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PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* APRIL 2009

"For The Secret Of The Care Of The Patient Is In Caring For The Patient."

4-1 TOWARD A RESTORATIVE MEDICINE—THE SCIENCE OF CARE

The good physician knows his patients through and through. Time, sympathy and understanding must be lavishly dispensed. The reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity. "For the secret of the care of the patient is in caring for the patient." *("The Care of the Patient" by Francis Peabody JAMA 1927; 88: 877-82, several months after he had been diagnosed with an inoperable cancer.*)

Peabody added: "The clinical picture is not just a photograph of a man sick in bed, it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes, and fears."

Many at that time believed that the key to personal medical care was the home visit. These visits allow physicians to learn about the life circumstances of their patients, including financial anxiety, and domestic incompatibility, and about their own (the physician's) personal qualities such as self-centeredness, altruism, and gentleness.

In 1977, a half century after Peabody, a new medical model was proposed that essentially incorporated Peabody's approach. A bio-psycho-social approach was proposed, with a central focus on the person. This placed the patient's narrative at the center of the clinical evaluation.

The patient-centered approach to patient care is crucial for high-quality care. How the interview is conducted matters. An open-ended narrative interview allows the patient to become personally engaged with the interviewer, facilitates rapport, elicits individual attitudes and feelings, and clarifies the meaning of illness to the patient. An effective clinical encounter should elicit attitudes and feelings as well as facts.

An essential quality of a clinician is an interest in humanity. Such interest is no less apparent in physicians today than it was in Peabody's time.

Please read the entire abstract. Times have changed—some for the better, some for the worse.

Young physicians rightly focus their attention on application of the "scientific" medicine learned in medical school. They focus on not missing a critical diagnosis. And applying the correct treatment. for the physical disease.

Wisdom comes with age. It takes time to develop an ongoing empathetic relationship with patient and family—a luxury not often afforded to medical specialists. Primary care clinicians have a great

advantage in this respect. Specialists are just as empathetic as primary care clinicians, but they focus more on the organ. And they do it with exceptional skill. The time for emotional connectedness with patient and family is limited.

The article mentions home visits. They were part of general practice when I started. There is some interest in reviving home visits CITE as part of the remit of the "medical home".

I remember, when I was a child, the frequent home visits of "our doctor". He became part of the family. He would always sit down and chat. He was my role-model.

When Co-Payments Are Increased, Initiation Of Therapy Is Delayed

4-2 COST SHARING (CO-PAYMENTS) AND THE INITIATION OF DRUG THERAPY FOR THE CHRONICALLY ILL

Health care plans have responded to rising prescription costs by restricting payments. This has resulted in increased co-payments for drugs by policy-holders..

This study examined whether increasing co-payments (cost-sharing by patients) affects the initiation of drug treatment.

Identified patients with newly diagnosed hypertension, hypercholesterolemia, and diabetes. (n = over 17 000). Identified disease-specific prescribed medications. The majority of patients received multiple prescriptions.

Primary outcome = the time until initiation of the prescription drug therapy, defined as the number of days between a patient's first diagnosis and the time of filling of the first disease-specific prescription.

When co-payments were doubled, the % of patients with newly-diagnosed hypertension, who initiated therapy at one year after the increase, fell from 55% to 40%. Compliance also fell for patients receiving prescriptions for hypercholesterolemia and diabetes.

The effect of doubling co-payments depended on the patient's history of prescription drug use. Compared with patients with no drug use in the year prior to the index date, patients with any drug use in that period initiated therapy earlier, and were much less sensitive to price.

Chronically ill patients are sensitive to the cost of prescription drugs. Out-of pocket costs prevent patients from promptly initiating medically necessary care.

The % of newly diagnosed patients who had not initiated a drug to treat hypertension, hypercholesterolemia, and diabetes by 5 years was 21%, 36% and 33%.

Conclusion: High cost-sharing delays the initiation of drug therapy for patients with newly diagnosed chronic diseases.

During my years of practice, I assumed that patients were taking their medications.

I frequently asked patients to bag all their medication for review at the office visit. Many did not respond to this request. I could not understand why. Perhaps because they did not have the prescription filled or were not taking it regularly.

Prescribing multiple drugs undoubtedly lowers compliance.

Cost is an important factor in the benefit/harm-cost ratio of medications.

The recent willingness of several major pharmacies to offer generics at $4 for one-month's supply or $10 for 3 month's supply is most welcome. This should increase compliance. Since all doses of drugs cost the same, use of a pill cutter will further decrease cost.

The most empathetic physician guided by the best of evidence-based practice will not benefit a patient who cannot afford the medications prescribed.

An Inexpensive, Convenient Way To Reduce Multiple Risk Factors For Cardiovascular Disease

4-3 EFFECTS OF A POLYPILL (*Polycap*) ON RISK FACTORS IN MIDDLE-AGED INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Low-dose aspirin, beta-blockers, antihypertension drugs, and statins—each reduces incidence of cardiovascular disease (**CVD**). One combination pill including all drugs could potentially reduce incidence of CVD more efficiently and cheaply than each drug given separately.

Can one pill deliver an effect similar to the additive effects of each component given separately? What degree of reduction in BP and LDL-cholesterol can be achieved in people with "normal" levels? Will the pill be well tolerated? Do unexpected interactions occur when these drugs are given in a single pill? Does aspirin reduce the BP-lowering effect of antihypertension drugs?

The pill (actually a capsule) contained 5 drugs (all generics): 3 antihypertension drugs (thiazide, beta-blocker, and ACE inhibitor); a statin; and aspirin, all in low doses (except atenolol): hydrochlorothiazide, 12.5 mg; atenolol 50 mg; ramipril 5 mg; simvastatin 20 mg; and aspirin 100 mg.

Recruited over 2000 individuals ages 45-80, who had no history of CVD. All had at least one risk factor for CVD.

Randomly assigned individuals into one of nine groups; 412 received the Polycap (5 drugs); 8 groups of 200 each received various combinations of 1,2, 3, or 4 drugs.

Effect on BP: The Polycap (3 antihypertension drugs) reduced BP by about 7/5 mmHg—a greater reduction than any combination of 2 other antihypertension drugs. A subgroup analysis compared effect

of the Polycap on patients with BP under 140 and over 140. Systolic was reduced by 6/5 mmHg in the former group, and by 8/6 mm Hg in the latter.

Lipids: LDL-cholesterol was reduced slightly more in the simvastatin-alone group than in the Polycap group (-32 mg/dL vs -27). The effect of simvastatin in lowering LDL-c was evident in participants with levels below the median as well as in those above the median (- 25 mg/dL in the former vs -36 mg/dL in the latter). In diabetic patients, both the absolute and proportionate LDL-c reduction was greater than in those without diabetes.

Heart rate: Reduced by 7 beats per minute in both Polycap and atenolol alone groups.

Urinary thromboxane (effect of aspirin): Any group containing aspirin alone or aspirin + BP drugs lowered thromboxane by 348 ng/mmol creatinine vs 283 for Polycap.

Adverse effects: Withdrawals overall = 15%, mainly because some participants perceived little benefit. Rates and reasons for discontinuation were similar across all 9 groups; drug-specific adverse effects in 4% overall.

Adverse effects in the Polycap group: dizziness/hypotension 6%; cough 5%; fatigue 2%; creatinine increase over 50% 9%; SGPT doubled 3%.

Tolerability and safety were similar to that of single low-dose drugs, suggesting no increase in drug-specific adverse effects of the Polycap. "An analysis by one or more active components in the pill suggests similar rates of drug discontinuation, allaying concern that the Polycap would have increased rates of side-effects and intolerability as the number of components increased."

Conclusion: This formulation could be inexpensive, and conveniently used to reduce multiple risk factors for cardiovascular disease.

The polypill concept is intriguing. Interest seems to continue. I doubt the concept will die.

At present, millions of patients in the USA are already taking several, or all, of the individual prescription drugs. This adds expense and inconveniences.

"Risk Factor Thresholds: Their Existence under Scrutiny" Law and Wald BMJ 2002 324; 1570-76

Interventions to lower BP, cholesterol, and other risk factors reduce the risk of CVD regardless of initial levels. The goal is not to "normalize" risk factors, but to reduce them as much as possible. This means targeting all risk factors for everyone at risk, rather than by the level of the risk factor.

A given reduction in the risk factor reduces risk of disease by a constant proportion of the existing risk regardless of the initial level of the risk factor.

"A Strategy to Reduce Cardiovascular Disease by More than 80%" BMJ June 28, 2003: 326: 1419-23

The original concept of the polypill was proposed by Wald and Law. They based their concept on the observation that, regardless of initial levels of risk factors, even if within "normal" limits, lowering them further (down to an undetermined level) leads to an absolute and proportional reduction in risk. (By this criterion, all persons in developed countries have some risk factors.)

This original article suggested giving a daily combination of low-dose drugs to all individuals 55 years of age and older—without prescreening and follow-up This could be a means of reducing risk of CVD in the general population. The lower the risk factor, the lower the risk of disease down to levels well below average Western values. BP-lowering should not be limited to people with "high blood pressure", nor lowering cholesterol levels limited to people with "high cholesterol". The constant proportional relation means there is value in modifying risk factors regardless of the level of the risk factor. All reversible risk factors should be changed, not just those judged "abnormal".

Adverse drug effects are much lower when low doses are given than when average doses are given.

Our terminology now regards extreme values as indicating a diseased state (hypertension; hypercholesterolemia; osteoporosis; obesity) and average values as being "normal" (normotensive; normocholesterolemic) Clinical guidelines specify risk factor thresholds.

"Normal" levels are arbitrary and artificial.

Should Primary Care Physicians Test Patients With IBS For CD?

4-4 YIELD OF DIAGNOSTIC TESTS FOR CELIAC DISEASE IN INDIVIDUALS WITH SYMPTOMS SUGGESTIVE OF IRRITABLE BOWEL DISEASE

In community surveys, the prevalence of irritable bowel syndrome (**IBS**) varies between 5% and 20% depending on the criteria used for diagnosis.

Prevalence of celiac disease (**CD**) in the U.S. is almost 1%.

IBS and CD are prevalent conditions that share a common set of symptoms.

Guidelines in the U.K. recommend routine exclusion of CD in all patients with symptoms of IBS.

This systematic review and meta-analysis estimated the prevalence of CD in adults who met the diagnostic criteria for IBS.

Case series and case-control studies that used serological tests for CD were eligible for inclusion.

Serological tests for CD included: IgA-class A antigliadin antibody (**AGA**); endomysial antibody (**EMA**); and tissue transglutaminase antibody (**tTGA**).

Yield of IgA-class AGA-testing in individuals meeting diagnostic criteria for IBS:

Seven studies reported data in 1104 subjects with IBS. Pooled prevalence of persons who met diagnostic criteria for IBS who tested positive for AGA = 4%.

Five studies offered duodenal biopsy to individuals who tested positive for AGA.

Biopsy was consistent with CD in only 8 of 27 individuals with positive AGA.

Yield of EMA or tTGA-testing in individuals meeting diagnostic criteria for IBS:

Thirteen studies used either test in 2021 individuals; 41 (2%) tested positive.

Five studies (n = 1147) provide data on duodenal biopsy in those testing positive; 33 of 36 had histological changes consistent with CD. Thus, 33 of 1147 (2.9%) individuals in 5 studies had biopsy-confirmed CD.

Odds ratio in case-control studies:

Five case-control studies followed 1) Cases (n = 952) who met diagnostic criteria for IBS vs 2) Controls (n = 1798; no IBS). All received biopsy. 34 cases (3.6%) had biopsy proved CD vs 12 controls (0.7%). Odds ratio = 4.34. Again no significant difference between types of IBS.

In persons meeting diagnostic criteria for IBS, the prevalence of positive serological tests for CD was about 3%. The prevalence of biopsy-proved CD was about 3% in those with positive diagnostic tests for CD.

The prevalence of biopsy-proved CD was similar between subtypes of IBS (diarrhea predominant, constipation predominant, and mixed).

Conclusion: The prevalence of CD in patients meeting diagnostic criteria of IBS is in the region of 3%, EM antibody and tTG antibody testing should be the preferred serological tests.

Primary care physicians who encounter patients with symptoms of IBS should consider screening for CD.

The investigators found that constipation-predominant IBS was just as likely to be related to CD as diarrhea-related IBS. This surprised me.

Clinicians may be more likely to screen for conditions that have a major and immediate effect on health (eg, breast cancer, prostate cancer and CVD) than for conditions that have minor and less immediate effects. Just as gamblers in Las Vegas may be more likely to play a slot machine that has a big jackpot.

Glucose Control Is Still Beneficial Long-term

4-5 GLUCOSE CONTROL IN TYPE-2 DIABETES: *Still Worthwhile And Worth Pursuing*

Two large studies in the 1990s demonstrated benefit of improved glucose control on *micro*-vascular complications (eyes, kidneys, and nerves).

The DCCT in patients with type-1 diabetes provided evidence that intensive glucose control led to approximately 60% reduction in the risk of progression of micro-vascular complications.

The UKPDS, in patients with type-2 diabetes, showed that 10 years of improved glycemic control resulted in a 25% reduction in micro-vascular complications.

Following publication of these studies, the benefit of improved glucose control in *micro*-vascular complications was no longer debated.

In 2008-09, three long-term clinical studies of glucose control and *macro*-vascular complications in type-2 diabetes were reported. They provided conflicting evidence of benefits of intensive control on macro-vascular complications.

ACCORD involved over 10 000 patients with a history of cardiovascular events or at increased risk. The study was stopped at 3.5 years because of an unexpected 22% increase in all-cause mortality in the intensively treated group.

VADT was similar to ACCORD, but included more cardiovascular events in the composite endpoints. Intensive control was associated with more hypoglycemia. There was no difference between treated and control groups in mortality or the composite primary outcome. A severe episode of hypoglycemia strongly predicted mortality.

ADVANCE enrolled over 11 000 high-risk patients who had known cardiovascular disease, or at least one risk factor. Intensive glucose control was not effective in reducing macro-vascular outcomes, but did not increase cardiovascular or all-cause mortality.

In sum, the trials suggest that a possible benefit on cardiovascular outcomes may be observed in patients with a shorter duration of diabetes, better glucose control, younger age, no previous cardiovascular disease, or fewer risk factors at the time of initiation intensive control.

Long-term follow-ups of the DCCT and UKPDS suggest that prior intensive glucose control may have beneficial effects lasting beyond the period of improved control. The DCCT patients were followed up for 11 years after the period of intensive control. During this period, glucose control was similar in the prior intensive group and the control group. In the intensive control group, seventeen years after beginning the trial, there was a 42% reduction in risk of any cardiovascular event and a 57% reduction in non-fatal MI, non-fatal stroke, or cardiovascular death.

Ten years after completion of the intervention phase of the UKPDS, glucose control no longer differed between groups, yet patients in the intensive-control group benefited. Differences in micro-vascular complications were maintained, and risk of MI was reduced by 15%, and all-cause mortality by 13%.

The mechanisms for this “legacy effect” are not known.

It seems reasonable to set the appropriate goal of HbA1c at less than 7% in younger patients. They are likely to have a shorter duration of diabetes, fewer risk factors, and no history of prior cardiovascular disease. They can sense hypoglycemia. A more liberal target of less than 7.5% would seem appropriate for older patients who have advanced diabetes-related complications, or who experience severe hypoglycemia.

This study is a good example of a mistake we may make when we transfer results of trials with limited applicability (older patients with long-standing diabetes, a history of cardiovascular disease, and risk factors other than diabetes itself) to the population of younger patients (with short duration of diabetes, no history of cardiovascular disease and fewer risk factors).

A Need For Consideration Of Vitamin D Status And Supplementation In Critically Ill Patients

4-6 VITAMIN D DEFICIENCY IN CRITICALLY ILL PATIENTS

Of the 1100 patients in their ICU, 17% had undetectable vitamin D levels.

This prospective study of vitamin D status was conducted in 42 patients referred from ICU to a Department of Endocrinology in Australia.

The investigators classified serum levels of 25[OH]D in ng/mL:

Sufficient	> 24
Insufficient	24 to 12
Deficient	<12 to 6
Undetectable	<6

Of the 1100 patients in their ICU, 17% had undetectable vitamin D levels. Among the 42 referred patients, prevalence of hypovitaminosis D was high—the mean serum level of 25[OH}D was 16 ng/mL. Three patients died of neoplastic disease. All 3 had undetectable serum levels of D.

Mean acute physiology scores (**APS**) and predicted mortality rates in 42 patients::

D level	APS	Predicted mortality rate (%)
Sufficient	34	16
Insufficient	45	35

Deficient 51 45

Vitamin D deficiency is associated with increased mortality.

Conclusion: "These findings highlight the need for consideration of vitamin D status and supplementation in patients in the ICU."

Vitamin D deficiency seems to have become a scourge. And repletion a panacea.

What a remarkable turn of events!

Look for more studies. Meanwhile, I see no harm in repletion in acutely ill patients, as well as in many others.

Vitamin D Insufficiency May Be A Significant Contributor To Neuropathic Pain In Type -2 Diabetes.

4-7 VITAMIN D AS AN ANALGESIC FOR PATIENTS WITH TYPE-2 DIABETES AND NEUROPATHIC PAIN

Hypovitaminosis D is highly prevalent in patients with type-2 diabetes (**DM-2**). Its impact on neuropathic pain has not been previously evaluated.

This prospective study included fifty-one patients (mean age 62) with DM-2. All had neuropathic pain (burning, tingling, numbness, and throbbing sensations), and reduced sensation to touch.

Measured serum 25[OH]D. All were D insufficient (< 24 ng/mL) Treated all with D3 tablets daily (mean dose = 2059 IU). Reevaluated patients at 3 months.

All patients were D insufficient (mean serum concentration = 18 ng/mL)

At baseline, mean score on a visual analogue pain (VAS) scale (range from 0 to 6) was 3.3—"distressing". Score on the McGill pain questionnaire was 32.

At 3 months, serum 25D concentrations increased from 18 to 30 ng/mL.

Vitamin D repletion resulted in a statistically significant reduction in pain scores. VAS score improved at 3 months to 1.7; McGill score improved to 19.

There is evidence that vitamin D is neurotrophic and modulates neuromuscular function, and neuronal growth and differentiation. Insufficiency may worsen diabetic nerve damage.

The definition of vitamin D deficiency is an ongoing debate. It is generally defined as serum 25[OH]D concentrations less than 20 ng/mL. The mean post-therapy D level in this study was 30 ng/mL. This was correlated with statistically significant pain reduction.

Conclusion: Vitamin D insufficiency is underrecognized, and may be a significant contributor to neuropathic pain in type -2 diabetes.

This study was little more than anecdotal. It is provocative.

Primary care physicians are frequently measuring vitamin D levels, and treating deficient patients with high doses—often 50 000 IU every week. At this dose it is non-toxic. Indeed, vitamin D may have one of the highest benefit/harm-cost ratios of any drug. I recently purchased D3 tablets 1000 IU for 3 cents each.

The association of D insufficiency related to DM-2 neuropathy should be tested by primary care physicians to determine clinically significant improvement. I doubt any drug company would launch a study. There would be little profit.

The ADA Will Likely Soon Propose Using Hba1c As A Diagnostic Test

4-8 HEMOGLOBIN A_{1c} POISED TO BECOME PREFERRED TEST FOR DIAGNOSING DIABETES

HbA1c appears to be on the threshold of official recognition as the preferred diagnostic test for diabetes.

A consensus statement was issued in 2008 calling for adoption of HbA1c as a screening and diagnostic test

The (*arbitrary*) cut-off point for diagnosis will probably remain in debate. A level of 6% or less has been defined by some authorities as normal; 6.1% to 6.9% as pre-diabetes; and 7.0% or greater as diabetes.

The test is looked upon more favorably than in 2003 (the last ADA recommendation) because the test is now more standardized. As of September 2007, certification from the National Glyco-hemoglobin Standardization Program required manufacturers to produce tests that result in reading that are within + or – 0.85% of true HbA1c levels from 4% and 12%.

The HbA1c test is easy to use. It should facilitate diagnosis earlier in the disease, when interventions are most successful.

“Probably more than 40% of people with diabetes are undiagnosed, and one reason might be that the test used most to diagnose diabetes requires fasting.”

I agree that more patients would be screened if HbA1c were used.

A range of + or – 0.8% may lead to false positive and false negative results. Patients with HbA_{1c} in the 6% to 7% range may require confirmation with a plasma glucose test.

The aim of diagnosis and treatment of diabetes is to reduce rate of macro-and micro-vascular complications. Complications of diabetes are much less likely at 6% or lower.

ABSTRACTS APRIL 2009

"For The Secret Of The Care Of The Patient Is In Caring For The Patient."

4-1 TOWARD A RESTORATIVE MEDICINE—THE SCIENCE OF CARE

"The most common criticism made at present . . . is that young graduates have been taught a great deal about the mechanism of disease, but very little about the practice of medicine—they are too 'scientific' and do not know how to take care of patients."

The good physician knows his patients through and through. Time, sympathy and understanding must be lavishly dispensed. The reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity. "For the secret of the care of the patient is in caring for the patient." *("The Care of the Patient" by Francis Peabody JAMA 1927; 88: 877-82, several months after he had been diagnosed with an inoperable cancer.*)

Peabody added: "The clinical picture is not just a photograph of a man sick in bed, it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes, and fears."

Many at that time believed that the key to personal medical care was the home visit. These visits allow physicians to learn about the life circumstances of their patients, including financial anxiety, and domestic incompatibility, and about their own (the physician's) personal qualities such as self-centeredness, altruism, and gentleness.

Peabody's JAMA article was organized around key issues:

1. Instruction in the treatment of disease:

Medicine is not a trade to be learned, but a profession to enter. "The treatment of a disease may be entirely impersonal; the care of the patient must be completely personal". In the hospital, the patient loses his personal identity, becoming a 'case'. He is really a sick man concerned not only about his failing heart, but his threatened future.

2. Patients who have "Nothing the matter with them":

Those who do not demonstrate objective organic pathology may be passed over lightly. A substantial proportion of patients fall into this category. Physiological disturbances arise from emotional disturbances which affect organic functioning. Symptoms usually resolve after cessation of the stressor. Yet for some, whose symptoms do not abate, Peabody concluded that scientific medicine was not scientific enough, and that cheerful reassurance and a placebo tonic were insufficient.

3. Importance of a personal relationship:

Peabody concluded his JAMA Classics article by pointing out that a physician who neglects the emotional life of a patient is as "unscientific as the investigator who neglects to control all the conditions that may affect his experiment".

The need for a new medical model:

In 1977, a half century after Peabody, a new medical model was proposed that essentially incorporated Peabody's approach.[1] A bio-psycho-social approach was proposed, with a central focus on the person. This placed the patient's narrative at the center of the clinical evaluation. Physiological and immunological studies convinced some clinicians that the clinical interview must focus on the person (the patient's attitudes, fears, and hopes) and not on disease alone. The goal of the clinical interview is not only to diagnose disease, but also to understand the meaning of the illness for the patient and to establish realistic hope about the prognosis.

A gesture of "hopelessness" was recognized as a clinical sign—when the patient, in the midst of the interview, sighs and reaches out toward the examiner. When this subtle reaching out is ignored, there is a flattening of facial expression and the patient's arms fall in resignation. It is a sign that the patient has given up. The gesture is a red flag to stop, listen, and console. If the physician attends to the signs of hopelessness, fear, and emotional disengagement, this primitive giving-up response can be averted.

Confiding relationships with the physician, family, and friends are among the most psychosocial protective factors.

Social engagement with the physician should engender trust and alleviate unrealistic anxiety.

Well-defined, organized neural circuits, linked to the autonomic nervous system, have evolved to gauge environmental risk and regulate adaptive behavior in response to dangerous or life-threatening situations. The neuropeptides, oxytocin and vasopressin are linked to these circuits.

When the social environment is deemed safe and trustworthy, the patient establishes eye contact with the examiner, listens intently to what is said, and breathes freely; the heart rate is rhythmically synchronized with breathing—increasing during inspiration and decreasing during expiration. This synchronization results from the activation of the vagus nerve that innervates the lungs and heart, and is linked to neural regulation of the facial muscles of emotional expression and the middle ear muscles that extract human voice.

When threatened, social engagement is abandoned and the patients becomes hyper-vigilant, respiration and heart rate increase, and the sympathetic nervous system is engaged.

When despairing, the patient becomes listless and dissociated, physiologic and immune systems begin to disengage, and gastrointestinal symptoms and bradycardia ensue.

The experience of social trust may also be linked to the placebo response. Beliefs and expectations may modulate neuro-physiologic and neuro-chemical activity in the brain—in regions involved in perception, movement, pain, and various aspects of emotional processing.

The patient-centered approach to patient care is crucial for high-quality care. How the interview is conducted matters. An open-ended narrative interview allows the patient to become personally engaged with the interviewer, facilitates rapport, elicits individual attitudes and feelings, and clarifies the meaning of illness to the patient. An effective clinical encounter should elicit attitudes and feelings as well as facts.

Caution in using electronic medical records—when the physician continuously turns away to enter data into a computer. Issues are being raised about how the design of the electronic recording system, with its focus on gathering factual information, shapes physician's cognition. The nature of the patient-physician dialogue may be influenced by the structure of the electronic system.

An essential quality of a clinician is an interest in humanity. Such interest is no less apparent in physicians today than it was in Peabody's time.

JAMA April 23/29 2009; 301: 1710-12 "JAMA Classics", Commentary by James C Harris, Johns Hopkins University School of Medicine, Baltimore MD

1 Engel GL "The need for a new medical model; a challenge for biomedicine" Science 1997; 196: 129-36

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When Co-Payments Are Increased, Initiation Of Therapy Is Delayed

4-2 COST SHARING (CO-PAYMENTS) AND THE INITIATION OF DRUG THERAPY FOR THE CHRONICALLY ILL

Health care plans have responded to rising prescription costs by restricting payments. This has resulted in increased co-payments for drugs by policy-holders, and mandatory generic substitutions.

Former studies reported that cost is the leading reason why elderly patients do not fill prescriptions, skip doses, or take smaller doses. Experiencing adverse effects and beliefs about lack of benefit are less common reasons.

This study examined whether increasing co-payments (cost-sharing by patients) affects the initiation of drug treatment.

STUDY

1. Retrospective cohort study linked enrollment files, pharmacy claims, medical claims, and the salient features of health plan benefits for retirees of 15 large employers. Each employer offered one or more health plans to its elderly retirees (total of 31 different plans for almost 400 000 retirees; mean age 75). Between 10% and 24% of retirees had no prior prescription drug use.
2. Almost all plans provided a single drug benefit. Retirees had no choice of drug benefits.
3. Identified patients with newly diagnosed hypertension, hypercholesterolemia, and diabetes. (n = over 17 000).
4. Identified disease-specific prescribed medications. The majority of patients received multiple prescriptions. Many received 7 or more.
5. Primary outcome = the time until initiation of the prescription drug therapy, defined as the number of days between a patient's first diagnosis and the time of filling of the first disease-specific prescription.

RESULTS

1. For all study conditions, higher co-payments were associated with delayed initiation of therapy.
2. When co-payments were doubled, the % of patients with newly-diagnosed hypertension, hypercholesterolemia, and diabetes who initiated therapy at one year after the increase, fell from 55% to 40%.
3. Similarly, initiation of therapy fell for those for whom prescriptions had been issued for hypercholesterolemia and diabetes.
4. The effect of doubling co-payments depended on the patient's history of prescription drug use. Compared with patients with no drug use in the year prior to the index date, patients with any drug use in that period initiated therapy earlier, and were much less sensitive to price.

DISCUSSION

1. Chronically ill patients are sensitive to the cost of prescription drugs. Out-of pocket costs prevent patients from promptly initiating medically necessary care.
2. The initiation of drug therapy and sensitivity to price depend on a patient's prior experience

with use of prescription drugs. Patients with prior experience were more likely to adopt therapy earlier and were less sensitive to price.

3. The effect of increased co-payments on initiation of therapy was largest soon after diagnosis, but declined over time. However, most prescription drug initiation did occur soon after diagnosis.
4. The % of newly diagnosed patients who had not initiated a drug to treat hypertension, hypercholesterolemia, and diabetes by 5 years was 21%, 36% and 33%.
5. Twenty three % of patients with diabetes who survived a myocardial infarction—a group likely to be hypervigilant about controlling risk factors—did not use anti-diabetes medications.
6. Patients with no prior experience with drug therapy are prime targets for encouragement to adoption of appropriate treatment.
7. Adherence was poorer for those who began with high co-payments than for those who began with lower payments that gradually increased.

CONCLUSION

High cost sharing delays the initiation of drug therapy for patients with newly diagnosed chronic diseases.

Archives Intern Med April 27, 2009; 740-48 Original investigation, first author Matthew D Solomon, Stanford University School of Medicine, Stanford, California.

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An Inexpensive, Convenient Way To Reduce Multiple Risk Factors For Cardiovascular Disease

4-3 EFFECTS OF A POLYPILL (*Polycap*) ON RISK FACTORS IN MIDDLE-AGED INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Low-dose aspirin, beta-blockers, antihypertension drugs, and statins—each reduces incidence of cardiovascular disease (**CVD**). One combination pill including all drugs could potentially reduce incidence of CVD more efficiently and cheaply than each drug given separately.

This phase II trial examined the effects of a polypill on BP, lipids, heart rate, and urinary thromboxane; and assessed its tolerability.

Can one pill deliver as effect similar to the additive effects of each component given separately? What degree of reduction in BP and LDL-cholesterol can be achieved in people with “normal” levels? Will the pill be well tolerated? Do unexpected interactions occur when these drugs are given in a single pill? Does aspirin reduce the BP-lowering effect of antihypertension drugs?

These investigators designed The Indian Polypill Study (TIPS) to address these questions.

STUDY

1. The pill (actually a capsule) contained 5 drugs (all generics): 3 antihypertension drugs (thiazide, beta-blocker, and ACE inhibitor); a statin; and aspirin, all in low doses (except atenolol):
   Hydrochlorothiazide, 12.5 mg
   Atenolol 50 mg
   Ramipril 5 mg
   Simvastatin 20 mg
   Aspirin 100 mg.
   (All generics)
2. Recruited over 2000 individuals ages 45-80 who had no history of CVD. All had at least one risk factor for CVD (type-2 diabetes, BP > 140 or > 90 (but not over 160/100). smoking within 5 years, LDL-cholesterol > 120 mg/dL, HDL-cholesterol < 40 mg/dL, or obesity determined by increased waist/hip ratio.
2. None had an LDL-cholesterol over 170 mg/dL, creatinine greater than 2 mg/dL, potassium greater than 5.5 mmol/L, abnormal liver function, or asthma.
3. Randomly assigned individuals into one of nine groups; 412 received the Polycap (5 drugs); 8 groups of 200 each received various combinations of 1,2, 3, or 4 drugs.
4. Before randomization all subjects received a physical examination, EKG, blood tests,. and urine thromboxane concentration (testing effect of aspirin). Also measured creatinine and potassium at all visits and repeated all blood tests at 12 weeks.
5. Subjects were checked periodically for 12 weeks at which time the drugs were discontinued. A final visit was at 16 weeks. Recorded adverse events at each visit.

RESULTS (at 12 weeks):

1. Effect on BP: The Polycap (3 antihypertension drugs) reduced BP by about 7/5 mmHg—a greater reduction than any combination of 2 other antihypertension drugs. A subgroup analysis compared effect of the Polycap on patients with BP under 140 and over 140. Systolic was reduced by 6/5 mmHg in the former group, and by 8/6 mm Hg in the latter.
2. Lipids: LDL-cholesterol was reduced slightly more in the simvastatin-alone group than in the Polycap group (-32 mg/dL vs -27). The effect of simvastatin in lowering LDL-c was evident in participants with levels below the median as well as in those above the median (- 25 mg/dL in the

former vs -36 mg/dL in the latter). In diabetic patients, both the absolute and proportionate LDL-c reduction was greater in those without diabetes.

3. Heart rate: Reduced by 7 beats per minute in both polycap and atenolol alone groups.
4. Urinary thromboxane (effect of aspirin): Any group containing aspirin alone or aspirin + BP drugs lowered thromboxane by 348 ng/mmol creatinine vs 283 for Polycap.
5. Adverse effects: Withdrawals overall = 15%, mainly because some participants perceived little benefit. Rates and reasons for discontinuation were similar across all 9 groups; drug-specific adverse effects in 4% overall.
6. Adverse effects in the Polycap group: dizziness/hypotension 6%; cough 5%; fatigue 2%; creatinine increase over 50% 9%; SGPT doubled 3%. Polycap permanently discontinued in 16%, similar to other groups.

DISCUSSION

1. Polycap was non-inferior to its individual components in lowering BP and heart rate. It lowers LDL-c and urinary thromboxane substantially, but not to as great a degree as simvastatin alone and aspirin alone. The reason for the lesser lowering by Polycap vs simvastatin alone and aspirin alone is not known. Nevertheless, the reductions were substantial. The effects of the Polycap cannot be assumed to equal the combined effects of its individual components.
2. The investigators suggest that the Polycap has potential to reduce CVD by 62% and stroke by 48%.
3. “The reductions in blood pressure that we recorded in this non-hypertensive population with the Polycap could theoretically lead to about a 24% risk reduction in cardiovascular disease and about a 33% reduction in strokes in individuals with average blood pressure levels.”
4. The effect of the Polycap on LDL cholesterol was greater in participants with diabetes. Benefits may be larger in high-risk patients.
5. Tolerability and safety were similar to that of single drugs, suggesting no increase in drug-specific adverse effects of the Polycap. “An analysis by one or more active components in the pill suggests similar rates of drug discontinuation, allaying concern that the Polycap would have increased rates of side-effects and intolerability as the number of components increased.”
6. Future formulations of the polypill might change the mix of drugs.

CONCLUSION

This formulation could be inexpensive, and conveniently used to reduce multiple risk factors for cardiovascular disease.

Lancet April 18, 2009; 373: 1341-51 Original investigation by The Indian Polycap Study (TIPS) Funded by Cadila Pharmaceuticals, Ahmedabad, India Correspondence to: Salem Yusuf, McMaster University, Hamilton, Ontario, Canada (yusufs@mcmaster.ca)

These are surrogate endpoints. I look for additional studies, especially clinical endpoints.

I detected a good deal of "spin" in the article RTJ

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Should Primary Care Physicians Test Patients With IBS For CD?

4-4 YIELD OF DIAGNOSTIC TESTS FOR CELIAC DISEASE IN INDIVIDUALS WITH SYMPTOMS SUGGESTIVE OF IRRITABLE BOWEL DISEASE

In community surveys, the prevalence of irritable bowel syndrome (**IBS**) varies between 5% and 20% depending on the criteria used for diagnosis. The natural history often follows a chronic relapsing-remitting course. Symptoms include lower abdominal pain, diarrhea, abdominal distention, and bloating.

Celiac disease (**CD**) is a chronic enteropathy of the small intestine caused by intolerance to gluten. Symptoms include bloating, abdominal pain, and chronic diarrhea. Prevalence in the U.S. is almost 1%.

IBS and CD are prevalent conditions that share a common set of symptoms.

In contrast to IBS, symptoms of CD may resolve if the disease is recognized and gluten is excluded from the diet.

Patients with symptoms of IBS are often referred for a specialist's opinion and undergo invasive examinations to exclude an organic cause. Current guidelines for IBS discourage this approach, and recommend that the diagnosis of IBS be made on clinical grounds using symptom-based criteria, rather than following attempts to exclude all possible organic pathology.

The American Gastroenterological Association states that limited laboratories may be used: complete blood count, sed rate, and thyroid function tests.

The American College of Gastroenterology does not recommend investigation of patients with symptoms of IBS, but does suggest that testing for CD should be considered in patients with diarrhea.

Guidelines in the U.K. recommend routine exclusion of CD in all patients with symptoms of IBS.

Previous studies indicated that individuals meeting diagnostic criteria for IBS might be at higher risk for CD.

This systematic review and meta-analysis estimated: 1) pooled prevalence of CD in individuals meeting criteria for IBS, and 2) the odds ratio of CD in cases meeting criteria for IBS vs matched controls without IBS symptoms.

STUDY

1. Conducted a systematic review and meta-analysis to estimate the prevalence of CD in adults who met the diagnostic criteria for IBS.
2. Case series and case-control studies that used serological tests for CD were eligible for inclusion.
3. Serological tests for CD included: IgA-class A antigliadin antibody (**AGA**); endomysial antibody (**EMA**); and tissue transglutaminase antibody (**tTGA**).
3. Prevalence of positive serological indications of CD and biopsy-proved CD were extracted and pooled for all studies, and were compared between cases and controls using an odds ratio.

RESULTS

1. Yield of IgA-class AGA-testing in individuals meeting diagnostic criteria for IBS:
   A. Seven studies reported data in 1104 subjects with IBS. Pooled prevalence of persons who met diagnostic criteria for IBS who tested positive for AGA = 4%.
   B. Five studies offered duodenal biopsy to individuals who tested positive for AGA. Biopsy was consistent with CD in only 8 of 27 individuals with positive AGA.
2, Yield of EMA or tTGA-testing in individuals meeting diagnostic criteria for IBS:
   A. Thirteen studies used either test in 2021 individuals; 41 (2%) tested positive.
   B. Five studies (n = 1147) provide data on duodenal biopsy in those testing positive; 33 of 36 had histological changes consistent with CD. Thus, 33 of 1147 (2.9%) individuals in 5 studies had biopsy-confirmed CD.
3. Yield of duodenal biopsy after positive serological tests (of any type) in individuals meeting criteria for IBS:
   A. Seven studies offered biopsy to 1464 individuals. Pooled prevalence of CD was 4.2%
   B. Two studies reported prevalence of CD according to IBS subtype (constipation predominant, diarrhea predominant, and alternating). There was no difference between these three groups.
4. Odds ratio in case-control studies:
   Five case-control studies followed 1) Cases (n = 952) who met diagnostic criteria for IBS

vs 2) Controls (n = 1798). All received biopsy. 34 cases (3.6%) had biopsy proved CD vs 12 controls (0.7%). Odds ratio = 4.34. Again no significant difference between types of IBS.

DISCUSSION

1. In persons meeting diagnostic criteria for IBS, the prevalence of positive serological tests for CD was as high as 4%, depending on the test used. The prevalence of biopsy-proved CD was more than 4% in those with positive diagnostic tests for CD.
2. The positive predictive value (true positive to false positive ratio) of serology was 92% for EMAs or tTGAs compared with only 30% for IgA-class AGAs.
3. Individuals with symptoms suggestive of IBS were three times as likely to test positive for EMA or tTGA compared with controls without IBS, and more than 4 times as likely to have biopsy-proved CD.
4. In a large secondary-care case-control study, the odds ratio of biopsy-proved CD in those meeting Rome II criteria for diagnosis of IBS was 7.0. The odds ratio would be higher in secondary care because of selection bias. Patients with more severe symptoms are more likely to be referred. The prevalence of CD in these patients is higher. The present systematic review was not limited to secondary care. Primary care physicians who encounter patients with symptoms of IBS should consider screening for CD.
5. Costs per quality-adjusted life-year gained by diagnosis of CD are relatively low.
6. The prevalence of biopsy-proved CD was similar between subtypes of IBS (diarrhea predominant, constipation predominant, and mixed).
8. Because IBS is more prevalent than CD, it is possible that some patients will have both conditions. The diagnosis and treatment of CD may not improve all symptoms in some patients. Most patients with CD will improve on treatment.
9. Other long-term benefits of screening, diagnosis, and treatment of CD include: improved bone mineral density, less risk of non-Hodgkin's gastrointestinal lymphoma; improvements in anemia, infertility, recurrent fetal loss, and vitamin D deficiency.

CONCLUSION

The prevalence of CD in patients meeting diagnostic criteria of IBS is in the region of 4%,

The odds ratio of biopsy-proved CD in these patients is more than 4-fold greater than that of healthy controls.

EM antibody and tTG antibody testing should be the preferred serological tests.

Primary care physicians who encounter patients with symptoms of IBS should consider screening for CD.

Archives Intern Med April 13, 2009; 169: Review Article, first author Alexander C Ford, McMaster University Health Sciences Centre, Hamilton, Ontario, Canada.

1 Mainly Rome II criteria

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Glucose Control Is Still Beneficial.

4-5 GLUCOSE CONTROL IN TYPE-2 DIABETES: *Still Worthwhile And Worth Pursuing*

Proving the benefit of better glucose control on micro-vascular and macro-vascular complications has been difficult.

Two large studies[1,2] in the 1990s demonstrated benefit of improved glucose control on *micro*-vascular complications (eyes, kidneys, and nerves).

The DCCT in patients with type-1 diabetes provided evidence that intensive glucose control led to approximately 60% reduction in the risk of progression of micro-vascular complications.

The UKPDS, in patients with type-2 diabetes, showed that 10 years of improved glycemic control resulted in a 25% reduction in micro-vascular complications.

Following publication of these studies, the benefit of improved glucose control in *micro*-vascular complications was no longer debated.

The UKPDS suggested a tantalizing benefit in *macro*-vascular complications. Among the better controlled group there was a 16% reduction in risk of myocardial infarction. (Not statistically significant.)

In 2008-09, three long-term clinical studies[3,4,5] of glucose control and *macro*-vascular complications in type-2 diabetes were reported. They provided conflicting evidence of benefits of intensive control on macro-vascular complications.

. ACCORD involved over 10 000 patients with a history of cardiovascular events or at increased risk (mean age 62; duration of diabetes 10 years; BMI 32; median HbA1c 8.1%). HbA1c was lowered to a stable 6.4% in the treated group vs 7.5% in controls. The study was stopped at 3.5 years because of an unexpected 22% increase in all-cause mortality in the intensively treated group. Intensive therapy led to a greater weight gain, fluid retention, and episodes of severe hypoglycemia. The overall risk of the primary endpoint (non-fatal MI;

non-fatal stroke; and cardiovascular death) was reduced by 10%. (Not statistically significant.)

VADT was similar to ACCORD, but included more cardiovascular events in the composite endpoints, and fewer participants (n = 1800; mean age 60; BMI 31; duration of diabetes 12 years; mean HbA1c 9.4%). Intensive control reduced HbA1c to 6.9% for a median of 6 years vs 8.4% in controls. Intensive control was associated with more hypoglycemia. There was no difference between treated and control groups in mortality or the composite primary outcome. A severe episode of hypoglycemia strongly predicted mortality.

ADVANCE enrolled over 11 000 high-risk patients who had known cardiovascular disease, or at least one risk factor (mean age 66; BMI 28; diabetes duration 8 years). Few were using insulin. They were likely to have been entered somewhat earlier in the disease process than the other studies. During 5 years, the mean HbA1c was 6.5% in the intensive group vs 7.3% in controls. Intensive glucose control was not effective in reducing macro-vascular outcomes, but did not increase cardiovascular or all-cause mortality.

In sum, the trials suggest that a possible benefit on cardiovascular outcomes may be observed in patients with a shorter duration of diabetes, better glucose control, younger age, no previous cardiovascular disease, or fewer risk factors at the time of initiating intensive control.

Patients with long-standing diabetes are more likely to have autonomic neuropathy, and hypoglycemia unawareness. When these patients are treated intensively and hypoglycemia occurs, symptoms of hypoglycemia are blunted, and counter autoregulation fails. Cardiac denervation is often associated with silent myocardial ischemia and a predisposition to arrhythmia.

Long-term follow-ups of the DCCT and UKPDS suggest that prior intensive glucose control may have beneficial effects lasting beyond the period of improved control. The DCCT patients were followed up for 11 years after the period of intensive control. During this period, glucose control was similar in the prior intensive group and the control group. In the intensive control group, seventeen years after beginning the trial, there was a 42% reduction in risk of any cardiovascular event and a 57% reduction in non-fatal MI. non-fatal stroke, or cardiovascular death.

Ten years after completion of the intervention phase of the UKPDS, glucose control no longer differed between groups, yet patients in the intensive-control group benefited. Differences in micro-vascular complications were maintained, and risk of MI was reduced by 15%, and all-cause mortality by 13%.

The mechanisms for this “legacy effect” are not known.

Lipid and BP control, along with life-style interventions are essential for reduction of macro-vascular events in type-2 diabetes. Glucose control must still be undertaken.

It seems reasonable to set the appropriate goal of HbA1c at less than 7% in younger patients. They are likely to have a shorter duration of diabetes, fewer risk factors, and no history of prior cardiovascular disease. They can sense hypoglycemia. A more liberal target of less than 7.5% would seem appropriate for older patients who have advanced diabetes-related complications, or who experience severe hypoglycemia.

JAMA April 15, 2009; 1590-92 Commentary by Steven E Kahn, University of Washington, Seattle.

1 The Diabetes Control and Complications Trial (DCCT; !993)

2. The United Kingdom Prospective Diabetes Study (UKDPS; 1998)

3. Action to Control Cardiovascular Risk in Diabetes (ACCORD; 2008)

4. The Veterans Affairs Diabetes Trial (VADT; 2009)

5. Action in Diabetes and Vascular Disease Controlled Evaluation (ADVANCE; 2008)

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A Need For Consideration Of Vitamin D Status And Supplementation In Critically Ill Patients

4-6 VITAMIN D DEFICIENCY IN CRITICALLY ILL PATIENTS

Vitamin D deficiency is rarely considered or treated in critically ill patients. The prevalence of D deficiency and its significance in the intensive care unit (**ICU**) are not known.

Of the 1100 patients in their ICU, 17% had undetectable vitamin D levels.

This prospective study of vitamin D status was conducted in 42 patients referred from ICU to a Department of Endocrinology in Australia. Recorded demographic, physiological, and biochemical variables, and a Simplified Acute Physiology Score II (**SAPS II**) with a range of 0 to 169. Higher ranges indicate more severe organ dysfunction.

These investigators classified serum levels of 25[OH]D in ng/mL:

Sufficient	> 24
Insufficient	24 to 12
Deficient	<12 to 6
Undetectable	<6

Mean SAPS II scores and predicted mortality rates in 42 patients::

D level	SAPS II score	Predicted mortality rate (%):
Sufficient	34	16

Insufficient	45	35
Deficient	51	45

Among the 42 patients prevalence of hypovitaminosis D was high—the mean serum level of 25[OH}D was 16 ng/mL.

Three patients died of neoplastic disease. All 3 had undetectable serum levels of D.

Hypovitaminosis D was highly prevalent and associated with adverse outcomes, independent of hypocalcemia and hypoalbuminuria. Supplementation with calcium (mean dose 645 mg daily) and vitamin D (mean dose 820 IU) before admission was *not* protective in these patients.

The cause of hypovitaminosis D is probably multifactorial. Limited exposure to sun is probably an important factor. Altered D metabolism during critical illness cannot be ruled out.

Vitamin D deficiency is associated with increased mortality. This study cannot establish causality.

Vitamin D has pleotropic effects on immunity, endothelial and mucosal functions, and glucose and calcium metabolism. The association between hypovitaminosis D and common conditions (systematic inflammatory disease, septicemia, and cardiac and metabolic dysfunctions) in critically ill patients may be important. Deficient states may worsen existing immune and metabolic dysfunctions in critically ill patients.

CONCLUSION

"These findings highlight the need for consideration of vitamin D status and supplementation in patients in the ICU."

NEJM April 30 2009; 360: 1912-14 "Correspondence", first author Paul Lee, Garvan Institute of Medical Research, Sydney, Australia.

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Vitamin D Insufficiency May Be A Significant Contributor To Neuropathic Pain In Type -2 Diabetes.

4-7 VITAMIN D AS AN ANALGESIC FOR PATIENTS WITH TYPE-2 DIABETES AND NEUROPATHIC PAIN

Treatment of neuropathic pain in patients with diabetes is generally unsatisfactory.

Hypovitaminosis D is highly prevalent in patients with type-2 diabetes (**DM-2**). Its impact on neuropathic pain has not been previously evaluated.

This study evaluated the impact of vitamin D on neuropathic pain in patients with DM-2.

STUDY

1. Prospective study included fifty-one patients (mean age 62) with DM-2. All had neuropathic pain (burning, tingling, numbness, and throbbing sensations), and reduced sensation to touch. None had myositis, connective tissue disorders, inflammatory arthropathies, or recent trauma.
2. Evaluated severity of pain by 2 pain questionnaires.
3. Measured serum 25[OH]D and parathyroid hormone concentrations. All were D insufficient (< 24 ng/mL)
4. Treated all with D3 tablets daily (mean dose = 2059 IU).
5. Reevaluated patients at 3 months.

RESULTS

1. All patients were D insufficient (mean serum concentration = 18 ng/mL)
2. At baseline, mean score on a visual analogue pain (VAS) scale (range from 0 to 6) was 3.3—"distressing". Score on the McGill pain questionnaire was 32.
3. At 3 months, serum 25D concentrations increased from 18 to 30. Parathyroid hormone levels fell, but reductions were not statistically significant.
4. Vitamin D repletion resulted in a statistically significant reduction in pain scores. VAS score improved at 3 months to 1.7; McGill score improved to 19.

DISCUSSION

1. Severe D deficiency leads to osteomalacic myopathy, characterized by severe muscle weakness and pain in patients with levels < 12 ng/mL, with prompt resolution of symptoms following replacement.
2. Vitamin D insufficiency (12-24 ng/mL) has not been reported to be associated with neuropathic pain.
3. There is evidence that vitamin D is a neurotrophic substance and modulates neuromuscular function and neuronal growth and differentiation. Insufficiency may worsen diabetic nerve damage and may impair nocioceptor function.
4. The definition of vitamin D deficiency is an ongoing debate. It is generally defined as serum 25[OH]D concentrations less than 20 ng/mL. For osteoporosis prevention, a level above 24 may be necessary. Osteoporosis is prevalent in patients with diabetes.
5. The mean post-therapy D level in this study was 30 ng/mL. This was correlated with statistically significant pain reduction.
6. Vitamin D is increasingly recognized for its pleotropic effects, including improvement in

glycemic control.

7. These investigators advocate a trial of D in patients with neuropathic pain. It is unlikely to have adverse effects.

CONCLUSION

Vitamin D insufficiency is underrecognized, and may be a significant contributor to neuropathic pain in type -2 diabetes.

Archives Intern Med April 14, 2009; 168: 771-72 Research Letter. First author Paul Lee, Concord Repatriation Hospital, New South Wales, Australia.

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The ADA Will Likely Soon Propose Using Hba1c As A Diagnostic Test.

4-8 HEMOGLOBIN A_{1c} POISED TO BECOME PREFERRED TEST FOR DIAGNOSING DIABETES

HbA1c appears to be on the threshold of official recognition as the preferred diagnostic test for diabetes.

The American Diabetes Association will likely propose using HbA1c when revised recommendations are published later this year. A consensus statement was issued in 2008 calling for adoption of HbA1c as a screening and diagnostic test. The committee recommended that screening standards be established to prompt further testing and close follow-up, including HbA1c exceeding 6%, a fasting glucose of 100 mg/dL or greater, or a random plasma glucose 130 mg/dL or greater. A HbA1c of at least 6.5%, confirmed by a plasma glucose-specific test should establish a diabetes diagnosis. A screening test greater than 6.0% would produce a reasonable 66% true-positive result (false negative of 34%, and a true negative result of 98% (false positive of 2%).

However, the (*arbitrary*) cut-off point for diagnosis will probably remain in debate. A level of 6% or less has been defined by some authorities as normal; 6.1% to 6.9% as pre-diabetes; and 7.0% or greater as diabetes.

Unofficially, some primary care physicians have been using the HbA1c to diagnose diabetes because fasting blood glucose and oral glucose tolerance tests are considered burdensome.

The test is looked upon more favorably than in 2003 (the last ADA recommendation) because the test is now more standardized. As of September 2007, certification from the National Glyco-hemoglobin Standardization Program required manufacturers to produce tests that result in reading that are

within + or – 0.85% of true HbA1c levels from 4% and 12%.

The HbA1c test is easy to use. It should facilitate diagnosis earlier in the disease, when interventions are most successful.

“Probably more than 40% of people with diabetes are undiagnosed, and one reason might be that the test used most to diagnose diabetes requires fasting.”

Some authorities state that everyone should know their HbA1c (*as well as their cholesterol*).

JAMA April 15, 2009; 301: 1528 “Medical News and Perspectives” by Mike Mitka, JAMA staff.

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