

Internal Medicine

Evidence-based summaries of the
latest research in internal medicine

[ALERT]

ABSTRACT & COMMENTARY

Should the Physician Go Where the Sun Does Not?

By *Rahul Gupta, MD, MPH, FACP*

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

SYNOPSIS: In a meta-analysis of multiple prospective cohort studies, the lowest vitamin D metabolite (25-hydroxyvitamin D) quintile was associated with increased all-cause mortality, cardiovascular mortality, and cancer mortality.

SOURCE: Schöttker B, et al. Vitamin D and mortality: Meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. *BMJ* 2014;348:g3656.

Vitamin D is well known as the primary regulator of mineral and bone density. In addition to the key role it plays in the maintenance of musculoskeletal health, vitamin D has also emerged as a regulator of several non-skeletal systems' cellular processes, including immune, cardiovascular, and metabolic systems.¹ While it can be obtained through supplements and food supply, the main source of vitamin D remains endogenous through its production in the skin under the influence of solar ultraviolet B (UVB) radiation. The most commonly measured vitamin D metabolite is serum 25-hydroxyvitamin D (25(OH)D) because of its longer half-life (about

3 weeks) and up to 1000-fold higher serum levels compared with the physiologically active metabolite 1,25-dihydroxyvitamin D (half-life of a few hours). Studies have shown that since UVB exposure varies with the latitude of regions across the globe during the year, the mean 25(OH)D concentrations of populations also correspondingly fluctuate.² Ecological studies have suggested that mortality from several potentially life-threatening diseases such as cancer, cardiovascular diseases, and diabetes mellitus would increase with increasing latitude, in other words, with residence increasingly distant from the equator.³ Such data question the role of solar UVB radiation and vitamin D in reducing

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Meda Pharmaceuticals, Novartis, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

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Internal Medicine Alert.
ISSN 0195-315X, is published monthly by AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.
www.ahcmedia.com

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304
and at additional mailing offices.

POSTMASTER: Send address changes to Internal Medicine Alert,
P.O. Box 550669,
Atlanta, GA 30355.

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the risk of a large number of cancers and other chronic illnesses. However, it is unclear if and to what extent such influences on production and maintenance of sufficient vitamin D concentrations affect the prognostic association of low 25(OH)D concentrations with mortality.

To conduct their meta-analysis, Schöttker et al collected data from seven population-based cohorts from the United States and across Europe. All cohorts included a total of 26,018 men and women and all age groups (50-79 years), with the exception of one study that only recruited in the age range 70-79 years. The median follow-up time in individual cohorts varied between a little over 4 to almost 16 years, during which 6695 study participants died, including 2624 deaths from cardiovascular diseases and 2227 deaths from cancer.

Researchers found that the all-cause mortality was 1.57-fold higher (95% confidence interval, 1.36-1.81) among participants in the lowest quintile of serum vitamin D levels than among those in the highest quintile. Results were similar for cardiovascular-related mortality in patients with and without known cardiovascular disease (risk ratios, 1.7 and 1.4, respectively) and for cancer-related mortality in patients with histories of cancer (risk ratio, 1.7) but not in those without prior cancer. Analyses in which data were stratified by risk factors for vitamin D deficiency yielded similar results. No strong age, sex, season, or country-specific differences could be detected.

■ COMMENTARY

Reports from across the world indicate that hypovitaminosis D is widespread and is re-emerging as a major health problem globally.⁴ There may be several causes of vitamin D deficiency, including decreased dietary intake or absorption, reduced solar UVB exposure, reduced endogenous synthesis (reduced hydroxylation in liver and/or kidneys), end-organ resistance, or increased hepatic catabolism. In their meta-analysis, Schöttker et al found that people with the lowest 20% of vitamin D levels had almost 1.6 times increased mortality compared to people in the top 20%. Furthermore, there appeared

to be a dose response relationship, in that the highest mortality was found in people with the lowest vitamin D levels, and mortality rate decreased as vitamin D levels rose. However, these results are from epidemiological studies. This means that causation cannot be shown. It could be possible that factors such as preexisting medical conditions could have caused participants to stay indoors, thereby reducing the amount of time spent outside in the sun. The question of causality could be best answered by conducting randomized, controlled trials and some of these are ongoing.

Until we know more, it would be most optimum to follow current recommended guidelines for vitamin D supplementation, which themselves seem to have no clear consensus on the ideal cutoff values for vitamin D deficiency. According to the Institute of Medicine, a recommended daily allowance of 600 IU/d for ages 1-70 years and 800 IU/d for ages \geq 71 years, corresponding to a serum 25(OH)D level of at least 20 ng/mL (50 nmol/L), meet the requirements of at least 97.5% of the population.⁵ This recommendation assumes minimal sun exposure. However, other experts suggest a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults. Eventually, there may come a day when, supported by evidence, physicians across the globe may be prescribing varying doses of vitamin D supplementation based on geographic region, sex, and season. For now, we should pick one national recommendation on vitamin D supplementation and stick to it. ■

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ABSTRACT & COMMENTARY

Does Gluten Cause Health Problems in Patients Without Celiac Disease?

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: Gluten is a protein complex that may be inflammatory to humans and is increasingly recognized as a possible cause of numerous health problems such as irritable bowel syndrome, fibromyalgia, skin conditions, allergies, autoimmune arthritis, and neurodegenerative conditions.

SOURCE: Volta U, et al. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* 2014;12:85.

These Italian investigators enlisted 38 clinical sites (27 adult gastroenterology, 5 internal medicine, 4 pediatrics, and 2 allergy) to distribute a questionnaire aimed at identifying patients with health problems possibly associated with non-celiac gluten sensitivity. A total of 486 patients were identified over a 1-year period, most were female and the mean age was 38 years. The clinical symptoms associated with gluten were a variety of gastrointestinal (GI) complaints: abdominal pain, bloating, diarrhea and/or constipation, nausea, epigastric pain, GERD, and aphthous stomatitis. Other complaints included fatigue, fibromyalgia, headache, joint and muscle pain, “foggy mind,” dermatitis or skin rash, depression, and anxiety. The most frequent diagnoses in these patients were irritable bowel syndrome (47%), food intolerance (35%), and IgE mediated allergy (22%). The time lag between ingestion of gluten and the symptoms varied from a few hours to 1 day. Diagnostic tests for celiac disease were negative in these patients and those who underwent duodenal biopsy showed normal intestinal mucosa. The authors conclude that non-celiac gluten sensitivity appears to be associated with a large number of health problems.

■ COMMENTARY

Non-celiac gluten sensitivity is still medically undefined, but is emerging as a possible cause of multiple health problems. Dr. William Davis brought this to light with his 2011 book *Wheat Belly*.¹ Since then, there have been multiple reports of remission of conditions with the elimination of gluten, and their relapse when gluten is ingested.²⁻⁷ This area remains very controversial and is criticized by many leading food science centers.

Gluten is not a distinct chemical, but a protein

complex consisting of two types of proteins, gliadins and glutenins. Measurement of antibodies to these proteins is used to diagnose celiac disease. Patients with non-gluten sensitivity usually have negative tests for celiac, so the diagnosis requires food elimination and clinical judgment. Like other nutritional conditions using the food, withdrawing it and using it again has diagnostic validity.

William Davis describes in detail how modern wheat is much different than the original wheat used before the 1950s.¹ Through hybridization, wheat has become much more energy dense with 42 chromosomes compared with the 14 chromosomes of ancient einkorn wheat.

The number of clinical conditions associated with gluten ingestion is staggering. The strongest evidence seems to be with GI distress, skin conditions (my rosacea went away when I stopped gluten and comes back if I ingest it), allergies, and fibromyalgia. If these associations are borne out by controlled studies, the burden of disease could be markedly reduced. It is not clear how much of the population is gluten sensitive. The Italian study questionnaire was positive for a small percentage of patients, similar to the prevalence of celiac disease (around 2%). However, the real incidence is likely much higher. The association of chronic gluten ingestion and neurodegenerative conditions such as multiple sclerosis, Parkinson’s disease and other tremor, and even Alzheimer’s disease is alarming.⁸ These are described briefly by William Davis¹ and in more detail by neurologist Dr. David Perlmutter in his book *Grain Brain*.⁹

As we learn more about the power of nutrition and the intestinal microbiome, a new area of clinical medicine is opening up. The National Institutes of

[I am finding that the longer I am in medicine, the more I follow the words of Hippocrates, “Let food be thy medicine and medicine be thy food.”]

Health does not have an institute solely devoted to nutritional research, something that nutrition experts regret.¹⁰ I am finding that the longer I am in medicine, the more I follow the words of Hippocrates, “Let food be thy medicine and medicine be thy food.” ■

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ABSTRACT & COMMENTARY

Does Beef Get a Bad Rap?

By *Martin S. Lipsky, MD*

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Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

SYNOPSIS: Contrary to prevailing opinion, eating lean beef may not be bad and perhaps might even favorably affect systolic blood pressure and vascular constriction.

SOURCE: Roussel MA, et al. Effects of a DASH-like diet containing lean beef on vascular health. *J Hum Hypertens* 2014; June 19. [Epub ahead of print.]

Atherosclerosis is a leading cause of death in the United States and both elevated blood pressure and an unhealthy diet are considered risk factors. The American Heart Association and others recommend the Dietary Approaches to Stop Hypertension (DASH) diet as a dietary approach for reducing blood pressure and other cardiovascular disease risk factors. The DASH diet is low in saturated fatty acids and recommends that dietary carbohydrates come primarily from fruits, vegetables, and whole grains. It also recommends increasing multiple minerals (potassium, magnesium, and calcium) and fiber. As part of the DASH diet, individuals are advised to avoid or restrict beef because it is a rich source of saturated fat. However, there is little evidence about the effect on vascular health when incorporating lean beef into the DASH diet.

Roussel and colleagues studied four diets: a healthy American diet (HAD), DASH, Beef in an Optimal Lean Diet (BOLD), which is a DASH-like diet that

included 4 ounces of beef per day, and BOLD+, which included 5.3 ounces of daily beef. The study used a four-period, randomized, crossover design. Subjects were assigned to each type of diet for 5 weeks with a 1 week break between each dispensed diet. The study group consisted of 36 normotensive individuals between the ages of 30-65 years. Each participant received one daily meal at the study center from Monday through Friday with the remaining meals prepackaged for off-site consumption. Compliance was monitored via self-report. Participants were allowed to consume up to 8 ounces of caffeinated beverages daily and were limited to two servings of alcohol per week. Participants could continue their current exercise regimens, but were instructed not to change their routine during the study period.

Body weight was monitored and blood pressure measured at the beginning and end of each diet period. Pulse wave changes were measured using

an EndoPat technique, which can be used to assess endothelial function. It can also generate an augmentation index (AI) that correlates with arterial stiffness.

The results revealed a significant decrease in systolic blood pressure ($P < 0.05$) in subjects on the BOLD+ diet (111.4 ± 1.9 mmHg) vs HAD (115.7 ± 1.9 mmHg). There were no significant effects of the DASH and BOLD diets on systolic blood pressure. The AI was significantly reduced in participants on the BOLD diet (-4.1%). There were no significant effects of the dietary treatments on diastolic blood pressure or endothelial function as measured by peripheral arterial tonometry.

The authors concluded that maintaining a DASH-like diet that includes lean beef decreased systolic blood pressure in normotensive individuals and that incorporating beef in a heart healthy diet can reduce peripheral vascular constriction.

■ COMMENTARY

Recently, several studies have raised questions about the validity of many long-held dietary beliefs and recommendations. For example, after years of endorsing the importance of a good breakfast for losing weight, Dhurandhar and colleagues² failed to find a difference in weight loss for those attempting to lose weight with recommending eating or skipping breakfast. An even higher-profile publication was the recent meta-analysis questioning the effects of dietary fats on heart disease.³

This study by a Penn State research team adds to the growing body of work examining long-held dietary beliefs. Their findings suggest that lean beef can play a role in a heart-healthy diet. For those patients who prefer beef to fish or chicken, this should be viewed

as good news. It also adds to previous work by the same group which showed that the HAD, BOLD, and BOLD+ diets had similar effects on cholesterol when compared with the DASH diet and that these diets did not differ in their impact on glucose and insulin levels.

However, before we all head off to McDonald's for a Big Mac, it would be wise to note that the study group consumed not only lean beef but also ate very modest portions. A 4-ounce serving of beef used in the BOLD diet is about the size of a deck of cards and probably less than the typical household or most restaurant beef servings. Any advice about consuming lean beef should be combined with advice on portion size. Other concerns before extrapolating the findings include the small sample size and the relatively short-term nature of this study. It also did not examine the impact on individuals with existing hypertension.

As the authors note, there is a need for more clinical trials to clarify the role and mechanism(s) of action of the quantity and source of protein on blood pressure and vascular health in both normotensive and hypertensive individuals. At this time, perhaps the best way to clinically apply these findings is to tell those patients who have trouble restricting their beef intake that modest amounts (and define modest!) of lean beef in the context of a DASH-like diet appear to be okay and might even be beneficial. ■

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PHARMACOLOGY UPDATE

Human Insulin Inhalation Powder (Afrezza®)

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

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

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

A second inhalation rapid human insulin has been approved by the FDA. The first inhaled insulin (Exubera) was approved in 2006 and was withdrawn from the market by Pfizer due to low acceptance and poor sales after about 13 months on

the market. The current approval is human insulin delivered as microparticles using the MannKind Corporation's Technosphere technology and is marketed as Afrezza.

INDICATIONS

Inhaled insulin is indicated for use as a rapid-acting form to improve glycemic control in adult diabetic patients.¹ In type 1 diabetics, it must be used with long-acting insulin. It is not recommended for use in patients who smoke.

DOSAGE

Inhaled insulin is administered at the beginning of a meal. For insulin-naïve patients, the initial dose is 4 units with meals. For those on insulin, the dose is individualized and is based on injected insulin dose. Inhaled insulin is available as single-use cartridges of 4 and 8 units.

POTENTIAL ADVANTAGES

Inhaled insulin is more rapidly absorbed and provides higher insulin levels than injected insulin with effects about 2 hours earlier.^{2,3} It more closely mimics normal postprandial endogenous insulin release. Due to its pharmacokinetics and pharmacodynamics, inhaled insulin provides improved early postprandial glycemic control. The inhaler fits in one's palm and is much smaller and easier to use than the previous inhaled formulation (Exubera).

POTENTIAL DISADVANTAGES

Inhaled insulin may cause a decline in lung function.¹ A decline in FEV1 of $\geq 15\%$ occurred in 6% of those treated with inhaled insulin. This was noted within the first 3 months and continued for at least up to 2 years. It is contraindicated in patients with chronic lung disease. The drug comes with a boxed warning recommending spirometry in all patients prior to use. The package insert also recommends spirometry after 6 months of use and annually thereafter.¹ Inhaled insulin is eliminated more rapidly than injected insulin and may have suboptimal late postprandial glycemic control.² In the clinical trials, more patients experienced diabetic ketoacidosis with inhaled insulin than with injected insulin (0.43% vs 0.14%).¹ Dose titration is less precise as inhaled insulin is available as 4-unit and 8-unit single-use cartridges.

COMMENTS

Insulin delivered in the proprietary Technosphere technology is rapidly absorbed from the lungs but is less bioavailable than injected insulin. Its efficacy and safety were evaluated in both type 1 and type 2 diabetic subjects in 24-week active-controlled studies.¹ Type 1 diabetic subjects (n = 344) with a mean baseline HbA1c of approximately 7.93% were randomized to inhaled insulin or insulin aspart given at each meal. All subjects were on basal insulin. At week 24, change from baseline in HbA1c was -0.21% for inhaled insulin compared to -0.40% for insulin aspart (adjusted difference of 0.19; 95% CI; 0.02, 0.36). This met the preset non-inferiority margin of

0.4. Fewer subjects achieved HbA1c goal (7% or less) with inhaled insulin, 14% vs 27%. However, inhaled insulin produced lower fasting plasma glucose, -25 mg/dL vs 10 mg/dL from a baseline of 154 mg/dL and 152 mg/dL, respectively. In the study with type 2 diabetic patients, subjects with baseline HbA1c of about 8.26% and inadequately controlled on optimal or tolerable doses of metformin or two or more oral agents were randomized to inhaled insulin or placebo. Changes from baseline were -0.82% for inhaled insulin and -0.42% for placebo (adjusted difference of 0.4; 95% CI, -0.57, -0.23). Change from baseline fasting plasma glucose (175 mg/dL) was -11.2 mg/dL and -3.8 mg/dL, respectively. The most common adverse event was cough (25%).¹ Other adverse events (throat pain/irritation, headache) were infrequent (3-4%). In a 52-week subgroup analysis in type 2 diabetics randomized to inhaled insulin and insulin glargine or twice daily mixture of 70% aspart protamine suspension and 30% insulin aspart, similar change in HbA1c were reported but with less weight gain and fewer mild-to-moderate and severe hypoglycemic episodes.⁴ Patient satisfaction and acceptance have been reported to be good.⁵ Postprandial glucose levels ([PPG] 2-hour postprandial) and PPG AUC (0-360 minutes) were similar. However, AUC (0-180) were lower with the inhaled insulin arm and AUC (180-360) were lower with injected insulin. The most common adverse event is cough (26%).¹

CLINICAL IMPLICATIONS

Inhaled insulin appears to provide an effective delivery of postprandial insulin. Its long-term safety (particularly affecting the lungs) remains to be established. Acceptance on the patient and physician level is hard to predict. Although the inhalation system is easier to use than the previously marketed inhaled insulin (Exubera), it still does not obviate the need for long-acting insulin in type 1 patients. The need to monitor pulmonary function may also discourage use. Cost information is not yet available. ■

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PSA Screening: Game Over? Well, Maybe

Source: Barton MK. *CA Cancer J Clin* 2014;64:221-222.

In 2008, the United States Preventive Services Task Force (USPSTF) guideline made one of the first steps toward reducing the number of persons screened for prostate cancer by indicating the lack of value for persons ≥ 75 years. Four years later, their recommendations were updated into a guideline that advised *not* performing prostate cancer screening on any men, since benefits could not be confirmed to outweigh risks. So, game over?

A study performed under the leadership of faculty from the University of Chicago department of urologic surgery analyzed data from the National Health Interview Survey, an ongoing interview done annually on 87,500 people in the United States. The subgroup chosen for analysis in this report focuses on men in two age groups: 65-74 years and ≥ 75 years. Results of these populations when queried in 2005 and 2010 were compared.

Was the 2008 caveat issued by the USPSTF heeded? For men aged ≥ 75 years, investigators found no meaningful difference in the rates of prostate cancer screening comparing results from 2005 interviews (36% screened) and 2010 interviews (34% screened). The majority of these men reported that their physician had advised them to undergo the screening, with only about 25% of men reporting any discussion of potential disadvantages of prostate cancer screening.

Guidelines are only guidelines: That is, it is the artful application of clinical judgment to science that should produce therapeutic wisdom. Nonetheless, clinicians should always

carefully examine their process when acting in a way that is directly countercurrent to major national guidelines. ■

AF is Responsible for Even More Strokes

Source: Gladstone DJ, et al. *N Engl J Med* 2014;370:2467-2477.

Atrial fibrillation (AF) is the most potent predictive factor for risk of stroke. The good news is that stroke risk in AF patients can be reduced by more than two-thirds with use of currently available antithrombotic medications, while incurring only a minor risk ($< 1.0\%/yr$) of central nervous system bleed.

I guess the reason we use the words “idiopathic” and “cryptogenic” is because it is difficult for us to say “We just don’t know.” But package the answer in whichever jargon you like, cryptogenic stroke is an important public health issue, since approximately 25% of ischemic strokes are ultimately so-classified.

Before labeling a stroke cryptogenic, an evaluation for underlying pathology is generally performed, which includes scrutiny for AF, since that is so frequently a culprit and so importantly remedied. If AF was not detected in the proximate temporal vicinity of the stroke, can an “innocent” verdict be rendered as far as AF is concerned?

Sometimes, apparently not. Gladstone et al report on the results from cryptogenic stroke/TIA patients ($n = 572$), half of whom were randomized to 30-day post-event cardiac rhythm monitoring. AF of at least 30 seconds duration was identified in 16.1% of the patients who were monitored.

AF is responsible for a significant number of stroke patients who would not otherwise enjoy the benefits

of anticoagulation. More routine inclusion of longer monitoring will help to identify these patients. ■

Perioperative CV Adverse Events in Stroke Survivors

Source: Jørgensen ME, et al. *JAMA* 2014;312:269-277.

Once a person has experienced a stroke, risk for future cardiovascular events remains substantially elevated compared to a healthy population.

The perioperative period is known to be a time of increased risk for major adverse cardiovascular events (MACE), and it would be valuable to know the interval after which surgical procedures could be performed with minimum risk of MACE for stroke survivors: Is an operation safe 3 months after a stroke? 6 months? 1 year?

Jørgensen et al evaluated data from the Danish Nationwide Cohort Study ($n = 481,183$ elective noncardiac surgeries in adults) to examine the relative risk for MACE in the general population vs stroke survivors. Even distant from the event, risk for MACE was greater in stroke survivors compared to the healthy population (odds ratio [OR] = 1.46). Additionally, the risk of perioperative MACE was greatest in the time period most proximate to the stroke: OR was as high as 14.2 if surgery occurred within 3 months of stroke, reduced to 4.85 in the 3-6 months post-stroke interval, and reduced further to an OR of 2.47 if surgery was performed at least 12 months post-event. These data should provide impetus to advise stroke survivors that unless there is some urgency to an elective procedure, cardiovascular outcomes are best when elective surgery is performed at least 12 months from the date of the index event. ■

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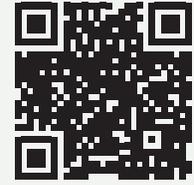
PEER REVIEWER

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CME INSTRUCTIONS

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CME QUESTIONS

1. In the study by Schöttker et al, researchers found an association between low levels of vitamin D and increased rate of all of the below *except*:
 - a. all-cause mortality.
 - b. cardiovascular mortality.
 - c. cancer mortality with prior cancer.
 - d. cancer mortality with current cancer.
2. Which of the following clinical conditions have been associated with gluten?
 - a. Irritable bowel syndrome
 - b. Dermatitis
 - c. IgE mediated allergy
 - d. Multiple sclerosis
 - e. All of the above

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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]

Changes in Office Visit Use Associated with Electronic Messaging and Telephone Encounters Among Patients with Diabetes in the PCMH

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