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HIGHLIGHTS APRIL 1999

4-1 RELATION BETWEEN FASTING PLASMA GLUCOSE AND GLYCOSYLATED HEMOGLOBIN

About 60% of a large cohort of patients newly diagnosed as having "diabetes", had a normal HbA1c. If this degree of glycemia persists, they would not be at risk of microvascular complications.

"We believe that diabetes should not be diagnosed in those with FPG levels less than 140 unless excessive glycosylation is present. Individuals without excessive glycosylation but with moderate elevations of FPG (110-139) should be treated with an appropriate diet and exercise. This diagnostic labeling achieves the goal of early intervention, without subjecting individuals to potentially negative labeling." JAMA April 7, 1999; 281: 1203-1210

4-2 WHEN IS DIABETES DIABETES?

If we agree that a FPG under 110 eliminates the risk of "diabetes" (at least for the immediate future), and that a FPG over 140 is diagnostic of "diabetes" with its risk of complications, this leaves a wide "grey zone" of 110 to 126 to 130. Where should the predictive cutpoint be set? The investigators suggest performing 2 diagnostic tests — FPG and HbA1c. This adds a measure of pathophysiologic abnormality (protein glycosylation) to the prediction of future complications. JAMA April 7, 1999; 281: 1222-24

4-3 GERIATRICS AND THE LIMITS OF MODERN MEDICINE

The editorial comments on 3 problems for old people:

1) Possible harm from treatment of proto-illness — risk factors which produce no symptoms or disease but thought to possibly cause subsequent disease. 2) Overtesting to establish a diagnosis, 3) Overtreatment by multiple specialists, all feeding on Medicare. NEJM April 22, 1999; 340: 1283-85

4-4 CRITERIA AND RECOMMENDATIONS FOR VITAMIN C INTAKE

Recommendations for vitamin C intake are under revision by the Food and Nutrition Board of the National Academy of Sciences.

"Adequate intake" (AI) is an intake level based on an observed or experimentally determined approximation of nutrient intake by a group of healthy people.

The primary use of the AI is a goal for the nutrient intake of individuals.

One AI calculation for vitamin C is 200 mg/d. . "For patients unable or unwilling to consume fruits, vegetables, or vitamin C-fortified foods, a supplement containing 200 mg should suffice." JAMA April 21, 1999; 281: 1415-23

4-5 EFFECTS OF WRITING ABOUT STRESSFUL EXPERIENCES ON SYMPTOM REDUCTION IN PATIENTS WITH ASTHMA AND RHEUMATOID ARTHRITIS

Patients with mild to moderately severe asthma or rheumatoid arthritis who wrote about stressful life experiences had clinically relevant improvements in health status. These gains were beyond those attributable to the standard medical care participants were receiving. JAMA April 14, 1999; 21: 1304-09

4-6 SCREENING MAMMOGRAPHY UNDER AGE 50

Advise women age 40-49 about the benefits and harms of mammography screening. (Young women overestimate their risk of dying of BC.)

Screen those who are eager for screening. Screen those with substantial risk factors, especially family history.

Those without particular risk factors might begin screening between age 45-50. JAMA April 28, 1999; 1470-72

4-7 OCCULT VITAMIN D DEFICIENCY IN POSTMENOPAUSAL U. S. WOMEN WITH ACUTE HIP FRACTURE

Many postmenopausal community-dwelling women presenting with hip fracture showed occult vitamin D deficiency. JAMA April 24, 1999; 281: 1505-11

4-8 DOUBLE BLIND, RANDOMISED STUDY OF CONTINUOUS TERBINAFINE COMPARED WITH INTERMITTENT ITRACONAZOLE IN TREATMENT OF TOENAIL ONYCHOMYCOSIS

Continuous terbinafine was significantly more effective than intermittent itraconazole in the treatment of toenail onychomycosis. It "should be the current treatment of choice for onychomycosis". BMJ April 17, 1999;318: 1031-35

4-9 LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION

When ECG evidence of left ventricular hypertrophy is present, the hypertrophy is advanced. This confers a risk of cardiac involvement several times greater than that attributed to the associated blood pressure level. Indeed, the risk is similar to that associated with a history of myocardial infarction. NEJM April 22, 1999; 340: 1221-27

4-10 MANAGING ATRIAL FIBRILLATION IN ELDERLY PEOPLE

The most effective way of minimizing the increased thromboembolic risk and treating symptoms is to return the rhythm to sustained sinus rhythm by electrical or chemical cardioversion. Restoration of sinus rhythm and maintenance of sinus rhythm after successful cardioversion may be enhanced by anti-arrhythmic drug therapy. "The optimal drug therapy has yet to be determined."BMJ April 24, 1999; 318: 1088-89

4-11 RECENT ADVANCES IN HAEMATOLOGY

Now, a new test (the serum transferrin receptor assay) is available, enabling more accurate differentiation. Transferrin is a protein that carries plasma iron. In iron deficiency anemia, the number of receptors increases. In anemia of chronic disease the number of receptors remains normal. BMJ April 10, 1999; 318: 991-94

4-12 PROBABILITY AT THE BEDSIDE: The Knowing of Chances or the Chances of Knowing

"Uncertainty is inherent in medical practice because patients present individual and complex medical circumstances. Physicians can never be certain how to transpose a biomedical theory or a clinical research finding to a particular case. In an act of interpretation, not application, physicians make clinical sense of a case, rather than placing it in a general category of cases. As interpreters, physicians draw on all their knowledge, including their own experience of patients, and laboratory-science models of cause and effect." Annals Int. Med. April 6, 1999; 130: 604-06

4-13 GRAPEFRUIT JUICE FOUND TO CAUSE HAVOC WITH DRUG UPTAKE

Grapefruit can both enhance absorption, perhaps to toxic levels, and reduce absorption, and lower effectiveness. No way to predict except by trial and error. Lancet April 17, 1999; 353: 1335

4-14 LOW DOSE SUBCUTANEOUS ADRENALINE TO PREVENT ADVERSE REACTIONS TO ANTIVENOM SERUM IN PEOPLE BITTEN BY SNAKES

Use of 0.25 mL adrenaline subcutaneously immediately before iv antivenom significantly reduced incidence of adverse reactions. BMJ April 17, 1999; 318: 1041-43

4-15 EFFECT OF ESTROGEN ON BRAIN ACTIVATION PATTERNS IN POSTMENOPAUSAL WOMEN DURING WORKING MEMORY TESTS.

Therapeutic doses of estrogen altered activation of specific brain regions during the performance of the sorts of memory function that are called upon frequently during any given day. JAMA April 7, 1999; 281: 1197-1202

4-16 DEFINITIONS OF EFFICIENCY

In healthcare, efficiency measures whether resources are being used to get the best value for the money.

"Adopting the criterion of economic efficiency implies that society makes choices which maximize the health outcomes gained from the resources allocated to healthcare. Inefficiency exists when resources could be reallocated in a way which would increase the health outcomes produced. " BMJ April 24, 1999; 318: 1136

4-17 COMPARISON OF ENDOSCOPIC LIGATION AND PROPANOLOL FOR PRIMARY PREVENTION OF VARICEAL BLEEDING.

In patients with high-risk varices, endoscopic ligation was safe and more effective than propanolol in the primary prevention of bleeding. Propanolol is modestly effective medical therapy. NEJM April 1, 1999; 340; 988-93

4-18 VENOUS THROMBOSIS

Thrombosis is a multicausal disease. Several coagulation defects may combine in one individual. There are thrombophilic families. The presence of genetic alterations in the coagulation process increases risk of thrombosis when combined with an acquired risk. Lancet April 3, 1999; 353: 1167-73

4-19 ACUTE HEROIN OVERDOSE

This reviews pharmacology, epidemiology, diagnosis, treatment, complications, and prevention.

"The concept of ‘take home’ naloxone as a method of preventing overdose-related deaths has recently been discussed. Despite misgivings, the potential opportunity to prevent thousands of heroin-related deaths warrants the dispassionate exploration of this option." Annals Int Med April 6, 1999; 130: 584-90

4-20 ANTIPHOSPHOLIPID ANTIBODIES AND THROMBOSIS

Autoantibodies specific for phospholipids (antiphospholipid antibodies) have long been recognized in systemic lupus erythematosis. They are associated with thrombotic complications and miscarriage. The terms are "lupus anti-coagulant" and "anticardiolipin" are used to describe these antibodies. The autoantibodies are heterogeneous. Their pathogenic role is not clear. Lancet April 17, 1999; 353: 1348-53

4-21 MINERALCORTICOID HYPERTENSION

"A high index of suspicion is needed in every hypertensive patient. Hypertensive patients with hypokalemia, together with those with severe hypertension (eg, those on triple therapy), or a family history of hypertension or stroke, should be screened for mineralcortocoid excess." Indeed, all patients with hypertension should have their electrolyte concentrations measured. Lancet April 17, 1999; 353: 1341-47

RECOMMENDED READING

4-3 GERIATRICS AND THE LIMITS OF MODERN MEDICINE

4-12 PROBABILITY AT THE BEDSIDE

4-16 DEFINITIONS OF EFFICIENCY

REFERENCE ARTICLES

4-11 RECENT ADVANCES IN HAEMATOLOGY

4-18 VENOUS THROMBOSIS

4-19 ACUTE HEROIN OVERDOSE

4-20 ANTIPHOSPHOLIPID ANTIBODIES AND THROMBOSIS

4-21 MINERALCORTICOID HYPERTENSION

4-1 RELATION BETWEEN FASTING PLASMA GLUCOSE AND GLYCOSYLATED HEMOGLOBIN

The WHO defined "diabetes" on the basis of a level of fasting glucose which is associated with increased likelihood of a specific micro-vascular complication (retinopathy).

The WHO criteria:

Diabetes: 1) fasting plasma glucose (FPG) concentration of 140 mg/dL (7.8 mmolL) or more, or a glucose concentration of 200 mg/dL (11.0 mmol/L) or more 2 hours after a 75 g glucose load, or both.

Impaired glucose tolerance: FPG less than 140 mg/dL and a 2 hour value 140-199 mg/dL

The cutpoints were based on 3 prospective studies in which subjects were given an oral glucose tolerance test and followed for up to 8 years.

The diagnosis of diabetes should be based on levels of glycemia that are associated with specific microvascular complications. Excessive glycosylation of proteins (forming advanced-glycosylation end-products) is widely accepted as a major, albeit not the only, pathogenic factor for microvascular complications.

There is a quantitative in-vivo link between glycosylated hemoglobin levels (HbA1c) and advanced-glycosylation end-product formation in human red cells. This compelling evidence is the basis for the use of glycosylated hemoglobin to monitor results of treatment.

The American Diabetes Association criteria:

In 1995, The ADA put forth new criteria for diagnosis of diabetes:

Diabetes: 1) FPG 126 or over (7.0 mmol/L), or 2) 2-hour plasma glucose of 200 or more after a 75g glucose challenge. The criteria should be confirmed by repeating the test on a different day. However the second criteria is not recommended for routine clinical use. The glucose tolerance test is essentially eliminated. This lowers the threshold from 140 to 126 mg/dL.

Impaired Fasting Glucose: Fasting glucose concentrations of 110 to 125 mg/dL. (6.1 to 6.9 mmol/L

Both the WHO and ADA criteria apply to asymptomatic patients.

The authors of this investigation suggest that, due to the importance of glycosylation in the pathogenesis of micro-vascular complications (especially retinopathy) in defining "diabetes", individuals with normal HbA1c levels should not be considered to have "diabetes". Labeling patients as "diabetic" exposes them to potentially negative insurance, employment, social, and psychological consequences and may create more harm than benefit.

This study determined to what extent individuals diagnosed as "diabetic" by the newer ADA criteria had or did not have excessive glycosylation (elevated HbA1c levels).

Conclusion: About 60% of the subjects had a normal HbA1c.

STUDY

1. Determined HbA1c levels in over 2800 individuals using 4 classifications:
   A. Normal – under 110 mg/dL
   B. Impaired fasting glucose (IFG) — 110 to 125 mg/dL
   C. "Diabetes" diagnosed by FBG 126 to 139
   D. "Diabetes" diagnosed by FPG 140 mg/dL or higher.
2. HbA1c levels were separated into intervals:
   A. Normal — determined in a subset of patients with FPG under 110 and a 2-hour post glucose challenge of under 140. The normal mean level of HbA1c was 5.3%. The standard deviation (SD) was 0.4%. Therefore the top normal for HbA1c (mean + 2 standard deviations) was 6.1%.
   B. Slightly elevated — upper limit of normal + 1% (6.1% + 1% = 7.1%)
   C. High —— higher than 7.1%

RESULTS

1.

	HbA1c		
	Normal (4.4-6.1%)	Slightly elevated (6.2 to 7.0%)	High (> 7.0)
Normal FPG (<110)	97%	3%	0.1%
Impaired fasting glucose (110-125)	87%	13%	0.2%
Diabetic by ADA (FPG 126-139)	61%	36%	3%
Diabetic by WHO (FPG 140 and above)	18%	32%	50%

2. The great majority of individuals diagnosed as having "impaired fasting glucose" (FPG 110-125) under the new ADA criterion had normal HbA1c levels. Few were high.
3. About 2/3 of patients diagnosed as "diabetes" by the new ADA classification (FPG 126-139) had a normal HbA1c.
4. A few patients with "diabetes" diagnosed by both criteria (FPG 140 and above) had normal HbA1c.

DISCUSSION

1. Sixty percent of individuals diagnosed as having "diabetes" by the ADA criteria (FPG 126-139) had a normal HbA1c. A minority had a HbA1c concentration associated with development or progression of micro-vascular complication

2. Determining the optimal level of glycemia depends on a balance between the medical, social, and economic costs in someone who is truly at substantial risk of adverse effects of the glycemia, and treatment is linked to measurement of excessive glycosylation, we believe that giving individuals with normal glycosylated hemoglobin levels the diagnosis of diabetes will lead to more harm than benefit (eg, employment, insurance, and possibly social and psychological disadvantages).
3. Unlike BP and cholesterol levels in which risk increases continuously even in the "normal" range, for diabetic retinopathy there is a threshold above which the risk for retinopathy increases markedly. In the Pima Indian study, the increased risk occurred in the 9th decile in which the minimum FPG was 136 mg/dL.
4. What would be lost by classifying people whose FPG is 126-139, but who have a normal HbA1c, as having impaired fasting glucose instead of diabetes? Most clinicians would agree that if a patient's HbA1c was less that 1% over the upper level of normal for the assay used (less than 7.1% in the group considered here), control is satisfactory and no drug therapy is necessary. "Therefore, patients diagnosed as 'diabetic' by the criteria 126-139 would be given dietary and exercise advice, but not pharmacological agents. The same would apply to those with impaired fasting glucose (110-125).
5. "We do not favor the return of the oral glucose tolerance test, but do favor an approach to the diagnosis of diabetes that consistently identifies equal risks for micro-vascular and neuropathic complications of hyperglycemia and one that can justify the potential negative insurance, employability, social, and psychological costs."
6. If diabetes were to be diagnosed by FPG levels of 126-139, in the US of those age 40-74, 1.8 million would be classified as diabetic, but 1 million would have a normal HbA1c and 648 000 would have mildly elevated HbA1c levels to a degree that would require only non-pharmacological intervention.
8. Given the importance of glcosylation in the genesis and development of diabetic complications, the authors suggest an alternative approach for the diagnosis of diabetes:

Fasting plasma glucose	HbA1c	Designation
< 110 mg/dL		Normal
110-139	6.2% to 7.0%	Impaired fasting glucose
110-139	>7.0%	Diabetes
140 and over		Diabetes

9. Patients with FPG consistently lower than 110 and consistently higher than 139 are readily classified as "normal" or as "diabetes".
10. For patients with FPG in the range of 110-139, HbA1c is determined to classify individuals as "impaired fasting glucose" or "diabetes".
11. In the range of 110 to 139, the HbA1c determines whether an individual has diabetes or impaired fasting glucose. A persistent HbA1c level over 1% above the upper normal range of the assay used makes the diagnosis of "diabetes".

CONCLUSION

About 60% of a large cohort of patients newly diagnosed as having "diabetes", had a normal HbA1c. If this degree of glycemia persists, they would not be at risk of microvascular complications of diabetes.

"We believe that diabetes should not be diagnosed in those with FPG levels less than 140

unless excessive glycosylation is present. Individuals without excessive glycosylation but with moderate elevations of FPG (110-139) should be treated with an appropriate diet and exercise. This diagnostic labeling achieves the goal of early intervention, without subjecting individuals to potentially negative labeling."

JAMA April 7, 1999; 281: 1203-1210 Special Communication" original investigation, first author Mayer B Davison, Charles R Drew University of Medicine, Los Angeles CA

Comment:

Classic symptomatic diabetes was not in dispute—diabetes is obviously present when the patient has classical symptoms of thirst, hunger, polyuria, and weight loss in the presence of a plasma glucose over 200. I believe we should abandon the clinical diagnosis "diabetes" except for such patients.

Classification of "diabetes" for epidemiologic purposes is a different matter. It should be defined at the outset of each study.

In no way does this indicate that individuals with fasting plasma glucose levels between 110 and 139 are "normal". Even if their HbA1c levels are entirely within the normal range, and they are not at risk of micro-vascular complications at the present, they are at increased risk of cardiovascular (macro-vascular) complications. Increased insulin levels, dyslipidemia, overweight, hypertension, and sedentary life-styles will be found in this group. This represents a golden opportunity for lifestyle changes which will make all the difference.

In addition, they should be followed closely to determine the gradual decline in glucose tolerance which inevitably occurs over time. RTJ

Note that the HbA1c concentrations cited in the article may not represent the normal range in a different laboratory. Methods have not been universally standardized. RTJ

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4-2 WHEN IS DIABETES DIABETES?

(This editorial comments and expands on the preceding.)

For laboratory tests, separation of normal from abnormal is inevitably arbitrary. Often, abnormality is based on a statistical process such as being greater than 2 standard deviations above a mean value for the population. In other cases, values are related to the likelihood of a particular laboratory value to be associated with a subsequent adverse event. (Eg, plasma glucose with risk of retinopathy.) If the laboratory value is abnormal (ie, predicts future disease), effective treatment could be instituted to prevent or delay onset of the disease.

If there is an effective, safe, simple, and inexpensive test for the risk factor, and treatment is available, then the test should be such that few cases are missed even though many false positives may occur.

If the test is complex and treatment is expensive and of questionable effectiveness, then it is important that the positive test truly indicates the risk and that there are few false positives.

We know that aggressive treatment of high plasma glucose will delay or prevent onset of micro-vascular complications. Thus, the emphasis is on not missing cases of diabetes. The ADA lowered the cutpoint for this reason.

If we agree that a FPG under 110 eliminates the risk of "diabetes" (at least for the immediate future), ant that a FPG over 140 is diagnostic of "diabetes" with its risk of complications, this leaves a wide "grey zone" of 110 to 126 to 130. Where should the predictive cutpoint be set? The investigators suggest performing 2 diagnostic tests — FPG and HbA1c. This adds a measure of pathophysiologic abnormality (protein glycosylation) to the prediction of future complications.

Although protein glycosylation is undoubtedly an important pathway associated with the development of complications, it is dangerous to assume it is the only path. The diagnostic scheme the authors propose has not been tested prospectively.

JAMA April 7, 1999; 281: 1222-24 Editorial by Frank Vinicor, Centers for Disease Control, Atlanta GA

Comment:

The argument is over the meaning of a word. I believe whether a patient has "diabetes" or not is the wrong question. The important point is whether the glucose levels are high enough to lead to future complications. I agree that the word "diabetes" is the wrong one for patients without symptoms and FBS levels 110 to 126 and even to 139. We should pay attention to any FBS over 110. These patients are not normal. They do have a condition that calls for a name. Perhaps "impaired glucose metabolism". This would be less harmful than labeling them with "diabetes".

In what way are these patients abnormal? Chiefly because FBS concentrations at this level are predictive of cardiovascular disease — more so than for microvascular disease. Here screening tests for other risks of cardiovascular disease (BP, lipid levels, sedentary lifestyle, overweight) are increasingly important and allow early preventive interventions. RTJ

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Read the Original!

4-3 GERIATRICS AND THE LIMITS OF MODERN MEDICINE

"Like a number of geriatricians, I have come to believe that modern medicine does not work well for old people. Old patients serve as a mirror, reflecting the limitations and sometimes the absurdities of modern medicine."

The editorialist comments on 3 areas that are problematic for old people

The medicalization of everyday life:

Medicine has expanded into almost all aspects of human existence. All cultural and personal aspects of the struggles of life from childhood to death have been brought under the rubric of physical and mental health. This removes much of human experience from the realm of personal wisdom and individual understanding, and places it in the realm of medicine, with its accompanying aura of biologic determinism and technological susceptibility.

Medicalization is not limited to behavior. New physical illnesses have been created too. The most important of these are the proto-illnesses – diseases that do not cause symptoms and produce no suffering, but are thought to be dangerous because there is a higher likelihood of a real disease later on. High blood pressure, high cholesterol, and colonic polyps are good examples. There are indeed benefits from recognizing proto-illness. Unfortunately there is also harm.

Medical care of the elderly has been expanded and technologized and focused so much on medicalization that we fail our most important task—providing relief from suffering. Attention to some proto-illnesses could benefit 80 and 90 year olds. But, 80-year-olds can ill afford the ceding of responsibility and loss of control inherent in medicalization. The challenges of very old age are spiritual, not medical. The appropriate role of the physician is as counselor, not as scientific expert.

The primacy of diagnosis:

One of the tenents of modern medicine is that we must diagnose accurately before we can treat. With current technology, diagnosis frequently translates into a direct visualization of the pathological process. What if we find pathology everywhere we look? Such is the case with the very old. Overtesting harms. Hiatus hernia occurs in three fourths of women in their 80s. Is this disease? The PSA test to screen for prostate cancer has resulted in an epidemic of diagnoses in older men who otherwise

would have lived happily without knowing they had cancer. The quadrupling of radical surgery in these patients is of no proven value.

The primacy of diagnosis reflects a confusion of means with ends. So little of what is done for old people seems aimed in any direct way at making the patient feel better.

But a scary part of this scenario is that geriatric patients may be grateful —thankful that his doctor has screened and found the prostate problem, or the carotid stenosis, or the coronary problem "in time".

Reimbursement for Medical Care:

Of the several ways to view medical care today, perhaps the most disturbing is the economic perspective. Consider hospitalization of an 80 year old for a complicated feeding process. Various specialists come around and perform their procedures, all feeding from Medicare. Overtreatment of an 80-year old borders on assault.

Evidence-based medicine is not kind to the elderly. This movement trusts only the products of randomized, controlled trials or, preferably meta-analyses of those trials. But subjects over age 75 are rarely found in such trials, rendering this population invisible to scientific medicine. If we teach what we know, and if we know only what we can measure in clinical trials, then we can say little of importance about the care of the elderly. "The most important resources required in caring for the very old – sufficient time and empathy – are not included in the critical pathways of managed care. "

Caring for the elderly:

"Part of why I love being a doctor for old people is that it is easy; the rules are simpler and success is clearer than when one is providing care for younger adults. With the elderly, there are real problems to confront, real suffering to relieve, and real courage to admire every day." What percentage of today's physician's time is spent on relieving suffering? Proto-illnesses cause no symptoms, so the satisfaction derived from treating them must be based on statistics of risk reduction. What is needed is a new model, a new mindset for physicians providing care for the very old. There are models which work better than the white-coat-scientist model. One alternative is the Hospice model. Many of the values of Hospice are appropriate for older patients who are not dying, including an understanding that each person is unique, a realization that everyone dies, a recognition that comfort and happiness are very important, an appreciation of the many unmeasurable adverse consequences of medical evaluation and treatments, a willingness to make compromises in carrying out plans, depending on changing circumstances, and an ability to treat without diagnosing.

It is often assumed that a focus on such pragmatic issues as preserving independence and relieving suffering comes at a cost of potential years-of-life lost. Withholding useless treatments does not enhance the quality of life at the cost of quantity. "It is disturbing how many of my middle-aged colleagues in academic medicine have horror stories regarding the medical care of their parents or in-laws. These anecdotes should be listened to. Their collective weight may be as close as we get to documentation of the failure of modern medicine with respect to the elderly. These rueful stories reveal the profound disjunction between our scientific rhetoric and or deepest desires for compassionate care."

"Data do not convey values, and the practice of medicine is about values."

NEJM April 22, 1999; 340: 1283-85 "Sounding Board" commentary by James S Goodwin, University of Texas Medical Branch, Galveston.

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4-4 CRITERIA AND RECOMMENDATIONS FOR VITAMIN C INTAKE

Recommendations for vitamin C intake are under revision by the Food and Nutrition Board **(FNB)** of the National Academy of Sciences. The last recommended daily allowance in 1989 was 60 mg. Since then, much data has become available on which new recommendations may be based.

The FNB developed new guidelines classifications for providing estimates of nutrition intakes. The concept of the recommended daily allowances **(RDA)** was expanded to include the following "Dietary Reference Intakes"

1. Estimated average requirements **(EAR).**

   This is the amount of nutrient estimated to meet the requirement of half of the healthy individuals in a life-stage and gender group. Half of the individuals would have values above the EAR value, and half below. If the SD of the EAR is not known, the coefficient is arbitrarily assumed to be 10%, and the RDA is therefore 1.2 X EAR. For vitamin C the EAR is 100 mg/d — that dose at which 50% of subjects' neutrophiles are saturated.

2. Recommended Daily Allowance (RDA)

   Using the EAR definition, the RDA is arbitrarily calculated by taking the EAR plus 2 standard deviations. Thus the RDA for vitamin C is 100 mg X 1.2 or 120 mg.

3. Adequate intake **(AI)**

   The FNB can decide that an EAR is indeterminate, and use the AI in place of the RDA. AI is an intake level based on an observed or experimentally determined approximation of nutrient intake by a group of healthy people.

   The primary use of the AI is a goal for the nutrient intake of individuals.

   One (of several) AI calculations for vitamin C is 200 mg/d. This is provided by 5 servings of fruits and vegetables daily, an amount available in the US diets now. (And the amount associated with a decreased cancer risk.) Tissues probably are saturated at 200 mg/d without apparent harm. The estimate of 200 mg accounts for the possibility that vitamin C from foods might decrease compared with pure vitamin C. At 200 mg/d, there are no known adverse effects, and possibly there are biochemical benefits. At 200 mg, deficiency will be prevented for more than 1 month if intake suddenly ceased. "For patients unable or unwilling to consume fruits, vegetables, or vitamin C- fortified foods, a supplement containing 200 mg should suffice.

4. Tolerable upper intake level **(UL)**

   The highest level of daily nutrient that does not pose adverse health effects to almost all individuals in the population. Because patients with preexisting hyperoxaluria may have increased risk of nephrolithiasis at vitamin C levels of 1 g or more, and because this dose might increase oxalate excretion in some healthy people, the UL is less than 1 g.

"Physicians can tell patients that 5 servings of fruits and vegetables per day (I believe this means 5 fruits and 5 vegetables. RTJ) may be beneficial in preventing cancer and providing sufficient vitamin C intake for healthy people, and that 1 g or more of vitamin C may have adverse consequences in some people."

JAMA April 21, 1999; 281: 1415-23 "Special Communication" first author Mark Levine, National Institutes of Health, Bethesda, MD.

Comment:

The article confused me. We now have 5 guidelines. Pick one:

5 fruits and 5 vegetables

Daily value (presently on supplement labels) — 60 mg

EAR — 100 mg

RDA — 120 mg

AI — 200 mg.

The article places the RDA of vitamin C at 120 mg. But the "adequate intake" (AI) at 200.
The "Daily Value" (DV) on my supplement is 60 mg. The general public will be confused should these recommendations be widely published. Simply tell patients they should take a total (dietary fruits and vegetables + supplements) of 200 mg daily.

Authorities are gradually increasing the recommended amount of vitamin D, folic acid, and now vitamin C. I try to eat 5 fruits and 5 vegetables daily. I consider the additional 60 mg in my supplement to be adequate. RTJ

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This is fascinating Read the Origianl

4-5 EFFECTS OF WRITING ABOUT STRESSFUL EXPERIENCES ON SYMPTOM REDUCTION IN PATIENTS WITH ASTHMA AND RHEUMATOID ARTHRITIS

Addressing patient's psychological needs produces physical as well as psychological benefits. Writing about emotionally traumatic experiences may have a surprisingly beneficial effect on symptoms, well-being, and health care use. A recent meta-analysis of writing exercises in which patients expressed their emotions reported improved health outcomes.

This study assessed whether writing about stressful life experiences would affect disease status in patients with asthma and rheumatoid arthritis **(RA).**

Conclusion: Writing was associated with clinically relevant improvements in health status.

STUDY

1. Randomized, controlled trial entered over 100 volunteer outpatients, half with RA, half with asthma.
2. Randomized to: 1) write about emotionally neutral topics (eg, about plans for their day), or 2) write about the most stressful event in their lives. The exercise occupied 20 minutes on 3 consecutive days.
3. All essays were anonymous. Participants did not discuss their writing with project staff, and were never in contact with each other as part of the study.

RESULTS

1. At 4 months:
   A. Asthma patients: The experimental group showed improvements in lung function. Mean predicted FEV1 improved from 64% to 76%. The control group showed no change.
   The asthma symptoms improved within 2 weeks.
   B. RA patients: experimental group improved in overall disease activity (a reduction from 1.65 to 1.19 on a 4 point scale). Controls did not change.
   The improvement in RA patients was not evident until 4 months.
2. Outomes at 4 months:

	Worse	No change	Improved
Control	22%	54%	24%
Experimental	4%	49%	47%

DISCUSSSION

1. Almost half of the experimental group met criteria for clinically meaningful improvement vs about a fourth of the control group.
2. Other studies report that writers of stressful life-situations show considerable emotional upset during the writing sessions with concomitant alterations in psychophysical measures (e.g., heart rate, BP).
3. The most common stressful topics were the death of a loved one, serious problems of a significant other, problems in relationships, and seeing or being in a major disaster.
4. The duration of improvement is not known.

CONCLUSION

Patients with mild to moderately severe asthma or rheumatoid arthritis who wrote about stressful life experiences had clinically relevant improvements in health status. These gains were beyond those attributable to the standard medical care participants were receiving.

JAMA April 14, 1999; 21: 1304-09 Original investigation, first author Josha M Smyth, North Dakota State University, Fargo

Comment:

Fascinating! Obviously suject to bias, but calls for replication. If writing about stress can benefit, how much more would talking with an empathic listener benefit? RTJ

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A Perennial Debate

4-6 SCREENING MAMMOGRAPHY UNDER AGE 50

Benefits of mammography mainly accrue to patients age 50 and older. Prestigious organizations differ in recommendations about age 40-49.

In 1993 the (US) National Cancer Institute (NCI) reported results of 7 randomized trials of mammographic screening for breast cancer **(BC).** For women over age 50, a 30% reduction in mortality from BC followed screening. For women 40-49, the reported 15% mortality reduction in BC mortality did not meet the usual statistical criterion for rejecting the null hypothesis. The number needed to screen to save one life is substantially higher in the younger group.

The NCI committee concluded that mammography did not significantly benefit women age 40-49.
More recent overviews from Sweden concluded there was indeed significant benefit in younger women — a 24% decrease in mortality. A second NCI conference degenerated into what was described as the "NCI brawl" — basically pitting treating physicians against epidemiologists. The competing values were "lives saved versus numbers screened to save one life".

Combined data indicate that regularly screening 1000 women age 40-49 would extend the life of one. The harms and costs of screening are considerable. Up to 24% false positives may occur, leading to anxiety, repeat mammograms, ultrasounds, and biopsies with ever increasing costs.

How should we advise our 40-49 year-olds? The editorialists make "A Reasonable Recommendation":

1) Advise women age 40-49 about the benefits and harms of mammography screening. (Young women overestimate their risk of dying of BC.)
2) Screen those with substantial risk factors, especially family history.

3) Screen those who are eager for screening.

4) Those without particular risk factors might begin screening between age 45-50.

"We recommend against using mammography in women age 40 to 49 as a quality-of-care indicator for health plans or provider organizations."

JAMA April 28, 1999; 1470-72 "Contempo 1999 Updates Linking Evidence and Experience" Commentary by Karen Antman and Steven Shea, Columbia University College of Physicians and Surgeons, New York, NY.

Comment:

I suspect that most clinicians tilt toward early screening, ignoring the epidemiological evidence. Younger women should be fully aware of the possibility of false positives and their consequent harms. A compromise — why not set the 50th birthday as the date for the first screen? RTJ

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4-7 OCCULT VITAMIN D DEFICIENCY IN POSTMENOPAUSAL US WOMEN WITH ACUTE HIP FRACTURE

Vitamin D is required for efficient absorption of dietary calcium and for normal bone mineralization. Reduction in vitamin D levels is associated with impaired calcium absorption, and a compensatory increase in parathyroid hormone (PTH) which, in turn stimulates bone resorption. This may contribute to hip fractures in postmenopausal women.

This study was designed to determine if postmenopausal women with hip fractures have low vitamin D and high PTH levels as compared with women admitted for elective joint replacement.

Conclusion: Women presenting with hip fracture showed occult vitamin D deficiency.

STUDY

1. Comparative case series entered 30 postmenopausal women (all osteoporotic) with acute hip fracture, and 68 admitted for elective joint replacement
2. Of those admitted for elective surgery, 17 were osteoporotic, and 51 were not.
3. Women taking estrogen replacement (46% of patients) were included. (Estrogen can affect bone, but not vitamin D levels).

RESULTS

1. The 30 women with osteoporotic hip fracture had lower levels of 25-hydroxyvitamin D (32 nmol/L), than women without osteoporosis admitted for elective joint replacement (50 nmol/L), and women with osteoporosis admitted for joint replacement (55 nmol/L)
2. Parathyroid hormone levels were higher in women with fractures than in women admitted for joint replacement.
3. Half of the women with fractures had deficient vitamin D (<30 nmol/L) and 37% had elevated PTH levels (greater than 6.84 pmol/L). 81% had urinary calcium levels below the median.
4. Levels of N-telopeptide, a marker for bone resorption, were greater in women with hip fractures.

DISCUSSION

1. In this study, among elderly community-dwelling women admitted for acute hip fracture low vitamin D

and high PTH levels were common.

2. This raises the question – will replacement with vitamin D lead to a reduction in incidence of hip fractures in older women? Supplements of 800 IU daily may be necessary to attenuate bone loss in this age group. And in patients with hip fracture will vitamin D supplements facilitate hip fracture repair and reduce future risk of fracture?
3. Vitamin D deficiency is preventable (and inexpensive).

CONCLUSION

Many postmenopausal community-dwelling women presenting with hip fracture showed occult vitamin D deficiency.

JAMA April 24, 1999; 281: 1505-11 Original investigation, first author Meryl S LeBoff, Brigham and Women's Hospital, Boston. MA

Comment: Vitamin D and calcium nutrition is a favorite subject in the flagship journals.

Older women may benefit from a vitamin D intake of 800 IU daily, and a calcium intake of 1200 mg/d.

The benefit/harm-cost of vitamin D and calcium supplementation is high. RTJ

4-8 DOUBLE BLIND, RANDOMISED STUDY OF CONTINUOUS TERBINAFINE COMPARED WITH INTERMITTENT ITRACONAZOLE IN TREATMENT OF TOENAIL ONYCHOMYCOSIS

Onychomycosis is one of the most common nail diseases, and one of the few that are curable. Systemic treatments include terbinafine [Lamisil], primarily fungicidal, and itraconazole [Sporanox], primarily fungistatic. Both represent a major advance over griseofulvin.

This study compared efficacy and safety of continuous terbinafine vs intermittent itraconazole.

Conclusion: Terbinafine was superior.

STUDY

1. Prospective, randomized, double-blind, parallel group trial lasted 18 months.
2. Randomized 500 patients. All had clinical and mycological diagnosis of dermatophyte onychomycosis of the toenail. Trichophyton species were the exclusive causative organism, chiefly T rubrum.
3. Randomized to 4 groups:
   a. Terbinafine 250 mg daily for 12 weeks (T-12)
   b. Terbinafine 250 mg daily for 16 weeks (T-16)
   c. Itraconazole 400 mg a day for 1 week every 4 weeks for 12 weeks; 3 one-week courses (I12)
   d. Itraconazole 400 mg a day for 1 week every 4 weeks for 16 weeks; 4 one week courses. (I-16)
4. Assessed mycological cure at 18 months. (Negative microscopy and culture.)

RESULTS

1. Cure rates

T-12	T-16	I-12	I-16
76%	81%	38%	49%

2. About half of the patients reported at least one adverse effect (nausea, headache, flu-like symptoms).
3. Most were considered mild and unrelated to the drugs. No differences between groups.

DISCUSSION

1. Terbinafine 250 mg daily for 3 to 4 months produced better cure rates at 18 months than itraconazole.
2. The better results may have been because terbinafine is fungicidal. Concentrations achieved in the nail are around 100-fold higher than the minimum fungicidal concentration of the drug.
3. The reported concentrations of itraconazole are on the borderline between fungistatic and fungicidal.

CONCLUSION

Continuous terbinafine was significantly more effective than intermittent itraconazole in the treatment of toenail onychomycosis. It "should be the current treatment of choice for onychomycosis".

BMJ April 17, 1999;318: 1031-35 Original investigation by the LION study group, first author E Glyn V Evans, University of Leeds, UK

Comment: Study supported by Novartis, maker of terbinafine. RTJ

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4-9 LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION

When ECG evidence of left ventricular hypertrophy (LVH) is present, the hypertrophy is advanced. This confers a risk of cardiac involvement several times greater than that attributed to the associated blood pressure level. Indeed, the risk is similar to that associated with a history of myocardial infarction.

The presence of ECG evidence of LVH combined with hypertension magnifies risk. And the clinical sequelae of coronary artery disease are worsened in patients with ECG evidence of LVH. Such patients have a six-fold increase in the likelihood of sudden death from cardiac causes.

Currently, there is not sufficient evidence to support the preferential use of one class of antihypertensive agents in patients with LVH. "Until such evidence is produced, the extent of the reduction in BP must be regarded as more important than the type of antihypertensive agent used.

NEJM April 22, 1999; 340: 1221-27 Editorial by Francis G Dunn and Marc A Pfeffer, Stobhill Hospital, Glasgow, Scotland.

See also: Report from the National Heart, Lung, and Blood Institute's Framingham Heart Study — " Trends in the Prevalence of Hypertension, Antihypertensive Therapy, and Left Ventricular Hypertrophy from 1950 to 1989" NEJM April 22, 1999; 340: 1221-27. The increasing use of antihypertensive medication has resulted in a reduced prevalence of high blood pressure and a concomitant decline in left ventricular hypertrophy in the general population. This may explain part of the considerable decline in mortality from cardiovascular disease observed since the late 1960s

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4-10 MANAGING ATRIAL FIBRILLATION IN ELDERLY PEOPLE

"Atrial fibrillation **(AF)** accounts for up to 36% of all strokes in elderly people."
Presenting symptoms include shortness of breath, palpitations, and fatigue. The loss of atrial systolic function (the "atrial kick") can reduce cardiac output by up to 50%, especially in those with coincident ventricular impairment. Symptoms can be reversed and cardiac output increased by restoring sinus rhythm.

The most effective way of minimizing the increased thromboembolic risk and treating symptoms is to return the rhythm to sustained sinus rhythm (SR) by electrical or chemical cardioversion. Cardioversion is safe, with an estimated risk of

thromboembolism less than 1%. It is most effective when delivered shortly after onset of the AF before structural changes in the atria have been established. "When the AF has been present for less than 48 hours, cardioversion is safe without prior anticoagulation."

Cardioversion is successful in 75% to 91% in patients of all ages. Success is less likely if the AF has been present for a long time (over 1 year), if atrial diameter is increased (over 45 mm), and heart failure is present. "Most studies found that increased age has no independent effect on the success of cardioversion. "

Restoration of sinus rhythm and maintenance of sinus rhythm after successful cardioversion may be enhanced by anti-arrhythmic drug therapy. "The optimal drug therapy has yet to be determined. "

Failing conversion to sustained SR, antithrombosis with warfarin reduces the risk of stroke by about 70%. The elderly are less likely to receive anticoagulation therapy than the young on the basis of age alone. Many physicians do not prescribe warfarin for elderly patients because of a higher risk of hemorrhage when the INR is maintained at 2.0 to 4. They use aspirin instead. But, aspirin has not been shown to be effective in the elderly. Two recent trials showed that anticoagulation to an INR of 1.5 to 3.0 is effective and safe in those over age 75.

BMJ April 24, 1999; 318: 1088-89 Editorial by Kate M English and Kevin S Channer, Royal Hamshire Hospital, Sheffield, UK

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REFERENCE ARTICLE

Distinguishing iron deficiency from anemia of chronic disease

4-11 RECENT ADVANCES IN HAEMATOLOGY

This article reviews some of the latest on anemias; hemophilia; disorders associated with increased risk of thrombosis (hypercoagulability; thrombophilia), including factor V mutations, prothrombin gene mutation, and hypercysteinemia.

Distinguishing anemia due to iron deficiency and anemia of chronic disease has been a difficult but common problem. Anemia of chronic disease is complex and involves inflammatory cytokines, reduced marrow response to erythropoietin, reduced red cell life span, and impaired reuse of iron.

In typical uncomplicated iron deficiency, mean cell volume and serum ferritin and iron concentrations are reduced and total iron-binding capacity is raised. But, cases are often not typical, and results of tests may seem conflicting.

Serum ferritin represents the iron stores. A reduced concentration generally indicates depletion. But, it is also an "acute phase protein". Concentrations are raised in inflammatory disorders (eg, rheumatoid arthritis).

Thus, concentrations may be normal (or even raised) in a patient with active rheumatoid arthritis, even if the patient is truly iron deficient.

If a patient with anemia of chronic disease is also iron deficient, the parameters for diagnosing iron deficiency are altered, making diagnosis difficult. Often a bone marrow stain for iron is the only way for accurately assessing reduced iron status.

Now, a new test (the serum transferrin receptor assay) is available, enabling more accurate differentiation. Transferrin is a protein that carries plasma iron. Cells that require iron have a transferrin receptor on their surface. The receptor binds plasma transferrin (with its bound iron atoms). The iron-transferrin-receptor complex then enters the cell. After unloading the iron, the transferrin-receptor complex moves back to the cell surface. The iron-free transferrin is dissociated from the receptor and is free to pick up another iron.

In iron deficiency anemia, the number of receptors increases. In anemia of chronic disease the number of receptors remains normal.

Assays for the transferrin receptor are performed by an enzyme-linked immunosorbent assay. The test seems as reliable as bone marrow examination. It should be valuable in patients with rheumatology disorders and other inflammatory disorders.

BMJ April 10, 1999; 318: 991-94 "Clinical Review" commentary by Drew Provan and Denise F O'Shaughnessy, Southampton General Hospital, UK

Comment: The concept of the iron-transferrin-receptor is new to me. Heretofore, distinguishing iron deficiency anemia from anemia of chronic disease has been difficult. RTJ

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Read the Original!

4-12 PROBABILITY AT THE BEDSIDE: The Knowing of Chances or the Chances of Knowing

"We use the term 'risk' as though its meaning is clear, but we rarely stop to think about what an extraordinarily peculiarly medical characteristic it is, particularly when applied to an individual patient. We do not measure it directly in our patients, as we would any other clinical variable, but rather in others who are in some way 'like' our patients. And it is not measured in another individual patient; we instead take the property of a group — for example the percentage of patients that dies — and call that our patients' risk. But when we transfer a number from a group to an individual patient its meaning can qualitatively change."

"Consider what would happen to 100 identical copies of Mr. Smith if each underwent the operation for stone described by Claude Bernard. Mortality was 40%.. Would 40 Mr. Smiths die? Or would all 100 Mr. Smiths either live or die, with 40% representing our uncertainty about which it would be?"

"Uncertainty is inherent in medical practice because patients present individual and complex medical circumstances.

Physicians can never be certain how to transpose a biomedical theory or a clinical research finding to a particular case. In an act of interpretation, not application, physicians make clinical sense of a case, rather than placing it in a general category of cases. As interpreters, physicians draw on all their knowledge, including their own experience of patients, and laboratory-science models of cause and effect."[1]

"Inevitably, however, a gap exists between what we understand in a given patient and what we are able to predict; this is where probability fits in." "Where does the locus of uncertainty reside — in the patient's body or in the physician's mind?"

Annals Int. Med. April 6, 1999; 130: 604-06 editorial by Steven N Goodman, Johns Hopkins University, Baltimore, MD

1. Quote from Tannenbum SJ "What Physicians Know" NEKM 1993; 329: 1268-71

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4-13 GRAPEFRUIT JUICE FOUND TO CAUSE HAVOC WITH DRUG UPTAKE

Previous studies showed that grapefruit juice enhances absorption of some orally administered drugs. (Eg, some HIV protease-inhibitors; some calcium blockers, statins.) This happens because the juice inhibits an intestinal drug-metabolizing enzyme, thus protecting the medication from being destroyed before it is absorbed.

Conversely, grapefruit juice can block uptake of some medications by activating the pump which ejects drug molecules out of the gut wall back into the lumen. A study in California[1] demonstrated that the juice reduced the absorption of digoxin, cyclosporine, losartan, and others. "Grapefruit juice seems to be unique in producing such a large dose-altering effect." It may affect the action of many other drugs which are affected by the drug-ejecting pump.

Lancet April 17, 1999; 353: 1335 Commentary from the Lancet staff.

1. Pharm Res 1999; 16: 478-85

Comment:

Thus, grapefruit can both enhance absorption, perhaps to toxic levels, and reduce absorption, and lower effectiveness. No way to predict except by trial and error. RTJ

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4-14 LOW DOSE SUBCUTANEOUS ADRENALINE TO PREVENT ADVERSE REACTIONS TO ANTIVENOM SERUM IN PEOPLE BITTEN BY SNAKES

Antivenom serum is the most effective, if not the only effective treatment available for snake bites. Adverse effects to polyspecific antivenom serum are common. Anaphylactic shock may occur.

Antihistamines counter only the effects of histamine release; hydrocortisone takes time to act. They will not be effective against adverse reactions that can develop almost immediately.

This study assessed the efficacy and safety of low dose subcutaneous adrenaline to prevent acute reactions to antivenom.

Conclusion: Low dose adrenaline effectively reduced adverse effects.

STUDY

1. Prospective, double-blind, randomized placebo-controlled trial entered over 100 patients after snake bite during the rice paddy harvesting season in Sri Lanka.
2. All were considered to require antivenom because of systemic evenomation or severe local reactions.
3. Randomized to: 1) 0.25 mL (1:1000) subcutaneous adrenaline, or 2) placebo injection immediately before administration of the antivenom.
4. Haffkine polyspecific antivenom serum (Haffkine Laboratories, India), an equine product was administered intravenously.

RESULTS

1. 11% of treated patients developed acute adverse reactions to antivenom vs 43% of controls. (Highly significant reduction.)
2. No severe reactions to the antivenom occurred in the treated group; 4 in the placebo group.
3. No significant adverse effects attributed to adrenaline.
4. No patient died.

DISCUSSION

1. A major concern regarding use of adrenaline is the potential risk of intracerebral hemorrhage resulting from the ability of certain venoms to increase risk. The combination adrenaline + venom might further

increase risk.

2. No hemorrhages occurred in this study.

CONCLUSION

Use of 0.25 mL adrenaline subcutaneously immediately before iv antivenom significantly reduced incidence of adverse reactions

BMJ April 17, 1999; 318: 1041-43 Original investigation, first author A P Premawardhena, University of Kelaniya, Sri Lanka

Comment: “venOM”? — “venIN”? My dictioinary defines venOM as “a poisonous secretion of some animnals”. VenIN is not defined. AntivenIN is defined as an antitoxin active against venOM. I am confused. What is the distinction>? Snake antivenin is available in the US (Wyeth-Ayerst; 1999 PDR p 3265) — a polyvalent horse serum capable of neutralizing toxic effects of venoms of rattlesnakes, copperheads, cottonmouth moccasins, and Fer-de-lance. RTJ

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4-15 EFFECT OF ESTROGEN ON BRAIN ACTIVATION PATTERNS IN POSTMENOPAUSAL WOMEN DURING WORKING MEMORY TESTS.

Some previous studies have suggested that estrogen has a positive influence on verbal memory in postmenopausal women. This study investigated the effects of estrogen on brain activation patterns in postmenopausal women as they performed memory tests.

Conclusion: Estrogen in a therapeutic dose altered brain activity patterns during performance of memory function tests.

STUDY

1. Double-blind, placebo-controlled, crossover trial randomized 46 postmenopausal women (mean age 51) to: 1) conjugated equine estrogen.1.25 mg/d, and 2) placebo.
2. Patients were crossed over with a washout period of 14 days.
3. Measured brain activation patterns using functional magnetic resonance imaging during tasks involving working memory.

RESULTS

1. During the estrogen periods, increased activity occurred in the inferior parietal lobule and right superior frontal gyrus accompanied by greater left-hemisphere activation
2. However, estrogen did not affect actual performance of the verbal and non-verbal memory.

DISCUSSION

1. "This study indicates that estrogen in a traditionally prescribed therapeutic dose produces significant alterations in brain activation patterns in postmenopausal women as they perform working memory tasks."
2. This suggests a functional plasticity of the memory systems in mature women.

CONCLUSION

A therapeutic dose of estrogen altered activation of specific brain regions during the performance of the sorts of memory function that are called upon frequently during any given day.

JAMA April 7, 1999; 281: 1197-1202 Original trial, first author Sally E Shaywitz, Yale University, New Haven, Conn.

Comment:

I abstracted this article as an example of the new non-invasive techniques measuring brain function. I do not pretend to understand the technology, but believe these methods have great promise.

Is this clinically applicable? — No. Much more study is needed, particularly regarding the actual performance of memory. (The study showed no effect.) However, with the increasing sophistication of the public in medical matters, women may be asking about this. Clinicians can inform them that the data are suggestive but not proven. This may tilt some patients into taking hormone replacement therapy. RTJ

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Read the Original! Efficacy?, Effectiveness?, Efficiency?

4-16 DEFINITIONS OF EFFICIENCY

"Economic Notes" describes 3 concepts of economic efficiency (achieving the most from scarce resources). In healthcare, efficiency measures whether resources are being used to get the best value for the money.

"Adopting the criterion of economic efficiency implies that society makes choices which maximize the health outcomes gained from the resources allocated to healthcare. Inefficiency exists when resources could be reallocated in a way which would increase the health outcomes produced. "

The three concepts of efficiency:

1) Technical -- using given resources to maximum advantage. Refers to the physical relationship between capital and labor on one side and health outcomes on the other. A technically efficient position is achieved when the maximum possible improvement in outcome is obtained from a set of resource inputs. (Eg, a recent trial found that a 10 mg daily dose of alendronate was as effective as a 20 mg dose. The lower dose was technically more efficient.)

2) Productive – choosing from different combinations of resources to achieve maximization of health benefits for a given cost, or the minimization of cost for a given health outcome. When different combinations of inputs are compared, the choice between interventions is based on the relative costs of the different inputs.

3) Allocative – achieving the right mixture of healthcare programs to maximize the health of society. This concept takes account, not only of the productive efficiency with which healthcare resources are used to produce health outcomes, but also the efficiency with which these outcomes are distributed to maximize the welfare of the community.

BMJ April 24, 1999; 318: 1136 "Economic Notes" commentary by Stephen Palmer and David J. Torgerson, University of York, UK

Comment:

This deals with trying to obtain maximum benefits for society at the lowest cost. The principle also applies to individuals. We should know the costs of drugs and procedures and enable patients to choose those that cost the least while

reaching equivalent benefits. Generics may be chosen over name-brand drugs. A pill cutter may allow a higher dose pill to be obtained at a lower cost per milligram, then cutting the pill into the desired dose. Drugs may be titrated to achieve the desired effect at the lowest dose. Newer, more expensive drugs can be avoided until their benefits are clearly demonstrated to warrant their higher costs. We should know the cost of all the drugs we prescribe.

I continue to be uncertain about the distinction between efficacy, efficiency, and effectiveness. This is an opportunity to clarify:

Efficacy relates to outcomes in investigative trials. Outcomes are almost invariably better in selected patients than they are when the same intervention is applied to the general population of patients.

Effectiveness relates to outcomes when the intervention is applied to the general population of patients. Outcomes will be less beneficial than for investigative trials of efficacy.

Efficiency relates to the concepts noted in the article. It is an economic concept. RTJ

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4-17 COMPARISON OF ENDOSCOPIC LIGATION AND PROPANOLOL FOR PRIMARY PREVENTION OF VARICEAL BLEEDING.

Bleeding esophageal varices carry a high mortality rate. A non-selective beta-blocker is the most effective primary-preventive therapy for patients with cirrhosis and large varices. However, side effects and lack of effective lowering of the hepatic venous pressure gradient reduce effectiveness.

Endoscopic sclerotherapy is currently not recommended as primary-preventive therapy for bleeding because results of studies conflict. Endoscopic variceal ligation is more effective and safer.

This study compared the beta-blocker propanolol [Inderal; generic] with endoscopic ligation for primary prevention of bleeding.

Conclusion: Ligation was safer and more effective.

STUDY

1. Prospective controlled primary-prevention trial entered 89 patients who had large varices (the great majority due to cirrhosis and over 5 mm in diameter). All were considered at risk for bleeding.
2. Randomized to 1) propanolol at a dose sufficient to reduce base-line pulse rate by 25%, or 2) ligation performed weekly until the varices were obliterated or so reduced in size that it was not possible to continue treatment.

RESULTS

1. Mean number of sessions to achieve complete variceal ligation = 3.
2. At 18 months bleeding occurred in 43% of the propanolol group; and 15% of the ligation group.
3. Three of the 45 patients receiving ligation bled before the ligations were completed.
4. Recurrence of the varices occurred in twenty percent of the ligation patients within 4 months.
5. No serious adverse effects from ligation.

DISCUSSION

1. Both beta-blocker therapy and ligation have been shown to reduce the risk of a first episode of bleeding.

2. This study confirmed benefit of propanolol reported by previous studies. (*At least medical therapy has some benefit. RTJ*)

3. But, ligation is superior.

4. Beta-blocker therapy must be continued for life. This raises problems with compliance.

5. Ligation led to obliteration in about a month.

6. Ligation should have a role particularly in patients with high-risk varices in whom beta-blockers are contraindicated or must be discontinued because of side effects.

7. "Our findings suggest the combination of both therapies should be evaluated."

CONCLUSION

In patients with high-risk varices, endoscopic ligation was safe and more effective than propanolol in the primary prevention of bleeding

NEJM April 1, 1999; 340; 988-93 Original investigation, first author Shiv K Sarin, Pant Hospital, New Delhi, India.

An editorial "Primary Prevention of Bleeding from Variceal Varices" in this issue of NEJM (pp 1033-35) comments: Of the patients with compensated cirrhosis (ie, no ascites, no encephalopathy, no severe jaundice) 30% have varices; of those with decompensated cirrhosis — 60%. The risk of bleeding is higher among those with severe liver dysfunction and those whose varices are large or have "red signs" — so called varices on varices.

Previous studies of beta-blocker therapy for prevention of first bleeding reported a 50% reduction in incidence of bleeding. And a lower mortality rate. The addition of isosorbide mononitrate resulted in a further reduction in rate of bleeding.

Results of sclerotherapy have been disappointing.

The editorialist thinks the study should not change the present clinical practice of giving beta-blockers for primary prevention of bleeding. Propanolol is inexpensive. "Patients deemed at high risk for bleeding should be given a nonselective beta-adrenergic drug, and for now, ligation should be reserved for patients who have contraindications to or intolerance to these drugs."

Comment:

I abstracted these articles to remind me that drug therapy can be beneficial. It may be most applicable in those areas where expert endoscopy is not readily available. RTJ

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REFERENCE ARTICLE

4-18 VENOUS THROMBOSIS

Over the past decade, knowledge about the etiology of venous thrombosis has advanced. Coagulation abnormalities can combine with acquired factors to increase the incidence of thrombosis.

These abnormalities are common in the general population. Understanding how genetic factors interact with environmental factors is the key to understanding why a certain person develops thrombosis at a specific point in time.

The acquired risk factors for thrombosis are well known (surgery, immobilization, cancer, trauma, etc.). Now we must add genetic risk factors. These include: high concentrations of factor VIII, hyper-homocysteinuria, factor V Leiden, abnormal prothrombins, protein C deficiency, protein S deficiency, and antithrombin deficiency. Thrombosis is a multicausal disease.

Several coagulation defects may combine in one individual. There are thrombophilic families. The presence of genetic alterations in the coagulation process increases risk of thrombosis when combined with an acquired risk.

Lancet April 3, 1999; 353: 1167-73 Review article by F R Rosendaal, Leiden University Medical Center, Netherlands.

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REFERENCE ARTICLE

4-19 ACUTE HEROIN OVERDOSE

This reviews pharmacology, epidemiology, diagnosis, treatment, complications, and prevention. "Acute heroin overdose is a common daily experience in the urban and suburban United States and accounts for many preventable deaths."

The heroin overdose syndrome consists of abnormal mental status, substantially decreased respiration, and constricted pupils. Most overdoses occur in the company of other drug abusers. Circumstantial evidence or history of heroin use aids diagnosis. Heroin-related deaths are strongly related to use of alcohol and other drugs.

Treatment includes airway management and parenteral naloxone [Narcan]. Hospital observation for several hours is necessary to observe for return of adequate ventilation and a normal level of consciousness. Observe for recurrence of hypoventilation and other complications including pneumonia and cardiogenic pulmonary edema.

"The concept of ‘take home’ naloxone as a method of preventing overdose-related deaths has recently been discussed. Despite misgivings, the potential opportunity to prevent thousands of heroin-related deaths warrants the dispassionate exploration of this option."

Annals Int Med April 6, 1999; 130: 584-90 Review article by Karl a Sporer, San Francisco General Hospital, CA.

Comment:

Naloxone is a potent antagonist of narcotics. It is highly lipid soluble and rapidly enters the CNS. It rapidly reverses the toxic effects of heroin. It does not have any agonistic properties of opioids. After iv injection the effects occur within 1 to 2 minutes and last on average about an hour. RTJ

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REFERENCE ARTICLE

4-20 ANTIPHOSPHOLIPID ANTIBODIES AND THROMBOSIS

Autoantibodies specific for phospholipids (antiphospholipid antibodies) have long been recognized in systemic lupus erythematosis. They are associated with thrombotic complications and miscarriage. The terms are "lupus anti-coaglulant"1 and "anticardiolipin"2 are used to describe these antibodies. The autoantibodies are heterogeneous. Their pathogenic role is not clear.

The antiphospholipid syndrome (APS) may be defined as the occurrence of thrombosis, recurrent miscarriage, or both in association with laboratory evidence of persistent antiphospholipid antibody.

Clinical manifestations are also heterogeneous and protean. Thrombosis affects arteries as well as veins. Stroke and occlusion of visceral and peripheral arteries may occur. Deep vein thrombosis and pulmonary embolism are venous manifestations. Thrombocytopenia may also occur.

Identification of the syndrome is clinically important because of the risk of recurrent thrombosis and the need for antithrombotic therapy in many cases.

Diagnosis and treatment are difficult. Existing laboratory tests are limited. Evidence-based guidelines for management are absent. Diagnostic difficulties arise because the antibodies can also appear in infections (eg, syphilis, HIV, hepatitis C), may be a secondary to drugs (eg chlorpromazine) and may be detected in apparently normal persons as well.

Long term anticoagulation therapy may be indicated in patients with antiphopholipid antibody-associated stroke and in patients with venous thromboembolism. The recurrence rate is high.

Lancet April 17, 1999; 353: 1348-53 Review article by M Greaves, Foresterhill, Aberdeen, UK

Comment:

I abstracted this article because my understanding of the anticoagulant-coagulant dichotomy was fuzzy. After reading the article, it remained fuzzy. Experts are confused as well. RTJ

1. This is confusing. Lupus anti-coagulant is an inhibitor of coagulation, yet the syndrome is one of thrombosis. Lupus anti-coagulant does not recognize a specific coagulation factor. It is recognized by an increased clotting time in a phospholipid-dependent coagulation test. "The paradoxical association between a prothrombotic state and the presence of antibodies with in vitro anticoagulant effects is not fully understood.
2. The anticardiolipin assay was first used as a serologic test for syphilis. It was also found positive in patients without syphilis many of whom went on to develop lupus. It is now determined by immunoassay.

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REFERENCE ARTICLE

4-21 MINERALCORTICOID HYPERTENSION

"Hypertension with hypokalemia and suppression of plasma renin activity is known as mineralcortocoid hypertension." It accounts for a small number of patients labeled as having "essential hypertension". Recognition is important because it is potentially reversible. The most common cause is primary aldosteronism due to an adrenal adenoma or adrenal hyperplasia.

Other types are described. Indeed, "Many patients with mineralcortocoid-based hypertension are now known to have normal serum potassium concentrations." (A variation in the definition. RTJ)

"A high index of suspicion is needed in every hypertensive patient. Hypertensive patients with hypokalemia, together with those with severe hypertension (eg, those on triple therapy), or a family history of hypertension or stroke, should be screened for mineralcortocoid excess." Indeed, all patients with hypertension should have their electrolyte concentrations measured.

The article goes on to discuss pathophysiology and differential diagnosis of various types of mineralcorticoid hypertension.

Lancet April 17, 1999; 353: 1341-47 "Seminar", review article by Paul M Stewart, Queen Elizabeth Hospital, Birmingham, UK.