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ABSTRACT & COMMENTARY

Is There a Connection Between Vitamin D and Fracture Prevention?

By David Fiore, MD

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

SYNOPSIS: After conducting an extensive investigation, researchers did not find that vitamin D prevents falls or fractures.

SOURCE: Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: A systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 2018; Oct 4. pii: S2213-8587(18)30265-1. doi: 10.1016/S2213-8587(18)30265-1. [Epub ahead of print].

Falls are a common and devastating risk for elderly patients. More than one-third of people older than age 70 fall annually.[1] Often, these falls cause fractures (most commonly in the hip), with more than a quarter of a million hip fractures occurring in the United States annually (most commonly in elderly women).[2] The role, if any, vitamin D and calcium play in preventing fractures has been an area of intense interest for years, with evidence for and against supplementation. Bolland et al attempted to address the issue of vitamin D supplementation and musculoskeletal health using a meta-analysis with "trial sequential analysis" (TSA). Sequential analysis is a statistical technique developed during World War II to expedite materials and weapons production while maintaining quality through sequential testing rather than predetermined sampling, which requires more samples. In medical studies, this technique allows investigators to assess outcomes periodically throughout a trial to predetermine thresholds for significance at various points in the trial rather than setting a large sample size a priori before the trial starts. Recently, this technique has been modified for use in meta-analyses as a tool to assess the statistical reliability as more studies with varying size and quality are added.[3]

Bolland et al found 81 trials with 55,537 participants that concerned the effect of vitamin D and/or calcium on several outcomes. The coprimary endpoints for this trial were at least one fracture,

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at least one hip fracture, and at least one fall. The authors presented multiple comparisons and subgroup analyses without finding a benefit of vitamin D or calcium supplementation, including high-dose vs. low-dose supplementation. The use of TSA allowed the authors to assess the effect at predefined estimates of potential benefit (or "futility boundaries") of 15%, 10%, and 5%. They did not find that there was benefit at any of these levels.

This meta-analysis is in agreement with the U.S. Preventive Services Task Force (USPSTF) guideline on vitamin D and calcium supplementation for primary prevention of fractures in community-dwelling adults as well as with a Cochrane Review on this subject.[4,5] Both the USPSTF guideline and the Cochrane Review failed to find evidence for a benefit of vitamin D or calcium for the prevention of fractures in those who have not sustained a prior osteoporotic fracture. Unfortunately, Bolland et al did not assess the efficacy of supplementation as secondary prevention for those who have already sustained a fracture.

■ COMMENTARY

In light of this extensive review of the literature on vitamin D supplementation, which revealed no evidence of benefit for preventing falls or fractures, and its agreement with other studies and guidelines, it is time to move away from testing average-risk elderly patients for "vitamin D deficiency" and recommending supplementation (notably, even the Endocrine Society recommends against routine screening and supplementation).[6] Patients should be advised to eat foods rich in vitamin D and calcium. Further, patients should safely expose themselves to adequate sunlight and engage in regular weight-bearing exercise as part of a healthy lifestyle, which will help protect them from future fractures. ■

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ABSTRACT & COMMENTARY

Neighborhood Socioeconomic Status Associated With Infection Risk, But Not Sepsis

By Betty Tran, MD, MSc

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

SYNOPSIS: Based on a large, national, prospective cohort study, lower neighborhood socioeconomic status was associated with a higher incidence of hospitalizations for infection (but not sepsis) at presentation.

SOURCE: Donnelly JP, Lakkur S, Judd SE, et al. Association of neighborhood socioeconomic status with risk of infection and sepsis. *Clin Infect Dis* 2018;66:1940-1947.

Community or neighborhood factors play a key role in determining outcomes in many diseases and overall health.[1-3] In addition, other investigators have reported that lower neighborhood socioeconomic status (nSES) is associated with increased sepsis hospitalizations and sepsis-related mortality, although these studies were localized to a specific city/state or used imprecise measures of nSES.[4-6]

Using prospectively gathered data from a study called the REasons for Geographic and Racial Differences in Stroke (REGARDS), a national cohort of more than 30,000 community-dwelling adults > 45 years of age with intentional oversampling of blacks and individuals from the southeast United States, Donnelly et al sought to examine further the association between nSES and hospitalization for infection and sepsis. nSES was summarized by a score comprised of several factors including: percentage of adults who completed high school and college; percentage of participants who work in professional, executive, or managerial jobs; median household incomes; median home value; and percentage of households receiving rental fees, interest, or dividends.

Regarding outcomes, ED visits and hospital admissions for serious infection were identified by trained abstractors. These abstractors reviewed medical records to confirm the existence of infection on first presentation as one reason for admission, with additional adjudication with physician review (if needed). There was excellent interrater agreement for presence of serious infection (Kappa = 0.92).

Hospitalizations for sepsis were defined as infection with two or more sepsis-related organ failure assessment (SOFA) score points. Additionally, hospitalizations for infection with two or more systemic inflammatory response syndrome (SIRS) criteria and two or more "quick" SOFA (qSOFA) criteria also were identified. Ten-year infection incidence per 1,000 person-years was examined across quartiles of nSES, with adjustment for several confounding factors (chronic kidney disease, age, race, education, sex, chronic lung disease geographic region, stroke, hypertension, alcohol use, smoking, myocardial infarction, and high-sensitivity C-reactive protein). The effects of potential mediators on the associations also were evaluated, including: individual income, physical weakness (based on the physical composite score on the 12-Item Short-Form Health Survey), self-reported exhaustion and physical activity, obesity, and diabetes.

The authors included 26,604 participants in the analysis. They observed significant variation among the nSES components across nSES quartiles. Participants in the lowest nSES quartile were disproportionately smokers, female, black, and nonusers of alcohol. Additionally, such subjects were disproportionately from the Stroke Belt, earned less annual income than others, had attained less education, and were more likely to present with comorbidities, abnormal biomarker labs, and reduced functional status.

After adjusting for participant characteristics, Donnelly et al noted that infection incidence was 0.84-fold lower for the highest quartile vs. lowest quartile of nSES. However, after adjustment, the authors noted no association between quartiles of nSES and sepsis incidence as defined by SOFA or qSOFA scores. Donnelly et al found that comorbid diabetes, physical weakness, and participant income produced modest (at least 10%) indirect effects on the association between nSES and infection risk.

Overall, infection type was similar across nSES quartiles, with respiratory infections listed as the most common. Median length of stay was longer for participants in the lowest nSES quartile, but the authors found no significant differences in SOFA scores or percentages of in-hospital death among nSES quartiles.

■ COMMENTARY

Donnelly et al have expanded on prior efforts to explore the complex association between social determinants of health and risk of hospitalization for infection and sepsis. Compared to prior studies, the Donnelly et al investigation features several strengths. First, data were collected prospectively as part of a national cohort. Second, the definition of nSES used was much more granular, based on census block groups and incorporating multiple domains as opposed to a single proxy such as insurance status.[6] Outcomes were measured more accurately based on medical abstraction and published criteria for sepsis (e.g., SOFA scores) as opposed to ICD-9 codes.[4] Third, follow-up was fairly extensive at 10 years. Finally, the mediating role of several factors was examined, providing hypotheses for further explorative and intervention-based studies. For example, individual income was found to mediate the association between nSES and infection risk, suggesting factors such as social isolation, reduced food availability, and lack of transportation may be targeted areas that could reduce hospitalizations for infection.

Overall, no association was found between nSES and sepsis incidence, to the extent that hospitalizations for infection may portend future hospitalizations for sepsis. However, the findings from this study support the premise that improving sepsis outcomes might be achieved outside of focusing exclusively on inpatient care by way of improvements in decreasing healthcare

disparities that result in infection hospitalizations. This could include social interventions such as improving safe transportation options as well as improved aggressive medical management of chronic diseases such as diabetes. As such, findings from this study are a helpful reminder for us to think outside the box in our attempts to improve sepsis outcomes. ■

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ABSTRACT & COMMENTARY

Who Really Needs Intensive Blood Pressure Control?

By Michael H. Crawford, MD

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

SYNOPSIS: A patient baseline characteristics level analysis of the SPRINT and ACCORD trials resulted in the creation of a simple algorithm for identifying high-risk patients who experienced fewer major cardiac events without increased serious adverse events from intensive blood pressure therapy.

SOURCE: Wang S, Khera R, Das SR, et al. Usefulness of a simple algorithm to identify hypertensive patients who benefit from intensive blood pressure lowering. *Am J Cardiol* 2018;122:248-254.

Recent large randomized trials have driven a move toward more aggressive blood pressure (BP) control. However, the downsides to such an approach have been downplayed.

Investigators from Dallas sought to develop an algorithm that would inform physicians about which patients were most likely to benefit from intensive BP lowering using patient-level data from two large randomized trials: SPRINT and ACCORD. The authors of both trials compared intensive treatment (systolic BP < 120 mmHg) to standard treatment (systolic BP < 140 mmHg) but enrolled different patient populations. In both trials, investigators enrolled about 10,000 patients, all diabetic in ACCORD and all nondiabetic in SPRINT. All available patient characteristics were included in developing the risk prediction model. The primary outcome was major adverse cardiovascular events (MACE).

In SPRINT, a subset of patients with high MACE was used to develop a decision tree that was tested on the remaining lower MACE risk patients (n = 8,357) and in 2,258 ACCORD patients in the standard glycemic control group. A decision tree model using three variables (age > 74 years, urinary albumin to creatinine ratio > 34, and history of clinical cardiovascular disease) identified 49% of SPRINT patients and 55% of ACCORD patients considered high risk for MACE. Intensive BP lowering reduced MACE in these high-risk patients in SPRINT (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.52-0.85) and ACCORD (HR, 0.67; 95% CI, 0.50-0.90), but not in the remaining lower-risk patients (SPRINT: HR, 0.83; 95% CI, 0.56-1.25; ACCORD: HR, 1.09; 95% CI, 0.64-1.83). Importantly, intensive BP therapy in the high-risk group did not increase the risk of serious adverse events. The authors concluded that this simple three-factor risk prediction model identified high-risk patients with systolic hypertension in whom the benefits of intensive therapy outweighed the risks.

■ COMMENTARY

One of the criticisms of the SPRINT study was the increased incidence of renal insufficiency and orthostatic symptoms in the intensive treatment arm. There was legitimate concern that older patients with stiff blood vessels would experience more harm than benefit. Also, the overall results of ACCORD suggested that there was no difference in MACE between the standard

and intensive arms of the study. Thus, some clinicians ignored SPRINT and the new guidelines it spawned. The hypothesis of the Wang et al study was that perhaps there is a high-risk group among the SPRINT and ACCORD patients who would benefit from more aggressive targets. The investigators analyzed the myriad clinical data in both trials and discovered a simple decision tree model that identified a high-risk group that benefited from intensive therapy in both trials. Also, intensive therapy did not increase the risk of serious adverse events in this same high-risk group.

The differences in four-year MACE were impressive. In SPRINT, 9.5% of the high-risk group experienced a MACE compared to 2.9% of lower-risk patients. In ACCORD, MACE was 11.5% in the high-risk group and 4.3% in the rest. The number needed to treat (NNT) was 39 in high-risk SPRINT patients and 29 in high-risk ACCORD patients. In the lower-risk SPRINT patients, the NNT was 244 but was not calculable for lower-risk ACCORD patients since the HR was > 1.0. The degree of BP-lowering in the high- and lower-risk patients in both trials was equivalent, so a treatment effect difference does not explain the results. Serious adverse events were not higher in the high-risk groups but were higher among lower-risk patients (HR, 1.16; 95% CI, 1.03-1.3). This risk predictor is unique because it targets patients with hypertension, not the general public. SPRINT and ACCORD patients already were a higher-risk group among hypertension patients. Despite this, further risk stratification was possible. Also, the new algorithm does not require extensive data. The only unusual aspect of the algorithm is the urine albumin to creatinine ratio, which clinicians usually do not obtain from hypertensive patients without chronic kidney disease. However, it is an inexpensive, easy-to-conduct test.

The major limitation to this study is that it was a retrospective analysis of two trials that only included higher-risk patients. Thus, we do not know if the new algorithm would perform as well in low-risk hypertensive patients. Also, only simple clinical and laboratory data were included in the trial databases. No sophisticated cardiovascular imaging or stress testing was available consistently; consequently, those were not included. It is possible that these more sophisticated and expensive tests would further stratify patients.

At this juncture, I agree with the authors. Despite the limitations of this study, this new algorithm and other insights potentially could inform hypertension management decisions. At the least, the concept that among hypertensive patients there are higher-risk patients who should have lower BP targets seems established. Exactly how to identify these higher-risk patients is evolving. ■

PHARMACOLOGY UPDATE

Human Papillomavirus Vaccine (Gardasil 9)

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

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

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

The FDA has approved a supplemental application to expand the indication for human papillomavirus 9-valent vaccine (HPV-9) to include men and women 27-45 years of age. HPV-9, a noninfectious recombinant vaccine, is distributed as Gardasil 9. The vaccine covers nine HPV types that are responsible for 90% of HPV-related cancers. Previously, the vaccine was approved for males and females 9-26 years of age.[1]

INDICATIONS

HPV-9 is indicated for women 9-45 years of age to prevent anal, cervical, vaginal, and vulvar cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; genital warts (acuminate, condyloma) caused by HPV types 6 and 11; and dysplastic or precancerous lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. These include cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS); anal intraepithelial neoplasia (AIN) grades 1, 2, and 3; CIN grade 1; vulvar intraepithelial neoplasia (VIN) grades 2 and 3; and vaginal intraepithelial neoplasia grades 2 and 3.[2]

HPV-9 is indicated for men 9-45 years of age to prevent anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58; genital warts (acuminate, condyloma) caused by HPV types 6 and 11; dysplastic or precancerous lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and AIN grades 1, 2, and 3.

DOSAGE

Recommended dose for patients age 9-14 years: a two-dose regimen (initially and six to 12 months later) or a three-dose regimen (initial and two to six months).[2]

For patients 15-45 years of age, a three-dose regimen is recommended. HPV-9 is available as a single-dose vial or prefilled syringe (0.5 mL).

POTENTIAL ADVANTAGES

The FDA's supplemental approval of HPV-9 expands the coverage of nine HPV types up to age 45 for men and women, thus potentially expanding the eradication of HPV-associated cancers.

POTENTIAL DISADVANTAGES

While the vaccine protects against the types of HPV that cause oropharyngeal cancer, effectiveness in preventing this common cancer in men has not been established and is not approved for preventing this cancer.[3] Preliminary data suggest a lower prevalence of oral infections of HPV types covered by the vaccine.[3] The persistence of immune response to HPV-9 has not been established.[3]

COMMENTS

The efficacy of HPV-9 for its expanded indication was based on a study of HPV-4 in 3,253 women 27-45 years of age.[2] The study comprised two phases: a base study and a long-term study extension. In the base study, there was a median follow-up of 3.5 years after the three-dose regimen. Women were randomized to HPV-4 or adjuvant control. The endpoint was a combined outcome of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. Vaccine efficacy was 87.7%, driven primarily by reduction of persistent infection. Efficacy against genital warts or cervical dysplasia was 95%.

In the extension phase (median of 8.9 years; n = 600), no cases of CIN or genital warts were observed. Effectiveness in men was inferred from data in women and immunogenicity data in men (n = 150) 27-45 years of age.

In a cross-study analysis, the ratio of geometric mean titer ranged from 0.72 to 0.82 for those 27-45 years of age relative to those 16-26 years of age. HPV-9 has been shown to be noninferior to HPV-4 in terms of immune response to HPV types 6, 11, 16, and 18 and 88-99% effective in preventing the additional five HPV types vs. HPV-4.

CLINICAL IMPLICATIONS

Based on data collected between 2011 and 2015, about 42,700 new cases of HPV-associated cancer occurred in the United States each year.[4] Cervical cancer was most common among women and oropharyngeal cancer among men. The authors of the National Health and Nutrition Examination Survey 2013-2014 reported the prevalence of vaccine type HPV among women 18-59 years of age was 5.5%.[5] In contrast, the prevalence in men in the same age range was 15.1%.[6] The expanded indication widens the eligible population for vaccination against HPV-associated cancers. However, one concerning finding was that among vaccine-eligible men, only 10.7% were vaccinated vs. 31.5% of eligible women.[7] Significant progress in eradication can be accomplished only if the expanded indication is coupled with a higher vaccination rate.[7] The cost for a three-dose regimen is $614.61. ■

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CME QUESTIONS

1. **Based on the Bolland et al study, what is the recommended dose of vitamin D supplementation for elderly women?**
   a. 400 IU daily
   b. 800 IU daily
   c. 50,000 IU monthly
   d. Supplementation is not recommended

2. **Based on the study by Donnelly et al, neighborhood socioeconomic status is associated with which of the following?**
   a. Hospitalization for infection
   b. Hospitalization for sepsis
   c. Hospitalization for septic shock
   d. All of the above

3. **In the study by Donnelly et al, which of the following was *not* found to be a modest (at least 10%) mediator in the association between neighborhood socioeconomic status and infection risk?**
   a. Diabetes mellitus
   b. Income level
   c. Obesity
   d. Physical weakness

4. **Systolic blood pressure targets should be lower in patients with:**
   a. known cardiovascular disease.
   b. age > 74 years.
   c. urinary albumin to creatinine ratio > 34.
   d. All of the above

CME OBJECTIVES

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

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

[IN FUTURE ISSUES]

Infections Associated With Travel to the United States

Primary Headaches: Look, Listen, and Diagnose Rather Than Image

Prophylactic Antibiotics for Acute Aspiration

Internal Medicine [ALERT]

ECG Review

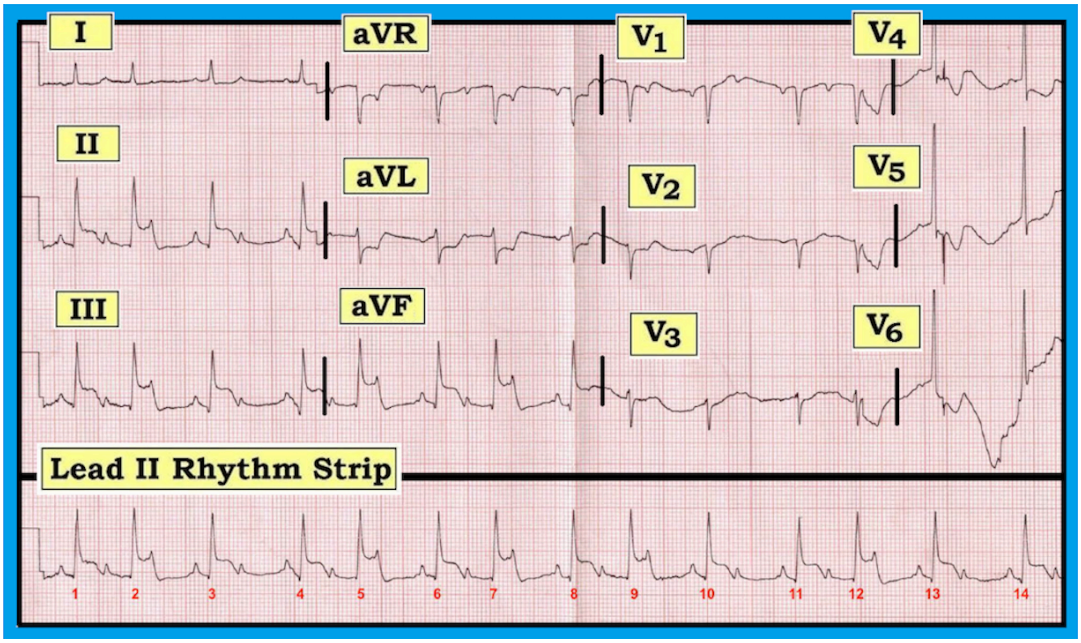
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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

Identify 4 Major Findings in New-onset Chest Pain Patient

The ECG in the figure below was obtained from a patient with new-onset chest pain. He was hemodynamically stable at the time this tracing was obtained.



In addition to the artifact that is most pronounced in the lateral chest leads, there are four major findings. Admittedly, two findings are subtle. How many findings can you identify? The ventricular rhythm is fairly rapid and irregular. Clearly, atrial activity is present. Use of calipers would be the easiest way to confirm that P waves are regular. Since the QRS complex is narrow, the mechanism of the rhythm is supraventricular. If one steps back from the tracing, it should be apparent that there is a repetitive pattern (group beating) for QRS complexes, with alternating groups of one or two beats. That said, at this point in the interpretation process, one could defer further assessment of the rhythm until after studying the rest of the 12-lead ECG.

Finding 1. The most obvious finding on this ECG is the presence of ST-segment elevation in each inferior lead, with reciprocal ST-segment depression in lead aVL. In a patient with new-onset chest pain, this is diagnostic of acute inferior ST-segment elevation myocardial infarction (STEMI).

Finding 2. QRS amplitude is higher in the lateral chest leads. The presence of an R wave ≥ 18 mm in lead V6 satisfies voltage criteria for left ventricular hypertrophy (LVH). Although difficult to tell due to artifact, the ST-T waves in leads V5 and V6 suggest repolarization changes of LV "strain."

Finding 3. In addition to acute inferior infarction, one might suspect there is acute posterior MI. Usually, acute posterior MI is recognized by anterior ST-depression. It is possible the upright ST-T waves seen so commonly in the anterior leads of patients with LVH attenuated the anterior ST depression and that this is the reason anterior ST-T waves are so uncharacteristically flat.

Finding 4. Second-degree AV block and Mobitz Type I (AV Wenckebach) with alternating 3:2 and 2:1 AV conduction. The most common cause of group beating in association with acute inferior STEMI is Mobitz I second-degree AV block. If one focuses within the groups of two beats (i.e., beats #1-2, 4-5, 6-7, 8-9, and 11-12), it should be apparent that the PR interval increases until a beat is dropped. Then, the cycle begins again.

For further discussion on and more information about this case (including a laddergram that demonstrates the mechanism of the arrhythmia), please visit: https://bit.ly/2OxxHLy.