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## FOR

# PRIMARY CARE

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# HIGHLIGHTS AND *EDITORIAL COMMENTS* NOVEMBER 2004

**11-1 EFFECTS OF A LOW-GLYCEMIC LOAD DIET ON RESTING ENERGY EXPENDITURE AND HEART DISEASE RISK FACTORS DURING WEIGHT LOSS.**

This study determined whether dietary composition can influence the physiological adaptations of a weight-reducing diet as assessed by resting energy expenditure. It also determined if cardiovascular risk factors would be reduced on a low GL diet.

Randomized 39 overweight and obese adults (BMI at least 27; age 18 to 40) to low calorie diets. All subjects were in generally good health. Follow-up on diet = about 10 weeks.

The higher GL diet (lower-fat) was generally consistent with National Cholesterol Education Program guidelines for a heart-healthy diet.

| Composition of the diets: | Run-in diet | Low-GL diet (higher fat) | Higher GL diet (lower fat) |
|---|---|---|---|
| % of energy needs | 100 | 60 | 60 |
| Kcal/d | 2600 | 1500 | 1500 |
| Glycemic load | 287 | 82 | 205 |
| Carbohydrate % of total kcal | 49 | 43 | 65 |
| Fat % total kcal | 37 | 30 | 18 |

| Outcomes at 10 weeks | Low GL diet | Higher GL diet |
|---|---|---|
| A. Resting energy expenditure | -96 kcal/d (- 6%) | -176 kcal/d (-11%) |

(*Although absolute resting energy expenditure decreased in both groups, subjects on the low GL diet continued to burn more calories per day than those on the higher GL diet. This would lead to more efficient and continuing weight loss, estimated to be in the range of several pounds per year.)*

B. Perception of hunger was less in the low GL diet subjects.

C. Insulin resistance, triglycerides, C-reactive protein, and BP improved more in the low GL diet group than in the higher GL diet.

"Incorporation of glycemic load principles into current dietary guidelines may aid in the treatment of obesity and prevention of cardiovascular disease and diabetes."

*This represents a continuing sea change in our thinking about benefits and risks of diets. What is the most beneficial diet? Are foods with a high glycemic load, which lead to continuing elevations in blood glucose, just as harmful as foods containing a high load of unsaturated fats?*

*Our US diets are high in sugar. I believe that a healthy diet should contain smaller amounts of sugar. This would suggest diets similar to the Mediterranean diet which is established as beneficial.*

*In the future, food manufacturers may be inclined to list the glycemic load of their products (especially if they are low).*

## 11-2 THE FAMILY HISTORY—More Important Than Ever

"Today, with medicine poised at the dawn of the genomic era, it is seductive to believe that such high-tech options have already become the most important genomic tools in health care." However, as so often happens in medicine, new developments do not eclipse the tried-and-true method; instead, they give it new meaning and power.

Most diseases are the result of the interactions of multiple genes and environmental factors.

Almost every patient today has access to a free, well-proven, personalized genomic tool that captures many of these interactions and can serve as the cornerstone for individualized disease prevention. This valuable tool is the family history **(FH).** It will remain highly relevant for years to come.

Government agencies are now spearheading a national campaign to encourage families to record their health histories. Thanksgiving Day, when families traditionally gather, has been designated as the *National Family History Day*. This will serve to remind us about the value of the FH.

The government has launched a web site which allows families to collect, organize, and maintain the family history.

*The article cites several web sites. One: www.hhs.gov/familyhistory*

*Most elderly patients will not have detained information about their forbearers. Individuals now age 70 and above may not have accurate information about their grandparents, but they can accurately add their own accounts and that of their cousins to the FH.*

## 11-3 DOSE SPARING WITH INTRADERMAL INJECTION OF INFLUENZA VACCINE

This randomized trial compared the immunogenicity and safety of intradermal *vs* standard intramuscular vaccine.

Healthy young adults were randomized to a single dose of: 1) Intramuscular injection of the standard 0.5 mL of trivalent vaccine containing at least 15 ug of hemagglutinin per strain, or 2) Intradermal injection of 0.1 mL containing at least 3 ug of hemagglutinin per strain. Injections were made in the deltoid region.

Subjects who received the intradermal injections (1/5 the standard dose) had increases in hemagglutination-inhibition antibody (HAI) titers by a factor of 12 to 19 for the three strains. This was similar to the intramuscular response (factors of 7 to 15).

On day 21, seroconversion and seroprotection rates were similar between groups.

The data clearly show that *intradermal* injection of 1/5 the dose the standard dose of commercial vaccine elicits immune responses that are similar or superior to those elicited by a full dose of vaccine given intramuscularly to healthy young adults. It is generally accepted that the HAI response represents a fair surrogate marker for protection.

*In times of vaccine shortage, we must decide whether to vaccinate a relatively few intramuscularly and induce a known response, or vaccinate many more intradermally with the hope of inducing a protective response in the majority. At present, I would be inclined to use the full intramuscular dose in elderly infirm persons, nursing home residents, and in those with impaired immunity and chronic diseases such as asthma, heart and*

*lung disease. If the supply was greatly impaired, and I had no other choice, I would give the ID dose. Combined half-dose IM and ID doses would save some vaccine.(And perhaps lead to greater immunity.)*

*The possibility of a pandemic of flu (predicted by many authorities as inevitable) would make ID vaccination more applicable.*

*Obviously the ID dose is preferable to no dose. I believe smaller doses, both IM and ID, will produce an adequate response in many persons.*

*Make sure the injection is not made into fat tissue. Immune response will be inadequate. In very obese persons, an intradermal injection may be preferable. The standard needle might not reach muscle.*

*I remember a vaccine shortage in the late 1950s or early 60s. We opted to give (on an empirical basis) intradermal vaccine to many more recipients than would have received it if the vaccine were given IM at full dose.. We had no data on the response. Now it seems this was not such a bad idea.*

**11-4 THE SU.VI.MAX STUDY: Trial of Health Effects of Supplementary Antioxidants.**

This study tested the efficacy of *nutritional doses* of supplements containing a mixture of antioxidant vitamins and minerals in reducing incidence of cancer, CVD, and all-cause mortality in a general population.

Subjects were randomized to: 1) vitamin-mineral supplement, or 2) placebo daily

The daily supplement contained:

| | |
|---|---|
| Ascorbic acid | 120 mg |
| Vitamin E | 30 mg |
| Beta-carotene | 6 mg |
| Selenium | 100 ug |
| Zinc | 20 mg |

There was a statically significant protective effect in men, but not in women:

Cancer incidence in men:

Intervention 3.5%; Placebo 4.9%. Absolute difference = 1.4% NNT 7 years = 71

Total mortality in men

Intervention 1.6%; Placebo 2.5% Absolute difference = 0.9 NNT 7 years = 111

The authors speculate that the difference in outcomes of men *vs* women might be due to a generally lower intake and plasma concentration of antioxidants (especially beta-carotene) in men. Indeed, baseline serum concentrations were lower in men.

The study reinforces the general recommendation of a life-long diversified diet containing an abundance of foods rich in antioxidants.

*Is the putative benefit of supplements clinically important? I believe it is.*

*How can we apply this information to primary care in the USA?*

*I believe at this time we should advise against high doses of individual vitamins and minerals. There is no evidence of benefit and there is evidence of possible harm.*

*I believe it is likely that any benefit from supplements will be in individuals whose nutritional status is borderline. In primary care practice, we cannot assess the nutritional status of every individual patient. I believe*

*therefore that a routine recommendation for a daily low-dose supplement for adults is reasonable. Although in adequately nourished individuals this may not bring any benefits in protecting against cancer or cardiovascular disese, the supplements do contain, as an added attraction, vitamin D and folic acid which may bring benefits.*

**11-5 IS PSA TESTING STILL USEFUL?**

Dr. Thomas A. Stamey (Stanford University School of Medicine), who is considered to be the "father" of PSA testing, says it is no longer a useful tool for screening for PC. In fact, it may be causing unwarranted treatment for a typically slow-growing tumor. Dr. Stamey drew his conclusions after studying over 1300 consecutive radical prostatectomies. Over time, there was a linear decrease in most parameters associated with PC. During the first 5 years of screening, 91% of cancers were palpable, the mean PSA was 25 ng/mL, the mean age was 64, and cancer volume was over 5 $cm^3$. During the last 5-years of screening, 17% were palpable, the mean PSA was 8 ug/mL, the mean age was 59, and the cancer volume was 2.4 $cm^3$. When PSA screening was first introduced, high levels were associated with a 50% chance of having a large PC for which treatment was warranted. Over the past 5 years, the chance of having a large PC has fallen to 2%, presumably due to over screening. "Most prostate cancers we (*now*) remove need not be removed."

An estimated 230 000 men in the USA will be diagnosed as having PC this year; 30 000 are expected to die of PC. Dr. Stamey says the fear of dying of PC may be disproportionate to the odds of death. One study reported that the prevalence of PC was 8% in men in their 20s, and the percentage grew linearly to 80% in men over 70. "It's a cancer we all get if we live long enough."

There is ambivalence in the prostate-treatment community regarding screening. Some researchers remain convinced that screening effectively detects clinically significant PC and leads to a reduced mortality.

"Physicians continue to be concerned about diagnosing prostate cancer at the earliest stage when it is most treatable, while at the same time avoiding unneeded biopsies and treatment for prostate cancers that might not become clinically meaningful."

The mortality rate from the disease is low. But the reality is that some patients may benefit from early detection. Thus, PSA has lost some value, but it still may have some clinical relevance.

Patients at risk of overtreatment have a low, stable PSA with low-grade, low-volume cancers. We are detecting many low volume cancers that may not require treatment

*No doubt many men are now undergoing unnecessary treatments for PC. Undoubtedly some lives are saved. Where to draw the line?*

*I believe PSA should not be considered a "routine" screen (as is BP, blood glucose, and cholesterol). Patients should be fully informed about risks and benefits beforehand. I believe primary care clinicians should not even broach the subject when consulting with elderly men. Digital rectal examination is a more reasonable screen.*

*There are some guidelines when results of PSA are obtained in younger men. If the PSA is high, and if the rate of increase is rapid (eg, doubling time, or an increase of over 2.0 ug/year), biopsy is warranted. Surgery then depends on the grade of PC determined by biopsy.*

*When I was a child, almost all children and many adults underwent tonsillectomy. It seemed to be the mode. When we would consult with our European colleagues, they would admonish—"Hold onto your tonsils". I believe many man in the USA should "Hold onto your prostate".*

**11-6 SHARED MEDICAL DECISION MAKING: Problems, Process, Progress**

"Sharing with a patient who faces *tough* choices when he or she is ill is one of the true gifts of being in the medical profession." The patient-physician relationship is the sacrosanct epitome of professionalism with the goals of ensuring that patients receive the treatment best for them (science) and that the best treatment is carried out in the most efficient and compassionate manner (quality and safety).

"Physicians should never make a choice for a patient—even if the patient wants the physician to do so." Instead, physicians should ensure that the information used in the patient's decision-making is reasonable for the individual patient and that the patient understands the ramifications of choice. "The physician should be a navigator, not a pilot."

The consequences of a patient's choice cannot be shared with anyone else. Only the patient will suffer or enjoy the probabilistic outcomes associated with choosing one option over another. Only the patient will know how he or she feels about experiencing an adverse effect of a treatment or a reduced chance of an adverse outcome that a treatment is designed to alter. Patients must have time to reflect.

A decision that appropriately involves a patient requires viable options, and choosing one option over another must engender some element of risk. There has to be a definable trade-off of harm and benefit.

Some actions, however, are not really decisions to be made by the patient and do not require a patient's input. Patients need not decide if antibiotics are required for bacterial pneumonia. Sick patients should not be allowed to make decisions about treatments that are of clear value and that do not create significant levels of harm. If the significance of an adverse effect or harm is so minor compared with the benefit, no decision is required.

The conceptional framework for making a choice is understandable as a balance between harms and benefits weighed by the patient's values for gains and losses. Only the patient can do it. "Physicians cannot deny patients the opportunity and means to make their own choices."

*I enjoyed this thought-provoking commentary.*

*The demise of physician's paternalism and authoritarianism has transferred some decision-making to the patient. In some circumstances, the physician's responsibility must be to fully inform patients of the best evidence about harms as well as benefits of treatment. This enables patients to choose based on their individual circumstances. How strictly should* primary *care clinicians apply this principle?*

*Shared decision-making is applicable when the choices are "tough". I believe the process needs to be applied to relatively few patients seen in daily primary care practice. If this process were applied to every patient, practice would grind to a halt. The process would be more applicable to patients seen in specialty care (eg, oncology, surgery).*

*The comment about no need for patient- decision-making in clear-cut situations such as antibiotics for pneumonia may not be so simple for an elderly, infirm patient who does not wish to receive therapy. If the patients is competent and wishes to avoid therapy, this is his decision.*

*There are many obstacles to application of "shared decision" in the real world of primary care:*

*The patient may be incompetent.*

*What about decisions for children?*

*Patients are often medically illiterate.*

*There may be cultural and language barriers. In some cultures, patients may rely on family and will refuse to make their own choice. Some patients may defer to the physician asking "What would you do?" and may refuse to choose..*

*Estimates of benefit/harm may not apply to individual "real world" patients. The true benefit/harm ratio may not be well established. It may be subject to change as more information becomes available.*

*The patient's best choice is often not available. The patient may not be able to pay for the choice he makes. Insurance may not cover the costs.*

*How should the clinician respond when the patient chooses a course the physician considers futile?*

*I believe medical paternalism and authoritarianism is not dead yet.*

**11-7 EFFICACY OF BIVALENT L1 VIRUS-LIKE PARTICLE VACCINE IN PREVENTION OF INFECTION WITH HUMAN PAPILLOMA VIRUS TYPES 16 AND 18 IN YOUNG WOMEN.**

"Persistent infection with high-risk HPV types is the necessary cause of cervical cancer." HPV-18 and HPV-16 are the most prevalent types.

This study determined if vaccination against the common oncogenic types of HPV (16 and 18) could prevent development of cervical infection.

Double-blind trial randomized over 1100 healthy women between ages 15 and 25. All were initially cytologically negative and seronegative for 16 and 18, and negative for HPV-DNA by PCR.

Randomized to: Three injections of: 1) HPV 16/18 vaccine formulated with an adjuvant, or 2) Placebo injections at months 0, 1, and 6.

Vaccine efficacy against incident infection with 16/18 was 92%. Efficacy against persistent infection was 100%. It was 93% effective against cytological abnormalities associated with 16/18. Three episodes of atypical squamous cells of undetermined significance occurred in the vaccinated group; 33 in the placebo group

The vaccine was generally safe, well tolerated, and highly immunogenic.

*Other HPV types also cause cervical cancer. The final composition of the vaccine remains to be determined. The long-term protective effect is still not clear.*

*This is very exciting—likely to be the first vaccine to prevent cancer, and the first licensed vaccine to prevent a sexually transmitted disease.*

*Worldwide implementation might be an impossible task.*

**11-8 PREVENTING MICROALBUMINURIA IN TYPE 2 DIABETES.**

This study was designed to assess whether an angiotensin-converting-enzyme inhibitor or a non-dihydropyridine calcium-channel blocker, or the combination, would *prevent* microalbuminuria in patients with DM2 who had hypertension and *normal* urinary albumin excretion.

| Mean trough BP attained: | | Development of microalbuminuria (%): | |
|---|---|---|---|
| Trandolapril alone | 139/81 | Trandolapril alone | 6 |
| Verapamil alone | 141/82 | Verapamil alone | 11.9 |
| Both | 139/80 | Both | 5.7 |
| Placebo | 142/83 | Placebo | 10 |

Trandolapril alone significantly reduced the incidence of microalbuminuria in patients with DM2.

(NNT 4 years = 25)

In subjects with DM2 and hypertension, normoalbuminuria, and normal renal function, ACE-inhibitor therapy with trandolapril prevented the onset of microalbuminuria. A calcium blocker did not.

*Should all patients with DM2 receive an ACE inhibitor regardless of BP or microalbuminuria? This study would tilt toward this application. Patients with DM2 who have hypertension (systolic > 130) will likely develop microalbuminuria eventually.*

*COST: Drug store.com quotes telmisartan (Mavix 2 mg) about $1 per day*

*Enalapril (Generic 20 mg) about 20 cents.*

*Note that the target BP was not reached. ACE inhibitors have effects on the vasculature of the kidney and other endothelium exceeding their effect on BP.*

*What about angiotensin II blockers? A companion study in this issue of NEJM (pp 1952-61), first author Anthony H Barnett, University of Birmingham, Alabama, reports that the angiotensin II blocker telmisartan was as effective (but not more effective) than the ACE inhibitor enalapril (Generic) in providing long-term renoprotection in DM2. At present, ACE inhibitors are first-line therapy. Angiotensin II inhibitors are reserved for those who cannot tolerate ACE.*

**11-9 COMBINATION OF ISOSORBIDE AND HYDRALAZINE IN BLACKS WITH HEART FAILURE**

Endothelial dysfunction, impaired bioavailability of nitric oxide, and increased oxidant stress occur in HF. Augmentation of nitric oxide (by the nitric oxide donor, isosorbide) may be an alternative or supplemental approach to treatment of HF. Hydralazine may confer protection against degradation of nitric oxide induced by oxidative stress.

Studies have suggested that persons who identify themselves as black may have a less active renin-angiotensin system, and lower bioavailability of nitric oxide than those self-identified as white.

This study examined whether a fixed dose of isosorbide/hydralazine would provide additional benefits in blacks with advanced HF.

Black patients with grade III & IV HF were randomized to: 1) A fixed dose of isosorbide/hydralazine given by mouth daily, or 2) Placebo. Dose = 37.5 mg hydralazine + 20 mg isosorbide dinitrate three times daily. Dose could be increased to a total of 225/120 mg daily depending on absence of drug-induced side effects.

The study was terminated early owing to a significantly higher mortality in the placebo group.
(10% vs 6%; absolute difference = 4%; NNT for 10 months = 25)

There was an absolute reduction in first hospitalization for HF of 10%; and improvement in the quality-of-life score *vs* placebo of 2 points in a scale of 0 to 105.

*Would not white persons also benefit?*

*This remarkable study was facilitated by the Association of Black Cardiologists. It included patients from 161 centers. It needs independent confirmation. The study was supported by NitroMed. I wondered why a drug company would sponsor a study of drugs which can be readily obtained in generic form.*

*There is a substantial problem in classifying individuals in the USA as "black", and lumping them together as African-American. See the following commentary.*

**11-10 A RATIONAL BASIS FOR RACE**

Humans are not divided along clear color-based lines which are traditionally used in anthropological records. Some ask—Does race exist at all?

The problem occurs when society and the medical community generalizes findings to an entire group. Prostate cancer has a higher prevalence among African-American men. This does not mean that all African-American men have similar risks for prostate cancer.

The connection between self-identified race and genetic variation is very blurry. Culture, lifestyle, and social stress may play a greater role in disparity.

*Black "African Americans" are an extremely diverse group.*

*We often choose subsets of individuals for screening—race may be one. I believe divisions according to 'race" still has some clinical validity. The disparity between races in the USA is gradually disappearing.*

**11-11 LEFT VENTRICULAR HYPERTROPHY**: **The Next Silent Killer?**

Even mild increases in BP are associated with increased left ventricular mass **(LV mass).**

Left ventricular hypertrophy **(LVH)** is a risk factor for premature death and cardiovascular events. The Framingham study has reported that LVH, as confirmed by ECG, is associated with a mortality rate as high as that associated with a Q-wave myocardial infarction.

LVH associated with hypertension appears to be reversible. A long-term reduction in BP is associated with reductions LV mass.

Two articles in this issue of JAMA report that reductions in left ventricular mass in the setting of treatment for hypertension correlate with long-term cardiovascular outcomes. The first trial of hypertensive patients with LVH documented by ECG criteria, reported the greater the treatment-decrease in ECG markers of LVH, the greater the reduction in cardiovascular events. The second trial reported data obtained by echocardiography. Over time, reductions in LV mass with treatment of hypertension were associated with reduced risk of cardiovascular events.

"Active efforts to reduce left ventricular mass may have important clinical benefits." Treatment to reduce LV mass may follow a course similar to reductions in cholesterol and BP.

*I believe this is a clinically important point. Many primary care clinicians will have ECG available. If LVH is present, extra efforts should be taken to treat hypertension. A more careful follow-up is warranted.*

**11-12 MANAGEMENT OF FIBROMYALGIA SYNDROME**

The diagnosis of the fibromyalgia syndrome **(FMS)** is based on a history of widespread chronic, bilateral upper body, lower body, and spine pain, and the presence of excessive tenderness on applying pressure to 11 or more of 18 specific muscle-tendon sites. FMS has not been traced to any specific structural or inflammatory cause.

FMS is the second most common disorder observed by rheumatologists (after osteoarthritis). It has a prevalence of 2% in the US. It is much more common in women. Chronic pain syndromes such as FMS are defined by subjective symptoms. No discrete boundary separates FMS from chronic fatigue syndrome, irritable bowel syndrome, and chronic muscular headache. Mood disturbances are comorbid with all.

This article summarizes the findings of a report (based on a detailed literature search) commissioned by the American Pain Society to provide evidence-based guidelines for the optimal management of FMS. There are major limitations to the literature. Many treatment trials are of short duration and lack masking. No medical therapies have been specifically approved by the FDA.

Despite the chronicity and complexity of FMS, there are interventions that may have clinical benefit in primary care practice. Several drugs and non-medical therapies are suggested.

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**Richard James, M.D.**
**Editor**

# ABSTRACTS NOVEMBER 2004

***A Low Glycemic Load Diet May Aid in Treatment of Obesity and Prevent Cardiovascular Disese and Diabetes.***

**11-1 EFFECTS OF A LOW-GLYCEMIC LOAD DIET ON RESTING ENERGY EXPENDITURE AND HEART DISEASE RISK FACTORS DURING WEIGHT LOSS.**

The poor long-term efficacy of conventional obesity treatment has promoted the notion of a body weight *settling point.* Deviations in body weight from baseline elicit physiological adaptations that antagonize further weight change. During energy restriction, hunger increases (leading to increased energy intake), thyroid hormone

levels decrease, and reproductive and growth functions are down-regulated (leading to lower energy expenditure). The body weight *settling point* may best be conceptualized as representing the integrated influences of numerous genetic, behavioral, and environmental factors.

Resting energy expenditure **(REE)** declines as a result of weight reduction.

Glycemic load **(GL)** is the glycemic index of each food multiplied by the total carbohydrate amount ingested. It measures the increase in blood glucose following a meal. A high glycemic load diet appears to *stimulate* hunger and to *increase* voluntary food intake. A recent study examined the effects that glycemic load on REE. After 1 week of an energy-restricted diet providing 50% of predicted total energy requirements, REE decreased by 10% when the diet was high glycemic load compared with 5% when the diet was low-glycemic load. (Ie, REE seems to be lower when high glycemic index foods are provided in a weight-reduction diet, and higher when a low glycemic index diet is provided.) The resulting higher REE (associated with foods low in GL) would lead to greater continuing weight loss.

This study determined whether dietary composition can influence the physiological adaptations of a weight-reducing diet as assessed by REE. It also determined if cardiovascular risk factors would be reduced on a low GL diet.

Conclusion: A low glycemic load (low sugar) diet may aid in the prevention and treatment of obesity, cardiovascular disease, and diabetes.

STUDY

1. Randomized 39 overweight and obese adults (BMI at least 27; age 18 to 40) to low calorie diets. All subjects were in generally good health. Follow-up on diet = about 10 weeks.
2. Performed sophisticated metabolic studies during a run-in period with subjects on a weight-maintaining diet. And repeated the studies at the end of the 10-week restricted diet.
3. Randomized to: 1) a low glycemic-load diet [lower carbohydrate; higher fat], or 2) a higher GL diet [lower fat ;higher carbohydrate]. Both diets provided 60% of predicted energy requirements.
4. The mean daily predicted glycemic load was calculated as grams of available carbohydrate multiplied by the glycemic index of each food (using white bread as 100%) and summed over all foods.)
5. The higher GL diet (lower-fat) was generally consistent with National Cholesterol Education Program guidelines for a heart-healthy diet.
6. The low GL diet was designed to be as low in glycemic load as possible, while providing more than ample carbohydrate to prevent ketosis.
7. Composition of the diets:

| | Run-in diet | Low-GL diet (higher fat) | Higher GL diet (lower fat) |
|---|---|---|---|
| % of energy needs | 100 | 60 | 60 |
| Kcal/d | 2600 | 1500 | 1500 |
| Glycemic load | 287 | 82 | 205 |
| Carbohydrate % of total kcal | 49 | 43 | 65 |
| Fat % total kcal | 37 | 30 | 18 |

RESULTS

1. Participants in both groups lost weight equally—about 10% of their initial weight.

| 2. Outcomes at 10 weeks | Low GL diet | Higher GL diet |
|---|---|---|
| A. Resting energy expenditure | -96 kcal/d (- 6%) | -176 kcal/d (-11%) |

(*Although absolute resting energy expenditure decreased in both groups, subjects on the low GL diet continued to burn more calories per day than those on the higher GL diet. This would lead to more efficient, and continuing weight loss.)*

B. Perception of hunger was less in the low GL diet subjects,

C. Insulin resistance, triglycerides, C-reactive protein, and BP improved more in the low GL diet group than in the higher GL diet.

DISCUSSION

1. "The primary finding of this study was that physiological adaptations that serve to defend baseline body weight can be modified by dietary composition." On the low GL diet, REE declined by 96 kcal/d during weight loss *vs* a decline of 176 kcal/d in the higher GL diet.
2. The low GL diet produced favorable changes in insulin resistance, chronic inflammation, lipids, and BP compared with a conventionally recommended (higher GL) diet which was lower in saturated fat, cholesterol, and sodium.[a]
3. The REE difference could amount to weight loss of several pounds per year. An energy balance of – 80 kcal/d equals approximately that of walking 1 mile per day, or by decreasing sugar-sweetened soft drink consumption by 6 oz/day.
4. Epidemiological analyses have found associations between GL and high triglycerides, low HDL-cholesterol, and elevated c-reactive protein. A higher GL diet has also been associated with a higher risk of developing heart disease.
5. "We found that during weight loss, a diet focused on glycemic load reduction produced greater improvements in several important cardiovascular disease-related and diabetes-related endpoints than a diet focused on reduction of total and saturated fat in accordance with conventional practice.
6. "Incorporation of glycemic load principles into current dietary guidelines may aid in the treatment of obesity and prevention of cardiovascular disease and diabetes."

CONCLUSION

Physiological adaptations to a weight-reducing diet thought to antagonize ongoing weight loss, involving energy expenditure and hunger, can be modified by dietary composition.

A low glycemic load diet had beneficial effects on several obesity-related factors.

JAMA November 24, 2004, 292: 2482-90 Original investigation, first author Mark A Pereira, Children's Hospital, Boston Mass.

**a** See p 2485 for sample menus of both diets.

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***We Need to Make the Process of Collecting and Analyzing the Data Easier and Less Time Consuming.***

**11-2 THE FAMILY HISTORY—More Important Than Ever**

"Today, with medicine poised at the dawn of the genomic era, it is seductive to believe that such high-tech options have already become the most important genomic tools in health care." However, as so often happens in medicine, new developments do not eclipse the tried-and-true method; instead, they give it new meaning and power.

Most diseases are the result of the interactions of multiple genes and environmental factors.

Almost every patient today has access to a free, well-proven, personalized genomic tool that captures many of these interactions and can serve as the cornerstone for individualized disease prevention. This valuable tool is the family history **(FH).** It will remain highly relevant for years to come.

The FH predicts the risk of varied health concerns: heart disease, colorectal cancer, breast cancer, ovarian cancer, osteoporosis, asthma, type 2 diabetes, early stroke, and suicide, among many others.

Many patients are not aware of their FH. Many health professionals underuse this information in advising patients about how to maintain good heath.

The FH has long been regarded as a mainstay in caring for patients who are at increased risk of relatively uncommon, Mendelian (single gene) conditions: von Willebrand's disease, polycystic kidney disese, sickle cell disease, fragile X syndrome, hereditary hemorrhagic telangiectasia.

We do our patients a disservice if we fail to realize the value of FH in dealing with more common, multifactorial disorders as well. Many of those listed above are just as important on the paternal side as on the maternal side. By assessing a person's pretest risk, the FH can substantially alter the predictive value of screening tests.

We need to make the process of collecting and analyzing the FH data easier and less time consuming.

Government agencies are now spearheading a national campaign to achieve this goal. Thanksgiving Day, when families traditionally gather, has been designated as the *National Family History Day*. This will serve to remind us about the value of the FH.

The government has launched a web site which allows families to collect, organize, and maintain the family history.

Someday, perhaps not far off, detailed genotypic information will play an important and everyday role in guiding patient care. Meanwhile, it is important not to overlook what patients know about the health of their families.

NEJM November 25, 2004; 351: 2333-36 "Sounding Board", commentary, first author Alan E Guttmacher, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

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***Intradermal Injection Elicited Immunity in Healthy Young Adults***

## 11-3 DOSE SPARING WITH INTRADERMAL INJECTION OF INFLUENZA VACCINE

Dose-sparing strategies are now being studied in view of the critical shortage of flu vaccine this year,

This randomized trial compared the immunogenicity and safety of intradermal *vs* standard intramuscular vaccine. The immune system in the skin has been recognized as a desirable target for vaccination. The barrier function of the skin's immune system can be exploited for vaccination. Over 25% of the body-surface area is covered by dendritic cells, a form of antigen-presenting cell whose function is to recognize foreign antigens and initiate an effective immune response.

Delivery into the skin is effective for several vaccines (eg, bacille Calmette-Guerin; smallpox)

Intramuscular injection of vaccine bypasses the skin's immune system and delivers antigens into tissue that has no important resident population of antigen-presenting cells. Antigen delivered to muscle tissue is thought to be picked up by transient antigen-presenting cells or simply to circulate to the draining lymph node. Only small volumes of fluid can be injected into the skin. Direct dose-to-dose comparisons are difficult to conduct.

Conclusion: In young adults, immune responses were similar.

STUDY

1. Randomized, open-label trial entered 100 healthy adults age 18 to 40.
2. Randomized to a single dose of: 1) Intramuscular injection of 0.5 mL of trivalent vaccine containing at least 15 ug of hemagglutinin per strain, or 2) Intradermal injection of 0.1 mL containing at least 3 ug of hemagglutinin per strain. Injections were made in the deltoid region.
3. Measured changes in hemagglutination-inhibition antibody (HAI) titers. Compared seroconversion and seroprotection rates.

RESULTS

1. Subjects who received the intradermal injections (1/5 the standard dose) had increases in hemagglutination inhibition antibody titers by a factor of 12 to 19 for the three strains. This was similar to the intramuscular response (a factor of 7 to 15).
2. On day 21, seroconversion and seroprotection rates were similar between groups.
3. Local reactions were significantly more frequent among the intradermal recipients. But reactions were mild.

DISCUSSION

1. "Our results support the use of a dose-sparing strategy for influenza vaccination." The data clearly show that, in healthy young adults, intradermal injection of 1/5 the standard dose of commercial vaccine elicits immune responses that are similar or superior to those elicited by a full dose of vaccine given intramuscularly. It is generally accepted that the HAI response represents a fair surrogate marker for protection.
2. Standard tuberculin syringes and needles can be used with multidose vials of vaccine to increase the supply by a factor of about 5.
3. It is possible that elderly persons and young children or those with underlying medical conditions may not respond as well.

CONCLUSION

Intradermal injection of 1/5 the dose of influenza vaccine in healthy young adults elicited immunogenicity similar to the response to full-dose intramuscular vaccine.

NEJM November 25, 2004; 351: 2295-301, Original investigation, first author Richard T Kenney, Iomai, Gaithersburg, Maryland.

Several other articles addressing this issue appeared in NEJM

"Serum Antibody Responses after Intradermal Vaccination against Influenza", *NEJM November 25.2004; 351: 2286-94*, first author Robert B Belshe, Saint Louis University, St. Louis, MO reported similar responses to intradermal injections among persons age 18 to 60, but not among those over age 60. The vaccine was given intradermally by a novel tuberculin syringe with a 30-guage beveled needle that protruded 1.5 mm from a plastic disk to limit skin preparation, thus ensuring administration intradermally. This would facilitate administration to large groups.

"Influenza Vaccination with 1/10 the Full Dose" *NEJM November 25, 2004; 351: 2339-40* "Correspondence to the Editor", first author Curtis L Cooper, University of Ottawa, Canada, reports a study of 29 young adults randomized to: 1) a single, intramuscular dose of 1.5 ug of each of the three hemagglutinin antigens (1/10 the regular dose, or 2) a full intramuscular dose. The resultant mean hemagglutination-inhibition titers, although generally lower in response to the small dose, were considered adequate for immune protection.

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***Associated with Lower Cancer Incidence and All-Cause Mortality in Men, But Not in Women.***

**11-4 THE SU.VI.MAX STUDY**

Epidemiological studies have shown a strong relationship between intake of antioxidant vitamins, minerals, and foods rich in these nutrients and the risks of cancer and cardiovascular disease (CVD).

However, randomized, placebo-controlled *primary prevention* trials of these nutrients taken in high doses have not confirmed any benefits. Some suggest harmful effects.

This study tested the efficacy of *nutritional doses* of supplements containing a mixture of antioxidant vitamins and minerals in reducing incidence of cancer, CVD, and all-cause mortality.

Conclusion: After 7 years, low-dose supplements were associated with lower cancer incidence and all-cause mortality in men, but not in women.

STUDY

1. A randomized, placebo controlled trial followed over 13 000 adult men and women in a general population in France for a median of 7.5 years. Individuals were not selected for risk factors.
2. Randomized to: 1) Vitamin-mineral supplement, or 2) Placebo daily
3. The supplement contained:

Ascorbic acid 120 mg

| | |
|---|---|
| Vitamin E | 30 mg |
| Beta-carotene | 6 mg |
| Selenium | 100 ug |
| Zinc | 20 mg |

(*This is about twice the usual dose contained in supplements in the USA. Our daily supplements contain many more vitamins and minerals. RTJ)*

4. Outcomes = incidence of cancer and ischemic CVD.

RESULTS

1. There was a statically significant protective effect in men, but not in women.

Cancer incidence in men:

Intervention 3.5%; Placebo 4.9%. Absolute difference = 1.4% NNT 7 years = 71

Total mortality in men

Intervention 1.6%; Placebo 2.5% Absolute difference = 0.9 NNT 7 years = 111

2. At baseline, average serum values of beta-carotene and vitamin C were lower in men. When divided into quintiles of baseline beta-carotene concentrations, the incidence of cancers in men was lower in the highest quintile compared with the lowest quintile. (RR = 0.55). The RR for CVD was 0.57.
3. The reduction in cancer incidence in men extended to all types: thyroid, genital, skin, respiratory, digestive tract, and oral cavity.

DISCUSSION

1. Antioxidants were associated with lower cancer risk and total mortality in men but not in women.
2. There was no major effect on ischemic CVD.
3. This trial differs from previous primary prevention trials. It examined lower (supplementary) doses of antioxidants, not pharmacological doses. Only one trial (in China) used a balance of several antioxidants in nutritional doses. It reported a lower incidence of cancer in a nutritionally compromised population.
4. The authors speculate that the difference in outcomes of men *vs* women might be due to a generally lower intake and plasma concentration of antioxidants (especially beta-carotene) in men. Indeed, baseline serum concentrations were lower in men.
5. The study reinforces the general recommendation of a life-long diversified diet containing an abundance of foods rich in antioxidants.

CONCLUSION

A well-balanced supplementation of antioxidant nutrients at doses that might be reached with a healthy diet that includes a high consumption of fruits and vegetables, had protective effects against cancer and all-cause mortality in men.

Archives Int Med November 22, 2004; 164: 2335-42 Original investigation by *The Supplementation en Vitamines et Mineraux Antioxydants (SU. VI. MAX) Study*, first author Serge Hercberg, Institut National de la Sante et de le Recherche Medical (INSERM), Paris, France.

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***"Most Prostate Cancers We Remove Need Not Be Removed."***

**11-5 IS PSA TESTING STILL USEFUL?**

The American Cancer Society recommends that physicians offer PSA testing and digital rectal examinations for prostate cancer **(PC)** annually beginning at age 50 in men who have at least a 10-year life expectancy.

Now, Dr. Thomas A. Stamey (Stanford University School of Medicine), who is considered to be the "father" of PSA testing, says it is no longer a useful tool for screening for PC. In fact, it may be causing unwarranted treatment for a typically slow-growing tumor. Dr. Stamey drew his conclusions after studying over 1300 consecutive radical prostatectomies. Over time, there was a linear decrease in most parameters associated with PC. During the first 5 years of screening, 91% of cancers were palpable, the mean PSA was 25 ng/mL, the mean age was 64, and cancer volume was over 5 $cm^3$. During the last 5-years of screening, 17% were palpable, the mean PSA was 8 ug/mL, the mean age was 59, and the cancer volume was 2.4 $cm^3$. When PSA screening was first introduced, high levels were associated with a 50% chance of having a large PC for which treatment was warranted. Over the past 5 years, the chance of having a large PC has fallen to 2%, presumably due to over screening.

During the first 5 years of screening, 6 histological cancer parameters had statistically significant relationships to PSA. During the last 5 years, the only factor PSA levels predicted was an enlarged prostate, a common occurrence in aging men.

"Most prostate cancers we (*now*) remove need not be removed."

Elevated PSA levels may indicate PC, but are also associated with benign prostate enlargement, inflammation, and infection. Originally, a high PSA level correlated with detection of large tumors which posed the greatest risk of death. Today, however, PSA screening has become widespread, and testing triggers biopsy at much lower scores. Greater numbers of small cancers are being found—cancerous tumors that do not necessarily require aggressive treatments which can leave impotence, incontinence, and bowel disorders.

PSA can detect PC early, but this can lead to overly aggressive treatment. An estimated 230 000 men in the USA will be diagnosed as having PC this year; 30 000 are expected to die of PC. Dr. Stamey says the fear of dying of PC may be disproportionate to the odds of death. One study reported that the prevalence of PC was 8% in men in their 20s, and the percentage grew linearly to 80% in men over 70. "It's a cancer we all get if we live long enough."

There is ambivalence in the prostate-treatment community regarding screening. Some researchers remain convinced that screening effectively detects clinically significant PC and leads to a reduced mortality.

The *Prostate Cancer Education Council* is promoting screening nationwide. The *Prostate Cancer Foundation* issued a *Report to the Nation on Prostate Cancer* urging improved management and treatment while noting a debate on the use of screening and the optimal score threshold for biopsy. The foundation

commented…“Physicians continue to be concerned about diagnosing prostate cancer at the earliest stage when it is most treatable, while at the same time avoiding unneeded biopsies and treatment for prostate cancers that might not become clinically meaningful.”

The mortality rate from the disease is low. But the reality is that some patients may benefit from early detection. Thus, PSA has lost some value, but it still may have some clinical relevance.

Once PC is diagnosed, and the patient hears the word “cancer”, he will prefer removal to eliminate the cancer. He may not understand the risk of adverse effects.

Patients at risk of overtreatment have a low, stable PSA with low-grade, low-volume cancers. We are detecting many low volume cancers that may not require treatment.

There is still no consensus. Many remain skeptical of its value, saying it remains unknown whether it saves lives.

We need a better test. Meanwhile surveillance to detect those with more rapid growth may be a conservative approach.

JAMA November 17, 2004; 292: 2326-27 “Medical News and Perspectives”, commentary by Mike Mitka, JAMA Staff

Comment:

Dr. Stamey’s report is contained in *Journal of Urology* October 2004

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***“A Mathematical Core Wrapped in Compassion, Humility, and Responsibility.”***

**11-6 SHARED MEDICAL DECISION MAKING: Problems, Process, Progress**

“Sharing with a patient who faces *tough* choices when he or she is ill is one of the true gifts of being in the medical profession.” The patient-physician relationship is the sacrosanct epitome of professionalism with the goals of ensuring that patients receive the treatment best for them (science) and that the best treatment is carried out in the most efficient and compassionate manner (quality and safety).

“Physicians should never make a choice for a patient—even if the patient wants the physician to do so .” Instead, physicians should ensure that the information used in the patient’s decision-making is reasonable for the individual patient and that the patient understands the ramifications of choice. “The physician should be a navigator, not a pilot.”

The consequences of a patient’s choice cannot be shared with anyone else. Only the patient will suffer or enjoy the probabilistic outcomes associated with choosing one option over another. Only the patient will know how he or she feels about experiencing an adverse effect of a treatment, or a reduced chance of an adverse outcome that a treatment is designed to alter. Is the benefit of undergoing a prostatectomy for cancer worth the chance of becoming impotent or incontinent? Only the patient can decide. “Since no one else knows, no one else should decide.” In this sense, “shared decisions making” does not exist.

Some actions, however, are not really decisions to be made by the patient and do not require a patient’s input. Patients need not decide if antibiotics are required for bacterial pneumonia. Sick patients should not be allowed to

make decisions about treatments that are of clear value and that do not create significant levels of harm. If the significance of an adverse effect or harm is so minor compared with the benefit, no decision is required.

A decision that appropriately involves a patient requires viable options, and choosing one option over another must engender some element of risk. There has to be a definable trade-off of harm and benefit.

"Shared medical decision making really does not pertain to sharing choices, but rather involves sharing information." How do physicians inform patients about the consequences of the choices they must make? The patient must first have something to reflect upon. Some quality-of-life trade-off exists if the difference in the probabilistic outcomes associated with choices is known. If not known, a choice cannot be made. Reasonable estimates must be available for the individual's marginal benefit, and for the marginal harm. The patients must have time to reflect.

The conceptional framework for making a choice is understandable as a balance between harms and benefits weighed by the patient's values for gains and losses. Only the patient can do it. "Physicians cannot deny patients the opportunity and means to make their own choices."

"In essence, medical decision making is a mathematical core wrapped in compassion, humility, and responsibility."

JAMA November 24, 2004; 292: 2516-18 "Commentary "by Robert A McNutt, Rush University School of Medicine, Chicago, IL

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***Efficacious in Prevention of Incident and Persistent Cervical Infections.***

**11-7 EFFICACY OF BIVALENT L1 VIRUS-LIKE PARTICLE VACCINE IN PREVENTION OF INFECTION WITH HUMAN PAPILLOMA VIRUS TYPES 16 AND 18 IN YOUNG WOMEN.**

Cervical cancer is the most important manifestation of human papilloma virus **(HPV)** infection. It is one of the leading causes of cancer mortality in women worldwide. Almost 80% of cases occur in developing countries.

High-risk HPV DNA has been discovered in almost 100% of cases confirmed by expert histology. "Persistent infection with high-risk HPV types is the necessary cause of cervical cancer." HPV-18 and HPV-16 are the most prevalent types.

This study determined if vaccination against the common oncogenic types of HPV (16 and 18) could prevent development of cervical infection.

Conclusion: The vaccine was efficacious in prevention of incident and persistent cervical infections.

STUDY

1. Double-blind trial randomized over 1100 healthy women between ages 15 and 25. All were initially cytologically negative and seronegative for 16 and 18, and negative for HPV-DNA by PCR.
2. Randomized to: Three injections of: 1) HPV 16/18 vaccine formulated with an adjuvant, or 2) Placebo injections at months 0, 1, and 6.

3. Followed for up to 27 months for HPV infection by cervical cytology and self-obtained cervicovaginal samples. Determined incident and persistent infections by PCR, cytological abnormalities, and cervical carcinoma in situ. (CIN).

RESULTS

1. Vaccine efficacy against incident infection with 16/18 was 92%. Efficacy against persistent infection was 100%.
2. It was 93% effective against cytological abnormalities associated with 16/18. Three episodes of atypical squamous cells of undetermined significance occurred in the vaccinated group; 33 in the placebo group.
3. The vaccine was generally safe, well tolerated, and highly immunogenic.

DISCUSSION

1. The bivalent HPV 16/18 virus-like particle vaccine, given over 6 months with 3 injections, was highly efficacious in preventing incident and persistent HPV 16/18 infections.
2. The study provided evidence for the close relation between persistent HPV infection and the development of *cytological* abnormalities.
3. The study was not powered to estimate efficacy for *histopathologically* confirmed cervical lesions.
4. The authors suggest that the adjuvant enhances immune response (compared with antigen alone). The immune response from vaccination may persist for a longer time than the response from a naturally acquired infection.
5. If the vaccine does indeed prevent cervical cancer, it would reduce the costs of repeated cervical screening and treatment for cervical cancer.

CONCLUSION

A bivalent HPV vaccine was efficacious in prevention of incident and persistent 16/18 cervical infections and associated cervical abnormalities.

Lancet November 13, 2004; 364: 1757-65 Original investigation by the HPV Vaccine Study Group, fist author Dianne M Harper, Dartmouth Medical School, Hanover, NH, USA.

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***"Microalbuminuria Can Be Prevented"***

**11-8 PREVENTING MICROALBUMINURIA IN TYPE 2 DIABETES.**

About 1/3 of patients with type 2 diabetes **(DM2)** will eventually have progressive deterioration of renal function. Microalbuminuria is the first sign of renal dysfunction. (Endothelial dysfunction, however, is not necessarily confined to the kidney). When microalbuminuria develops, it is seldom reversible. It progresses to overt proteinuria in up to 40% of patients. A high percentage to these patients will progress to chronic kidney disease and ultimately require dialysis.

Many patients with microalbuminuria will die of cardiovascular disease. In patients with DM2 and renal disease, lowering BP and the levels of urinary albumin effectively reduces the risk of cardiovascular disease as well as end-stage renal disease.

Treatment with the ACE inhibitor enalapril (*Generic*) over 6 years has been reported to decrease the incidence of microalbuminuria in *normotensive* patients who had DM2. An unresolved issue is whether any drugs can *prevent* microalbuminuria in patients with DM2 and hypertension.

This study was designed to assess whether an angiotensin-converting-enzyme inhibitor or a non-dihydropyridine calcium-channel blocker, or the combination would *prevent* microalbuminuria in patients with DM2 who had hypertension and *normal* urinary albumin excretion.

Conclusion: The ACE inhibitor trandolapril decreased the incidence of microalbuminuria. The calcium blocker did not.

STUDY

1. Followed over 1200 patients with DM2. All were over age 40 (mean age 62). All had albumin excretion under 20 ug per minute. (Microalbuminuria was defined as an overnight excretion of 20 to 200 ug per minute.) All had serum creatinine levels under 1.5 mg/mL, and untreated systolic BP over 130/85.
2. At baseline, the mean duration of DM2 was 8 years; mean HbA1c 6%; trough BP 150/87; urinary albumin 5 ug/min; serum creatinine 0.9 mg/dL.
3. Randomized to: 1) the ACE inhibitor trandolapril (*Mavix* 2 mg/d ), or 2) the non-dihydropyridine calcium blocker sustained-release verapamil ( *Generic* 240 mg /d); 3) both; or 4) placebo.
4. The target BP was 120/80. If the target was not reached, additional antihypertension drugs were allowed.
5. Primary end point = development of microalbuminuria (over 20 ug/min).
6. Follow-up = 4 years.

RESULTS

1. Mean trough BP attained:

| | |
|---|---|
| Trandolapril alone | 139/81 |
| Verapamil alone | 141/82 |
| Both | 139/80 |
| Placebo | 142/83 |

Development of microalbuminuria (%):

| | |
|---|---|
| Trandolapril alone | 6 |
| Verapamil alone | 11.9 |
| Both | 5.7 |
| Placebo | 10 |

2. The glomerular filtration rate did not change in any group.

DISCUSSION

1. Trandolapril alone significantly reduced the incidence of microalbuminuria in patients with DM2. (NNT 4 years = 25)
2. Verapamil alone or added to trandolapril had no effect.
3. Preventing (or delaying) onset of microalbuminuria is a key goal for reno-protection.
4. “Microalbuminuria can be prevented in type 2 diabetes.”

CONCLUSION

In subjects with DM2 and hypertension, normoalbuminuria, and normal renal function, ACE-inhibitor therapy with trandolapril prevented the onset of microalbuminuria.

NEJM November 4, 2004; 351: 1941-51 Original investigation by the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) investigators, first author Peiro Ruggenenti, Mario Negri Institute for Pharmacological Research, Bergamo, Italy.

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***Slowed Progression of HF in Blacks***

**11-9 COMBINATION OF ISOSORBIDE AND HYDRALAZINE IN BLACKS WITH HEART FAILURE**

Neurohormonal inhibitors alone or in combination slow the progression of left ventricular dysfunction, and reduce the rates of death and complications in patients with heart failure **(HF).**

Endothelial dysfunction, impaired bioavailability of nitric oxide, and increased oxidant stress occur in HF. Augmentation of nitric oxide (by the nitric oxide donor, isosorbide) may be an alternative or supplemental approach to treatment of HF. Hydralazine may confer protection against degradation of nitric oxide induced by oxidative stress.

Studies have suggested that persons who identify themselves as black may have a less active renin-angiotensin system, and lower bioavailability of nitric oxide than those self-identified as white.

This study examined whether a fixed dose of isosorbide/hydralazine would provide additional benefits in blacks with advanced HF.

Conclusion: Addition of fixed doses of isosorbide/hydralazine to standard therapy for HF in blacks was efficacious and increased survival.

STUDY

1. Randomized over 1000 adult patients (mean age 57) self-identified as of African descent, who had class III or class IV HF. All were receiving stable doses of standard therapy for HF (a variety of ACE inhibitors, beta-blockers, digoxin, spironolactone, and diuretics). All had left ventricular ejection fraction under 35%.
2. Randomized to: 1) A fixed dose of isosorbide/hydralazine given by mouth daily, or 2) Placebo.
   Dose = 37.5 mg hydralazine + 20 mg isosorbide dinitrate three times daily. Dose could be increased to a total of 225/120 mg daily depending on absence of drug-induced side effects.
3. Primary end-point = a composite score of death from any cause, a first hospitalization for HF, and change in quality-of-life. Mean follow-up = 10 months.

RESULTS

1. The study was terminated early owing to a significantly higher mortality in the placebo group.
   (10% vs 6%; absolute difference = 4%; NNT for 10 months = 25)

2. The mean composite score was significantly better in the treatment group: absolute reduction in first hospitalization for HF = 10%; and improvement in the quality-of-life score *vs* placebo of 2 points in a scale of 0 to 105.
3. Survival differences emerged at about 6 months, and widened thereafter.
4. Headache and dizziness were more common in the isosorbide/hydralazine group. (*I could not find any record of withdrawals. RTJ*)

DISCUSSION

1. Nitric oxide regulates cardiovascular processes including myocardial hypertrophy, remodeling, vascular function, inflammation, and thrombosis.
2. There is substantial evidence that endothelial dysfunction and impaired bioavailability of nitric oxide occur in patients with HF and contribute to the pathophysiology. “This study, however, does not establish that these mechanisms explain the benefit of isosorbide/hydralazine”.
3. Studies have shown significant differences between blacks and whites in the response to pharmacotherapy of HF.
4. Isosorbide/hydralazine therapy in black persons can slow the progression of HF.

CONCLUSION

The addition of a fixed dose of isosorbide/hydralazine to standard therapy of HF was associated with increased survival among blacks with advanced HF.

NEJM November 11, 2004; 351: 2049-57, Original investigation by the African-American Heart Failure Trial (A-heFT) Investigators, first author Anne L Taylor, University of Minnesota, Minneapolis

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***Some ask—Does Race Exist At All?***

**11-10 A RATIONAL BASIS FOR RACE**

(*This report comments on the preceding study*.)

Insights granted by the Human Genome Project have helped dispel the deep-rooted myths about differences conferred by race, and the health disparities attributed to such divisions.

Why are medical researchers now designing drugs for specific groups? The fact is that humans are identical across 99.9% of their genome. Humans are not divided along clear color-based lines which are traditionally used in anthropological records. Some ask—Does race exist at all?

Some authorities suggest that, as traditionally understood, race is not a biologically meaningful concept. Human populations do exhibit genetic differences (due to different ancestries), and also differences in disease susceptibility. The problem occurs when society and the medical community generalizes these findings to the entire group. Prostate cancer has a higher prevalence among African-American men. This does not mean that all African-American men have similar risks for prostate cancer.

The connection between self-identified race and genetic variation is very blurry. Culture, lifestyle, and social stress may play a greater role in disparity.

Three ethical challenges in regard to genome research remain:

1. Avoiding genetic determinism
2. Preventing genetic discrimination.
3. Ensuring equal access for all to the benefits of genetic research.

Lancet November 20, 2004; 364: 1845-46 "World Report", commentary by David Lawrence

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***Treatment to Reduce LV Mass May Follow A Course Similar to Reductions in Cholesterol and BP.***

**11-11 LEFT VENTRICULAR HYPERTROPHY: The Next Silent Killer?**

An increase in mass of the left ventricular muscle is intimately associated with most chronic diseases of the heart. Classically, left ventricular hypertrophy **(LVH),** which represents an extreme increase in left ventricular mass, has been thought to represent a reaction to pressure or volume overload. In the short run, an increase in left ventricular mass **(LV mass**) may be beneficial by allowing the heart to compensate for increased wall stress and hemodynamic compromise. In the long run, it is harmful.

Even mild increases in BP are associated with increased LV mass.

LVH is a risk factor for premature death and cardiovascular events. The Framingham study reported that LVH, as confirmed by ECG, is associated with a mortality rate as high as that associated with a Q-wave myocardial infarction. But, the ECG may be a relative insensitive marker for LVH. Echocardiography detects milder increases in LV mass which are prognostically important.

The LVH associated with hypertension appears to be reversible. A long-term reduction in BP is associated with reductions LV mass.

LVH is not often thought of as a "standard" risk factor. Little data are available on the impact that reversing LVH may have on outcomes.

Two articles in this issue of JAMA [1,2] report that reductions in left ventricular mass in the setting of treatment for hypertension correlate with long-term cardiovascular outcomes. The first trial, of hypertensive patients with LVH documented by ECG criteria, reported the greater the treatment-decrease in ECG markers of LVH, the greater the reduction in cardiovascular events. The second trial reported data obtained by echocardiography. Over time, reductions in LV mass with treatment of hypertension were associated with reduced risk of cardiovascular events. The benefit of reductions in LV mass was independent of other potential confounders.

"Active efforts to reduce left ventricular mass may have important clinical benefits." Treatment to reduce LV mass may follow a course similar to reductions in cholesterol and BP.

How should clinicians respond to these observations? Patients being treated for hypertension may be followed by serial ECG or, if conveniently available, by echo. Failure of LV mass to respond might be an impetus for more aggressive therapy, especially of those with borderline increase in BP. The studies . . ."Support the role

of evaluating of left ventricular hypertrophy at the time of hypertension diagnosis and, at the very least, for considering changes in left ventricular mass when tailoring long-term antihypertensive therapy."

JAMA November 17, 2004; 2396-98 Editorial, first author Julius M Gardin, St John Hospital and Medical Center, Detroit Mich.

1 "Regression of Electrocardiographic Left Ventricular Hypertrophy during Antihypertensive Treatment and the Prediction of Major Cardiovascular Events" *JAMA November 17, 2004; 292: 2343-49* first author Peter M Okin, Cornell University Medical Center, New York.

2 "Prognostic Significance of Left Ventricular Mass Change During Treatment of Hypertension" *JAMA November 17, 2004; 292: 2350-56* first author Richard B Devereux, Cornell Medical Center, New York

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***FMS is the Second Most Common Disorder Observed by Rheumatologists***

**11-12 MANAGEMENT OF FIBROMYALGIA SYNDROME**

The diagnosis of the fibromyalgia syndrome **(FMS)** is based on a history of widespread chronic, bilateral upper body, lower body, and spine pain, and the presence of excessive tenderness on applying pressure to 11 or more of 18 specific muscle-tendon sites. FMS has not been traced to any specific structural or inflammatory cause.

This American College of Rheumatology classification criteria for diagnosis of FMS provides a nearly 85% sensitivity and specificity for differentiating FMS from other musculoskeletal pain.

FMS is the second most common disorder observed by rheumatologists (after osteoarthritis). It has a prevalence of 2% in the US. It is much more common in women. Chronic pain syndromes such as FMS are defined by subjective symptoms. They lack unique pathophysiological characteristics. No discrete boundary separates FMS from chronic fatigue syndrome, irritable bowel syndrome, and chronic muscular headache. Mood disturbances are comorbid with all. Abnormal pain processing (which has been demonstrated by brain imaging) may be a common characteristic. Patients with FMS have lowered mechanical and thermal pain thresholds, high pain ratings for noxious stimuli, and altered temporal summation of pain stimuli.

Psychosocial factors contribute to the clinical expression of FMS and related disorders.

This article summarizes the findings of a report (based on a detailed literature search) commissioned by the American Pain Society to provide evidence-based guidelines for the optimal management of FMS. There are major limitations to the literature. Many treatment trials are of short duration and lack masking. No medical therapies have been specifically approved by the FDA.

Despite the chronicity and complexity of FMS, there are interventions that may have clinical benefit in primary care practice:

Medication:

1. Strong evidence for efficacy

   Amitriptyline (*Generic*) a tricyclic antidepressant given at bedtime

2. Modest evidence for efficacy

Fluoxetine (*Generic; Prozac;* a SSRI. a selective serotonin reuptake inhibitor) 20-80 mg given at bedtime.

A number of drugs have been found ineffective, including NSAIDs, corticosteroids, hypnotics.

Non-medical therapies:

1. Strong evidence for efficacy.

Cardiovascular exercise

Cognitive behavior therapy

Group education sessions

Combinations of above.

JAMA November 17, 2004; 292: 2388-95 Clinical Review, first author Don L Goldenberg, Tufts University School of Medicine, Boston, Mass.

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