published comprehensive approach to diabetes management.[2] However, 90% of patients with diabetes are managed not by endocrinologists, but by primary care providers (PCPs), the vast majority of whom have never seen, read, or discussed the AACE or ADA guidelines for diabetes management. Perhaps PCPs and mid-level practitioners have become more ambitious and proficient in screening patients for diabetes. PCPs are introducing and titrating basal insulin sooner during the course of treatment. PCPs are being forced to intensively manage more patients with diabetes, as access to endocrine specialists is often difficult.

Second, new and novel drugs are being utilized to treat patients with diabetes. We are now focusing on getting patients to their prescribed target, while minimizing one's risk of weight gain and hypoglycemia. Thus, the use of GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and even disposable insulin delivery devices (patch pumps) have provided patients with safe, painless, and effective pharmaceutical agents.

I recently participated in a needs assessment for a CME provider and asked 300 PCPs how they choose a second-line therapy following metformin. More than 70% of the respondents said they simply reach into the sample cabinet and pull out the first drug that touches their hand. If this is the case, PCPs should be provided with additional training related to the disease mechanisms of type 2 diabetes. Type 2 diabetes results from eight specific defects. As such, we should be prescribing medications and promoting lifestyle interventions that could potentially reverse each of these defects. Managing diabetes should not be a crap shoot. We should employ "smart pharma bombs" in a pre-emptive attack to salvage the beta cell.

Third, 72 million Americans have prediabetes and 30% of these patients will progress to clinical diabetes every 3 years. We must place more emphasis on disease prevention as well as on racial disparities, health care accessibility, and means by which we can improve our management of obesity.

Diabetes is not going away anytime soon. In fact, by the year 2050, 30% of adults in the United States will have clinical diabetes. Enjoy the good news while you can. ■

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Pharmacology Update

Mixed Pollen Extract Sublingual Tablets (Oralair)

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

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

THE FDA HAS APPROVED THE FIRST MIXED POLLEN EXTRACT sublingual tablet as immunotherapy to treat hay fever. The extract contains common grasses in the United States (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass). The product is manufactured by Stallergenes S.A. in France and distributed by GREER Laboratories as Oralair.

Indications

The mixed allergen extract is indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or pollen-specific IgE antibodies for any of the five grass species in patients 10-65 years of age.[1]

Dosage

The recommended dose for ages 10-17 is 100 index of reactivity (IR) on day 1, 2 × 100 IR on day 2, and 300 IR

thereafter. For ages 18-65, the dose is 300 IR daily. The tablet is given sublingually, starting at least 12 weeks before the expected onset of each grass pollen season, and continued throughout the season.[1] The tablet should be placed under the tongue until completely dissolved for at least 1 minute, and then swallowed. The tablets should not be taken with food or beverage, and no food or beverage should be taken 5 minutes after dissolution. The first dose should be given under the supervision of a physician and the patient should be monitored for at least 30 minutes for possible severe systemic or local allergic reactions. The tablets are available as 100 IR and 300 IR. IR is based on skin reactivity and is tested for Bioequivalent Allergy Unit with Timothy grass pollen as the reference (Summary Basis).

Potential Advantages

The tablets provide a more convenient alternative to allergy shots and may have fewer systemic reactions.[3]

Potential Disadvantages

Sublingual administration may be less effective than subcutaneous injection.[3-6] The allergen extract can cause systemic allergic reactions (anaphylaxis) or severe local reactions (laryngopharyngeal swelling).[1] An epinephrine auto-injection should be prescribed to patients receiving these extracts. Patients taking medication that may counteract the effect of epinephrine (e.g., beta-blockers, alpha-adrenergic blockers) should not be prescribed the allergen extract. The extract is contraindicated in patients with severe, uncontrolled asthma or a history of any severe systemic reactions. Common adverse events (vs placebo) in adults are oral pruritus (25% vs 5%) and throat irritation (22% vs 4%).

Comments

The efficacy of mixed pollen extract was evaluated in five double-blind, placebo-controlled trials of which four were natural field studies and one an environmental exposure study.[1] Three of the natural field studies were for one season and one was for three seasons. In the 1-year studies, subjects were randomized to the mixed allergen extract or placebo starting 4 months before the grass pollen season and throughout the season. The primary endpoints included the daily Rhinoconjunctivitis Total Symptom Score ([RTSS], range 0-18, sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular symptoms), daily Rescue Medication Score (RMS, range 0-3, antihistamines = 1, nasal steroids = 2, oral steroid = 3), and the daily Combined Score (CS) equally weighing symptom and rescue medications. In the U.S. adult study, daily CS was reduced by 28% (95% confidence interval [CI]; -43 to -13), RTSS, -23% (-38 to 7.5), and RMS - 47% (-74 to -19). For the European adult study, results were -30%, -29%, and -30%, respectively. For children and adolescents, results were -30%, -31%, and -30%. In the long-term study, reductions in the CS were -16% for year 1, and -38% in years 2 and 3. In the allergen environmental chamber study, subjects were challenged with four of the five allergens for 4 hours. Mixed pollen extracts showed a reduction of RTSS by 29% compared to placebo. The FDA criteria for efficacy of the extracts are reduction of CS at least 15% and the 95% CI upper limit of -10%.[2]

Clinical Implications

The mixed allergen extract tablets provide an effective and more convenient form of immunotherapy for hay fever. The relative effectiveness of sublingual vs subcutaneous immunotherapy is not completely clear. Some studies suggest that sublingual is less effective than subcutaneous, while a systematic review suggests that Oralair is at least non-inferior to subcutaneous administration.[7] The wholesale cost for Oralair is $300 for a 30-day supply. ■

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CME Questions

1. **Choose the correct recommendation from the American Geriatrics Society for prescribing vitamin D supplementation.**
   a. Vitamin D supplementation should always be coupled with calcium supplementation.
   b. Every community-dwelling senior should be supplemented with at least 1000 mg daily.
   c. Never begin supplementation of vitamin D without first measuring 25(OH)D serum levels.
   d. Vitamin D2 is favored because it is more effective than vitamin D3.
   e. Because of its long dosing interval, vitamin D3 can be given yearly.

2. **Which physical examination findings are most predictive of cardiovascular mortality in heart failure patients?**
   a. An enlarged apical impulse and a systolic murmur
   b. Hepatojugular reflux and a fourth heart sound
   c. Jugular venous distention and a third heart sound
   d. Pulmonary rales and peripheral edema

3. **Regarding the trend in long-term diabetes-related complications from 1990-2010, which statement is *false*?**
   a. Retinopathy has declined by 32% in patients with diabetes.
   b. The largest decline in long-term complications was noted in myocardial infarctions.
   c. The incidence of acute renal failure declined 28%.
   d. Although the incidence of complications is declining, the prevalence of diabetes is on the rise, implying that the frequency of long-term complications may accelerate in the future.

CME Objectives

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

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

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AMERICAN OSTEOPATHIC ASSOCIATION

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

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Colorectal Cancer Screening Through Stool DNA

Source: Imperiale TF, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014;370: 1287-1297.

In their most recent guidance on colon cancer screening (CCS), the American Cancer Society indicated that although a diversity of testing methods are available, since numerous patients are declining to be screened, "the best screening test is the one you can get done." This posture is an effort to reduce the number of unscreened persons, since when discovered early, most colon cancer is curable.

Stool DNA testing is not new. However, head-to-head clinical trials in the past decade have indicated that when compared to colonoscopy, sensitivity for detection of colon cancers and adenomas by older methods of stool DNA testing is lower. Stool DNA CCS is predicated on the fact that mutated and cancerous colonic epithelial cells are consistently excreted daily in the stool, even more commonly than blood is found. DNA panels for CCS, in theory, should be comparable to invasive screening methods, since abnormal DNA should be readily identifiable, and confirmatory colonoscopy and resection should follow. The tepid reception provided to CCS by the public is understandable: Many are put off by the preparation, expense, and inconvenience of colonoscopy. Additionally, in recently published clinical trials of persons undergoing screening colonoscopy, only a small percent actually harbor a cancer or advanced neoplasia (approximately 100 out of 3000 screenees), so it is easy to see why most folks will be correct when they think "it's probably not me."

Over the last decade, screening panels for stool DNA have been improved. Imperiale et al compared screening by fecal immunochemical testing (FIT) with stool DNA testing, based on a single stool sample for each, followed by colonoscopy in all patients, regardless of screening results.

Sensitivity for colon cancer was superior by DNA stool testing (92.3% vs 73.8%); similarly, sensitivity for high-grade dysplasia favored stool DNA testing (69.2% vs 46.2% sensitivity).

A positive FIT should lead to diagnostic colonoscopy; incorpration of stool DNA testing, when positive, might rightfully provide even further motivation. ■

Weight-Loss Surgery: Matching Expectations with Realities

Source: Li Z, Heber D. Managing weight loss expectations: The challenge and the opportunity. *JAMA* 2014;311: 1348-1349.

The degree of success of weight-loss surgery (WLS) for improvement in metabolic derangements such as type 2 diabetes is impressive. Bariatric surgery has even been associated with improved mortality in morbidly obese individuals. Not everyone, however, enjoys the same degree of weight loss, and even though the endpoint of WLS in the minds of clinicians may be improvements in metabolic status and cardiovascular risk, in the minds of patients, the primary endpoint may be more cosmetically oriented. That is, just how much weight am I going to lose?

To better understand the expectations of WLS patients, Li and Heber interviewed patients seeking WLS and asked them (preoperatively) questions to better understand how much weight they expected to lose, the minimum weight loss with which they would not be disappointed, and how much risk they were willing to bear as part of WLS.

On average, patients expected to lose 38% of their weight; the Swedish Obesity Study found that 75% of gastric banding patients lost < 20% of their weight. Even though almost all (84.8%) of the WLS patients understood and accepted that there was a risk of dying from surgery, about one-third of these would no longer be willing to shoulder that risk if the weight loss was only 20%.

WLS has confirmed sustained metabolic and even mortality benefits. However, clinicians must confirm that patients concretely understand these parameters before embarking on such procedures, since some patients may no longer be willing to undertake risk if personally disappointing weight loss results were to occur. ■

In Future Issues:

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