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WHITE RICE, BROWN RICE AND RISK OF TYPE-2 DIABETES [5-2]
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This document is divided into two parts

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

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

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**EDITORIAL COMMENTS** are the editor’s assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of *Practical Pointers*.

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

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

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

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Requests for “subscription” to rjames6556@aol.com
HIGHLIGHTS AND EDITORIAL COMMENTS  MAY 2010

5-1 GLYCATED HAEMOGLOBIN A1c FOR DIAGNOSIS OF DIABETES IN CHINESE POPULATION

Substantial evidence shows that HbA1c is a useful tool for diagnosis of diabetes. Recently, an international expert committee with members of the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation noted that a level of 6.5% is sufficiently sensitive and specific to identify people who are at risk of developing retinopathy and who therefore should be diagnosed as having diabetes.

This cross sectional epidemiological survey evaluated the efficiency of HbA1c in diagnosing diabetes and identified the optimal threshold in an adult Chinese population.

Apparently healthy Chinese (n = 4886) age 20-79 (median = 50 ) participated in this cross sectional epidemiological survey. An oral 75 g glucose tolerance test (the “gold standard”) was done in all participants. The dataset included 3748 people with normal glucose tolerance, and 301 with diabetes.

Constructed a receiver operating characteristic curve (ROC), using thresholds 1, 2, 3, and 4 standard deviations of HbA1c (0.4%) above the mean of 5.5%. The corresponding HbA1c levels were: 5.9%, 6.3%, 6.7%, and 7.1%. The area under the ROC curve (0.865) represented the diagnostic accuracy of HbA1c alone for detecting undiagnosed diabetes.

With the ROC curve, determined the best trade-off between true positive tests and false positive tests. (Perfect trade-off would be 100% true positives and 0% false positives, indicated by the upper left corner of the graph)

Of all 4 HbA1c levels, a HbA1c of 6.3% represented the best trade-off. (Ie, the closest distance to the upper left corner of the ROC curve.)

Sensitivity and specificity for detecting diabetes:

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>True positive (%)</th>
<th>False positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>6.3</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>6.5</td>
<td>51</td>
<td>2.0 (US standard)</td>
</tr>
<tr>
<td>6.7</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>7.1</td>
<td>26</td>
<td>0.2</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126 and above</td>
<td>57</td>
<td>0</td>
</tr>
</tbody>
</table>

When the diagnosis of diabetes was confirmed by a glucose tolerance test, only 63% of patients with diabetes were correctly diagnosed by the HbA1c of 6.3%.
When the diagnosis of diabetes was confirmed by a glucose tolerance test, only 57% of patients with diabetes were correctly diagnosed by fasting plasma glucose of 126 or more.

Conclusion: “HbA1c threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults, and had sensitivity similar to that of using a fasting plasma glucose of 7.0 mmol/L.” (126 mg/dL)

This is a long and complex study. I abstracted it with difficulty and in detail, at risk of causing confusion, not because of its specific application to ethnic groups. It describes the difficulty we have in diagnosing diabetes when the marginal cut-off points are approached.

It is easy to diagnose diabetes when the blood glucose is very high. (Years ago we depended on symptoms of excessive thirst, urination, unexplained weight loss, and glycosuria.) A very high spot blood glucose and a very high HbA1c will also diagnose diabetes. A very low spot blood glucose and a very low HbA1c will rule it out.

It is likely that a high HbA1c (ie, 7.5%) will lead to more organ damage than 6.5% and a non-diagnostic level of 6.4% will cause some organ damage.

A problem arises as the cut points reach equivocal levels. If we inform a patient she does not have diabetes based on a HbA1c of 6.4% (vs the US cut-off point of 6.5%) we may miss the diagnosis. She may have a reasonable chance of actually having diabetes. The same goes for a fasting plasma glucose of 125.

I believe it is prudent to inform patients who have borderline cut-points that they have impaired sugar metabolism, strongly advise lifestyle changes and inform them that the disturbance will be reversed if diet, weight, and exercise are improved.

Labeling patients with a life-time diagnosis of diabetes may be harmful.

The important point about the level of HbA1c: Is it high enough to cause or accelerate organ damage (kidney, retina, nerve, heart)? Younger patients who have borderline cut-off levels of HbA1c will benefit more over the years with better glucose control. Older patient have less to gain. Strict drug control of a marginally high HbA1c and a marginally high fasting plasma glucose may cause more harm than benefit.

Of course, symptomatic disease should be treated aggressively.

So, what is diabetes? Diabetes is a disease in which metabolism of glucose is disturbed and causes blood glucose levels to rise high enough and last long enough to cause or accelerate organ disease.
Substitution of Whole Grains, Including Brown Rice for White Rice, May Lower Risk Of DM-2

5-2 WHITE RICE, BROWN RICE, AND RISK OF TYPE-2 DIABETES IN US MEN AND WOMEN

Rice has been a staple food for centuries. By the 20th century, the advance of grain-processing technology made large-scale production of refined grains possible. Through the refining process, the outer bran and germ portions of the intact rice grains (brown rice) are removed to produce white rice that primarily consists of starchy endosperm.

Consumption of white rice generates a stronger postprandial blood glucose response as measured by the glycemic index (GI)\(^1\) than the same amount of brown rice. A systematic review (1999) found that the mean GI was 64 for white rice, and 55 for brown rice compared with 100 for glucose.

Higher GI has been consistently associated with elevated risk of type-2 diabetes (DM-2).

This study evaluated white and brown rice consumption in relation to DM-2

Prospectively ascertained diet and lifestyle practices and disease status among 39,765 men and 157,463 women in the Health Professionals Follow-up Study and two Nurses Health Studies 1984-2008. Subjects answered food frequency questionnaires at baseline and periodically.

Documented 10,505 incident cases of DM-2. (Follow-up = 20 and 22 years.)

Participants who ate at least 5 servings of white rice per week had 17% higher risk of developing DM-2 compared with those in the lowest category of intake of white rice.

There was a monotonically decreasing risk of DM-2 associated with increasing consumption of whole grains, including brown rice. In comparison with the lowest quintile of whole grain intake, the relative risk (RR) for the highest quintile was 0.73.

The replacement of 50 g of white rice (1/3 serving) per day with the same amount of brown rice was associated with lower risk. (RR = 0.84). When replacing 50 g of white rice per day with the same amount of whole grains, the RR was 0.64.

“In these 3 prospective studies of US men and women, we found that regular consumption of white rice was associated with higher risk of DM-2, whereas, brown rice was associated with lower risk.”

The current dietary guidelines identify grains, including rice, as one of the primary sources of carbohydrate intake, and recommends that at least half of carbohydrate intake come from whole grains.

Conclusion: Substitution of whole grains, including brown rice for white rice, may lower risk of DM-2. More carbohydrate intake should come from whole grains rather than from refined grains to prevent DM-2. 

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A healthy lifestyle includes a low glycemic load (GL) diet. This is best achieved by consuming low glycemic index foods in moderation.

The rapid blood glucose response to a high GL meal results in high insulin production. Over time, the excessive insulin-secretion of the pancreas may be impaired, leading to type-2 diabetes.

The blood glucose rise after a high GL meal causes increased insulin secretion, and leads to a reactive hypo-glycemia, increasing hunger and additional food intake. Obesity results. Low GL diets may lead to weight loss.

High GL are also associated with increased serum triglycerides, and decreased HDL-cholesterol and increased risk of cardiovascular disease.

Low GI foods and low GL diets improve the overall blood glucose response and better control of DM-2

Source: Linus Pauling Institute, Oregon State University,

Improves Blood Lipid Levels in A Dose-Related Manner

5-3 NUT CONSUMPTION AND BLOOD LIPID LEVELS

Nuts are rich in plant protein and fat, mostly unsaturated fat. They are a rich source of additional nutrients: dietary fiber, minerals and vitamins, as well as antioxidants and phytosterols.

Epidemiological studies consistently show that frequent nut consumption lowers risk of CHD--up to 37% lower in subjects who consume 4 or more servings of nuts per week, compared with those who seldom eat nuts.

In 2003, the US Food and Drug Administration issued a qualified statement that eating 1.5 oz of almonds, cashews, hazelnuts, macadamias, pecans, pistachios, walnuts, pine nuts, hazelnuts, or peanuts may reduce CHD risk.

This comprehensive MEDLINE search (1992-2004) identified 25 nut-consumption trials in which the dietary intervention was exclusively nuts.

Effects of nut consumption were similar in men and women, across all age groups, and were independent of the specific type of nut consumed.

Estimated changes from baseline (nut consumers vs controls):

<table>
<thead>
<tr>
<th>A.</th>
<th>mg/dL</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-c</td>
<td>-11</td>
<td>-5</td>
</tr>
<tr>
<td>LDL-c</td>
<td>-11</td>
<td>-7 (Overall)</td>
</tr>
<tr>
<td>&lt; 130</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>130-160</td>
<td>-10</td>
<td></td>
</tr>
</tbody>
</table>
>160   -18                        (Greater effect in persons with higher LDL)
HDL-c   +0.1                       +0.2                      (Essentially no change in HDL)
TG      - 3.1                      (Overall)
< 150   -1.0
> 150   -21                        (Greater effect in persons with higher TG)

B. Changes varied with baseline body mass index (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Total-c</th>
<th>LDL-c</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>-12%</td>
<td>-12%</td>
<td>-6%</td>
</tr>
<tr>
<td>25-30</td>
<td>-11</td>
<td>-9</td>
<td>-1</td>
</tr>
</tbody>
</table>
| >30   | -9      | -7    | -2  | (As BMI increased, benefits decreased.)

The estimated effects of nut consumption on lipids were dose-related:

At 20% energy from nuts
2.5 oz in a 2000 kcal diet:   - 4.5% for TG and - 6.5% for LDL-c

At 12% of energy from nuts
1.5 oz in a 2000 kcal diet:     -3.2% for TG and - 4.9% for LDL-c
(1.5 oz is recommended by the US Food and Drug Administration.)

The cholesterol-lowering effects of nut consumption are dose related and are most pronounced in subjects with higher baseline LDL-c or lower BMI.

Nuts lowered TG in subjects with hypertriglyceridemia, and also lowered the ratio of LDL-c to HDL-c and the ratio of TG to HDL-c.

The estimated overall reduction in LDL-c (7%) is modest compared with the effects of statins. The effect of frequent nut consumption is likely due to other factors as well. Epidemiological studies have reported a summary 37% reduction in risk of CHD, which is double that attributable to lowering LDL-c by 7%. Other beneficial effects of nuts include improved endothelial function, and lowering lipoprotein (a) levels. In addition, nut consumption is associated with a lower risk of developing type-2 diabetes.

Conclusion: Nut consumption improves blood lipid levels in a dose-related manner, particularly among subjects with higher LDL-c or with lower BMI.

Remarkably, peanuts have nutrients similar to tree nuts. Peanuts and peanut butter are universally available, are less expensive than other nuts, and are a convenient, delicious snack.

According to the US Dept. of Agriculture (1998) 1 oz of peanuts contains:

160 kcal; 1.9 g saturated fat; 6.0 g monounsaturated fat; and 4.4 g polyunsaturated fat.
One oz (2 tablespoons) of peanut butter contains about the same.
The recommended 1.5 oz of peanuts daily contains 240 kcal, about 12% of a 2000 kcal diet. If added to the regular diet, this would lead to considerable weight gain over one year.

Significantly Reduced Incidence and Mortality from CRC
5-4 ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN PREVENTION OF COLORECTAL CANCER

Screening can potentially prevent CRC because most arise from adenomas, predominantly symptomless growths that develop in 20-30% of the population.

Two thirds of CRCs and adenomas are located in the rectum and sigmoid.

Flexible sigmoidoscopy (FS) is well accepted, safe, and quick. It may be a suitable method for population screening.

This randomized trial examined the hypothesis that only one FS screen between ages 55-64 is cost effective, acceptable, and reduces CRC incidence and mortality. This is based on observations suggesting that most people who develop a distal colon cancer will have developed an adenoma by age 60, and removal of adenomas by sigmoidoscopy offers protection against distal CRC.

The trial entered (1994-1999) 170 432 men and women, age 55-64 (mean age 60) from multiple centers in the UK. Those with a family history of CRC or symptoms of CRC were managed outside the trial because randomization would not have been in their interest.

Randomized (ratio of 1:2) to: 1) intervention group (offered a flexible sigmoidoscopy), or 2) controls (not contacted).

All adenomas were removed.

Those with adenomas larger than 10 cm, 3 or more adenomas, tubulovillous or severe dysplasia, or malignant disease were referred for colonoscopy.

Of the subjects actually screened, 95% were discharged because there were no polyps, or only low-risk polyps. 5% were referred for colonoscopy.

CRC incidence and mortality over a mean of 11 years:
A. Controls (n = 112 939)

<table>
<thead>
<tr>
<th>Incidence of CRC</th>
<th>Cases</th>
<th>Rate per 100 000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>1192</td>
<td>98</td>
</tr>
<tr>
<td>Proximal</td>
<td>628</td>
<td>51</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>538</td>
<td>44</td>
</tr>
</tbody>
</table>
B. Screened (n = 40 621)  Cases  Rate per 100 000 patient-years

Incidence of CRC

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>215</td>
<td>48</td>
</tr>
<tr>
<td>Proximal</td>
<td>224</td>
<td>50</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>111</td>
<td>25</td>
</tr>
</tbody>
</table>

C. Hazard ratios (Screened vs controls)

<table>
<thead>
<tr>
<th>Location</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>0.50</td>
</tr>
<tr>
<td>Proximal</td>
<td>0.97</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>0.57</td>
</tr>
</tbody>
</table>

The estimated number of people needed to be screened to prevent one death due to CRC = 489.

There was a 43% reduction in death due to colorectal cancer in people who attended screening compared with controls.

There was no effect of screening on incidence of CRC in the proximal colon.

Economic analysis suggests that screening is cost-effective due to lower costs of treatment of CRC. Adequately trained nurses can undertake flexible sigmoidoscopy as competently as can Gastroenterologists. Public acceptance of nurse-led sigmoidoscopy screening is high.

Conclusion: Flexible sigmoidoscopy is a safe and practical test, and when offered only once to people between ages 55-64, confers a substantial and long-lasting protection from CRC.

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Relatively few persons in the US undergo colonoscopy.

I believe FS is not a substitute for colonoscopy. It is an added screening procedure.

Since sigmoidoscopy requires less elaborate preparation, is more convenient, can be performed by health-care personnel other than gastroenterologists, many more patients may be willing to accept it.

Screening sigmoidoscopy may be repeated periodically and augmented with fecal occult blood testing. Costs to patients and to society will be much lower.

Many CRCs were discovered during the one and only screening sigmoidoscopy and were successfully treated.

Metformin Induces B-12 Malabsorption and Low Serum Levels

5-5 LONG TERM TREATMENT WITH METFORMIN IN PATIENTS WITH TYPE-2 DIABETES AND RISK OF VITAMIN B-12 DEFICIENCY

This placebo-controlled trial examined the long-term effects of metformin on serum concentrations of B-12, folate, and homocysteine in patients with type-2 diabetes (DM-2).
The trial included 390 outpatients with DM-2, aged 30-80. All patients were receiving insulin. Patients were randomized to: 1) insulin + metformin 850 mg 3 times per day, or 2) insulin + placebo 3 times per day.

Serum levels of B-12, folate, and homocysteine were checked at 4, 17, 30, 42, and 52 months.

Defined deficiency of B-12 as below 150 pmol/L, and low levels as between 150 and 220 pmol/L.

Over the 52 weeks, mean B-12 in the placebo group remained stable. In the metformin group, mean levels fell in 4 months from a mean of 355 pmol/L to 300 pmol/L. Over the remainder of the study, mean B-12 levels continued to fall in the metformin group to about 280.

<table>
<thead>
<tr>
<th>Change at 52 weeks:</th>
<th>Placebo</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-12 concentration (pmol/L)</td>
<td>+ 0.2 (0%)</td>
<td>- 90 (- 19%)</td>
</tr>
<tr>
<td>Folate (nmol/L)</td>
<td>+ 1.01</td>
<td>+ 0.21 (Not statistically significant)</td>
</tr>
<tr>
<td>Homocysteine (umol/L)</td>
<td>+ 1.60</td>
<td>+ 3.28</td>
</tr>
</tbody>
</table>

At the end of the study:

| Deficiency of B-12 (%)     | 3       | 10 |
| Number needed to be treated (NNH) to cause deficiency | 14 |
| Hazard ratio for B-12 deficiency caused by metformin (vs placebo) | 5.5 |
| Low level of B-12 (%)      | 7       | 18 |
| Homocysteine levels (umol/L) | 18      | 22 |

Metformin significantly reduced concentrations of B-12. The decrease persisted and grew over time.

The finding of a decrease in B-12 during metformin treatment is not a novel finding. That the decrease is progressive is novel. Concentrations in some patients drop to the level at which most authorities agree that substitution is required.

Metformin is thought to induce malabsorption of B-12 and intrinsic factor in the ileum, an effect that can be reversed by increased calcium intake.

Treatment of B-12 deficiency is relatively easy, cheap, safe, and effective, in effect arguing in favor of treatment on the basis that treatment can do no harm. However, there is no consensus on the issue of whether “asymptomatic” deficiency should be treated.

It is reasonable to assume that harm will eventually occur in some patients with metformin-induced B-12 deficiency.
Conclusion: In patients with DM-2 treated with insulin, those additionally treated with metformin had a seven percentage point greater absolute risk of B-12 deficiency than those treated with placebo during a 4.3 year follow-up. “Our data provide a strong case for routine assessment of vitamin B-12 levels during long-term treatment with metformin.”

The authors do not mention any clinical manifestations of B-12 deficiency even though 10% of subjects taking metformin developed deficient levels.

Why does calcium reverse malabsorption?

Since metformin is used so frequently in primary care, how should the primary care clinician respond to this study? I believe it prudent to advise these patients to take a multivitamin tablet daily. This supplies the recommended daily value of B-12 (6 mcg) as well as vitamin D (400 IU) and others. It will cost 3 to 4 cents daily. It would be reasonable to take the vitamin between meals to avoid competition with metformin. And take a calcium supplement.

Both Are Associated With Improvement Over 2 Years

5-6 PIOGLITAZONE, VITAMIN E, OR PLACEBO FOR NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (NASH) is a common liver disease characterized histologically by hepatic steatosis, lobular inflammation, and hepatocellular ballooning. It progresses to cirrhosis in up to 15% of patients. It is closely associated with features of the metabolic syndrome: insulin resistance, obesity, hypertriglyceridermia, and type-2 diabetes.

This phase 3 study investigated whether either pioglitazone (to ameliorate insulin resistance) and vitamin E (to ameliorate oxidative stress) would improve NASH.

Multicenter, randomized, placebo-controlled, double-blind clinical trial assigned 247 adults with NASH to: 1) pioglitazone (Actos; Takeda) 30 mg daily, or 2) vitamin E 800 IU daily), or 3) placebo. No patient had diabetes. No subject consumed alcohol more than 20 g per day for women, and 30 g per day for men. None had other liver diseases or heart failure. All subjects were given a standardized set of pragmatic recommendations about lifestyle and diet.

Primary outcome = improvement in histological features of NASH assessed by use of a composite of standardized scores for steatohepatitis: lobular inflammation; hepatocellular ballooning; and fibrosis.

<table>
<thead>
<tr>
<th>Outcomes over 96 wk</th>
<th>Improvement (%)</th>
<th>NNT to benefit one subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>E vs placebo</td>
<td>43 vs 19</td>
<td>4</td>
</tr>
</tbody>
</table>
Pioglitazone vs placebo  34 vs 19  7 (Not statistically significant)

These data cannot be generalized to patients with diabetes, or those with cirrhosis.

Given that relapse occurred after discontinuation of the drugs, it is likely that they will have to be taken indefinitely. The weight gain with pioglitazone did not resolve after discontinuation. This also detracts from its long-term usefulness.

The unknown potential for adverse effects of the drugs must be factored into the decision about whether to use these drugs.

Conclusion: Vitamin E was superior to pioglitazone for treatment of NASH in adults without diabetes. Significant benefits of pioglitazone were observed in some of the secondary outcomes.

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I found this article difficult to abstract. I debated whether to include it. The full primary outcome is convoluted. (See the full abstract.) Although this drug therapy is not suited for primary care at this time, I believe we should keep it in mind.

NASH is a common and serious disease. Diagnosis is usually made by CT scan of the liver.

The study strongly suggests that both drugs are effective in treatment of NASH. But, the long-term adverse effects and effectiveness of pioglitazone and vitamin E used in this manner are not known. Look for further developments.

Weight loss remains the effective therapy. I included the article in part to point out the intransigence of overweight and obese patients. They know that they are at increased risk of disease and death, and NASH increases risk. Obesity is an unsolved problem.

At Present, “Genomics Are More Closely Aligned With Modern Science than With Modern Medicine”

5-7 TEN YEARS ON--THE HUMAN GENOME AND MEDICINE

(This editorial was written by Harold Varmus, former director of the NIH and Nobel prize winner for discovery of retroviral oncogenes.)

Now, after the first decade of a postgenomic world, only a handful of major changes have entered routine medical practice: some gene-specific treatments of a few cancers; some novel therapies for a few mendelian traits; and some strong genetic markers for assessing drug responsiveness, risk of disease, or risk of disease progression. Most of these can be traced to discoveries that preceded the unveiling of the human genome.
Implicated haplotypes collectively account for only a small fraction of the apparent heritable risk. More than one decade of genomics will be required to understand the inborn risks of most common disorders, such as diabetes and hypertension.

Despite remarkably rapid advances, genomics are more closely aligned with modern science than with modern medicine. Only a few selected items of that new information are widely used as guides to risk, diagnosis, or therapy.

Changes in the worlds of commerce, law, regulation, ethics, health insurance, and information technology are intersecting with the expanded role of genetics in medicine.

The practice of direct-to-consumer marketing, mainly identification of SNPs as putative markers of disease risk, has been among the most visible manifestations of genomics. Yet this practice is not regulated, lacks external standards for accuracy, has not demonstrated economic viability, or clinical benefit, and has the potential to mislead customers.

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Individuals who consent to genomic screening lack informed consent. They consent to the test, but the consent is not informed. They may be grievously misled. Informing patients that they have an increased risk of a certain disease does not inform how large the risk is, or whether a patient will ever develop the disease. For most screening tests, there is uncertainty about validity and clinical utility.

The likelihood of false positive tests is high. The test may be positive and “statistically significant” but clinically meaningless. The positive predictive value is very low. Patients may be informed that their risk is twice as great as average. This may mean risk is increased from 1% to 2%.

A positive screening test will cause increased anxiety, and lead to multiple follow-up tests further increasing concern, worry, and expense without any benefit.

In my view, offering and applying a screening test, not knowing and not being able to fully inform the patient about possible harms, is unethical.

Genomic screening has no place in primary care medicine. However, we may enjoy following developments while we learn more about it, while we try to improve the application of the valid screens we already have: family history, lifestyle factors, and established clinical and laboratory tests.

Screening should be sharply focused, and suggested, and supervised by an expert. It may have a place in high-risk families.

It will take decades of experience to settle on the clinical meaning of some genomic tests. We are still debating the effectiveness of breast and prostate cancer screening.

Ask: will the patient be better off knowing this information?
More efficient approaches to diagnosing diabetes are needed. Existing methods, fasting plasma glucose and the oral glucose tolerance test, require fasting and are inconvenient. This limits clinical application. HbA1c is convenient and easy to do without regard to fasting.

Lack of standardization has limited use of HbA1c in diagnosis. Several different methods have been used to determine levels. The National Glycohemoglobin Standardization Program has made progress in standardizing assays. High performance liquid chromatography is used in China.

Substantial evidence shows that HbA1c is a useful tool for diagnosis of diabetes. Recently, an international expert committee with members of the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation noted that a level of 6.5% is sufficiently sensitive and specific to identify people who are at risk of developing retinopathy and who therefore should be diagnosed as having diabetes. The committee examined data from three cross sectional epidemiological studies. However, the performance of HbA1c in the Chinese population remained unknown.

This cross sectional epidemiological survey evaluated the efficiency of HbA1c in diagnosing diabetes and identified the optimal threshold in an adult Chinese population.

STUDY
1. Apparently healthy Chinese (n = 4886) age 20-79 (median = 50 ) participated in this cross sectional epidemiological survey.
2. A standard oral 75 g glucose tolerance test (the “gold standard”) was done in all participants.
   Also measured HbA1c, fasting plasma glucose, and 2-hour post-load plasma glucose.
3. Diagnosed diabetes based on the 1999 WHO criteria.¹
4. Constructed a receiver operating characteristic curve (ROC), using thresholds 1, 2, 3, and 4 standard deviations of HbA1c (0.4%) above the mean of 5.5%. The corresponding HbA1c levels were: 5.9%, 6.3%, 6.7%, and 7.1%. The area under the curve was 0.856
5. With the ROC curve, determined the best trade-off between true positive tests and false positive tests. (Perfect trade-off would be 100% true positives and 0% false positives, indicated by the upper left corner of the graph.)
RESULTS
1. The dataset included 3748 people with normal glucose tolerance, and 301 with diabetes.
2. The area under the ROC curve (0.865) represented the diagnostic accuracy of HbA1c alone for detecting undiagnosed diabetes. HbA1c of 6.3% was closest to the upper left corner of the graph, indicating the best combination of true positives and false positives for diabetes.
3. As the number of SDs above the mean of 5.5% increased, true positives decreased and false positives also decreased.
4. Sensitivity and specificity for detecting diabetes;

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>True positive (%)</th>
<th>False positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>6.3</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>6.5</td>
<td>51</td>
<td>2.0 (US standard)</td>
</tr>
<tr>
<td>6.7</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>7.1</td>
<td>26</td>
<td>0.2</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126 and over</td>
<td>57</td>
<td>0</td>
</tr>
</tbody>
</table>
5. Thus, when the diagnosis of diabetes was confirmed by a glucose tolerance test, only 63% of patients with a HbA1c of 6.3% were diagnosed as having diabetes. And 4% were falsely labeled as diabetic.
6. Of all 4 HbA1c levels, a level of 6.3% represented the best trade-off between true positives and false positives.
7. In this Chinese population, a HbA1c of 6.5% (the US recommended diagnostic level) had a lower sensitivity (51% true positives compared with 63% true positives for 6.3%)
8. When the diagnosis of diabetes was confirmed by a glucose tolerance test, only 57% of patients with diabetes were correctly diagnosed by fasting plasma glucose of 126 or more.

DISCUSSION
1. The HbA1c threshold of 6.3% had a high specificity for detecting undiagnosed diabetes, and equal sensitivity to that of a fasting plasma glucose of 126 mg/dL and above.
2. Diabetes remains undiagnosed. In the US, for every 2 patients diagnosed as having diabetes, at least one other patient in the hospital may have unrecognized diabetes.
3. In this survey, more than 40% of people with diabetes were undiagnosed before the survey. More efficient identification of people with diabetes is thus essential.
4. Recent improvements in standardization of HbA1c have prompted reevaluation as a screening test. HbA1c is more reproducible than fasting plasma glucose as a diagnostic test for diabetes.

5. HbA1c can be done at any time at an office visit without fasting or other preparation of the patient. Both fasting glucose and the oral glucose tolerance test may be affected by short term lifestyle changes such as diet and physical exercise, HbA1c has no such limits.

6. Ethnic differences exist in the distribution of hyperglycemic categories. Only about 57% of Asian people with diabetes would be detected with the fasting plasma glucose criterion alone. “Our study confirmed the findings of the China National Diabetes Mellitus Survey, which suggested that a large number of people with diabetes (>40%) would be undiagnosed if only the fasting plasma glucose test was used.”

7. The National Health and Nutrition Survey in 1988-94 found differences between ethnic groups in the sensitivity and specificity of HbA1c (at 6.1%) for detecting undiagnosed diabetes. True positives ranged from 59% in the non-Hispanic white population to 84% in the Mexican-American population.

8. “We found that an HbA1c threshold of 5.9% provided the optimal sensitivity and specificity for screening for potential diabetes in the general Chinese population.”

9. In people at high risk of diabetes, (older age, high BMI) the proficiency of a HbA1c of 6.3% was superior to that of both fasting plasma glucose of 126 mg/dL and above, and a HbA1c threshold of 6.5%.

10. “This study should be validated by similar epidemiological and clinical studies.”

CONCLUSION

“HbA1c threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults, and had sensitivity similar to that of using a fasting plasma glucose of 7.0 mmol/L.” (126 mg/dL)

This threshold may be acceptable as a diagnostic criterion for diabetes in the Chinese population.

BMJ 2010;340: c2249  doi.10.1136/bmj.c2249
BMJ May 2010;340:1178  First author Yuqian Bao, Shanghai Diabetes Institute, Shanghai, China.

1. The WHO (1999) criteria:
   A. Diabetes:
      1) Fasting plasma glucose of 126 mg/dL or more. (To convert to mmol/L multiply by 0.05551)
      2) Post 2-hour glucose of 200 mg/dL or more, or
      3) Both.
B. Impaired fasting plasma glucose:
   1) 110 to 125 mg/dL
C. Impaired glucose tolerance:
   1) Fasting plasma glucose less than 110 and
   2) 2-hour post load plasma glucose 140 to 199
All cut points are arbitrary.

Substitution Of Whole Grains, Including Brown Rice For White Rice, May Lower Risk Of DM-2

5-2 WHITE RICE, BROWN RICE, AND RISK OF TYPE-2 DIABETES IN US MEN AND WOMEN

Rice has been a staple food for centuries. By the 20th century, the advance of grain-processing technology made large-scale production of refined grains possible. Through the refining process, the outer bran and germ portions of the intact rice grains (brown rice) are removed to produce white rice that primarily consists of starchy endosperm.

Consumption of white rice generates a stronger postprandial blood glucose response as measured by the glycemic index (GI) than the same amount of brown rice. A systematic review (1999) found that the mean GI was 64 for white rice, and 55 for brown rice.

Higher GI has been consistently associated with elevated risk of type-2 diabetes (DM-2)

In a Chinese population, high intake of white rice was associated with a monotonically elevated risk of developing DM-2.

In addition, brown rice consumption may impart beneficial effects on risk of DM-2 by virtue of its high content of multiple nutrients, fiber, vitamins, and minerals, which are lost during the refining and milling process.

Rice consumption in the US has been increasing, mostly white rice.

This study evaluated white and brown rice consumption in relation to DM-2

STUDY
1. Prospectively ascertained diet and lifestyle practices and disease status among 39 765 men and 157 463 women in the Health Professionals Follow-up Study and two Nurses Health Studies. 1984.-2008
2. Subjects answered food frequency questionnaires at baseline and periodically. Excluded
subjects with diabetes, cardiovascular disease, and cancer. Assessed brown rice and white rice consumption.

3. Categorized subjects into categories of rice consumption according to servings consumed:
   A. White rice: < 1 per month; 1 per week; 2 to 4 per week; and 5 or more per week.
   B. Brown rice: < 1 per month; 1 per month to 1 per week; 2 or more per week.

4. In a previous study these investigators assessed intake of whole grains. By definition, brown rice is a whole grain.

5. Determined incident DM-2 until 2008. (Follow-up = 20 and 22 years.)

6. Conducted a meta-analysis of the 3 studies to summarize the estimates of incidence of DM-2.

RESULTS

1. Documented 10 505 incident cases of DM-2.

2. After multivariate adjustments, participants who ate at least 5 servings of white rice per week had 17% higher risk of developing DM-2 compared with those in the lowest category of intake of white rice.

3. Brown rice was associated with lower risk of DM-2. When compared with participants who ate less than 1 serving per month, those who ate 2 or more servings per week had a relative risk (RR) of DM-2 of 0.89.

4. There was a monotonically decreasing risk of DM-2 associated with increasing consumption of whole grains, including brown rice. In comparison with the lowest quintile of whole grain intake, the RR for the highest quintile was 0.73.

5. Bran intake was associated with lower risk. In contrast with the lowest quintile of bran intake, the highest quintile of bran intake for men, the RR was 0.72, and for women, 0.82.

6. The replacement of 50 g of white rice (1/3 serving) per day with the same amount of brown rice was associated with lower risk. (RR = 0.84). When replacing 50 g of white rice per day with the same amount of whole grains, the RR was 0.64.

7. There were no interactions between rice consumption and other diabetes risk factors, including age, BMI, and various comorbidities.

DISCUSSION

1. “In these 3 prospective studies of US men and women, we found that regular consumption of white rice was associated with higher risk of DM-2, whereas, brown rice was associated with lower risk.”
2. Replacing white rice with the same amount of brown rice or whole grains was associated with a lower risk.

3. These associations were independent of lifestyle and other dietary risk factors for DM-2.

4. In Chinese women, white rice consumption accounts for 54% of total energy intake; in Japan 29%. In a Chinese study, white rice consumption of 2 servings per day (300 g or more) was associated with a 78% increase in risk of DM-2 compared with consumption of less than 200 g/d.

5. Depending on the botanical structure, amylase content, and processing methods, both white rice and brown rice demonstrated a wide variety of glycemic index values. In general white rice generates a relatively stronger postprandial glucose response and insulin levels than the same amount of brown rice.

6. The higher glycemic index of white rice is likely the consequence of disrupting the physical structure of the grains during the refining process in which almost all the bran and some of the germ are removed as well as vitamins, minerals, and phytoestrogens, many of which may be protective against DM-2. Intact rice grains contain nearly exclusively insoluble fiber, which is consistently associated with improved insulin sensitivity.

7. The consistency of the results across all 3 cohorts indicates that the findings are unlikely due to chance.

8. The current dietary guidelines identify grains, including rice, as one of the primary sources of carbohydrate intake, and recommends that at least half of carbohydrate intake come from whole grains.

CONCLUSION
Substitution of whole grains, including brown rice for white rice, may lower risk of DM-2.
More carbohydrate intake should come from whole grains rather than from refined grains to prevent DM-2.

Archives Internal Medicine, June 14, 2010; 170: 961-69  Original investigation, first author
Qi Sun, Harvard School of Public Health, Boston Mass

1 Whole grains and a low glycemic index (GI) and a low glycemic load (GL) are important measures of a healthy lifestyle. The literature is full of studies demonstrating benefits of low GI and GL diets.
Glycemic index:
GL is determined in several ways. The best I have read comes from the University of Sydney, Australia:
1) Ten healthy adults are given 50 grams of glucose to ingest.
2) Blood glucose levels are determined frequently (every 15-30 minutes) over the next 2 hours.
3) A blood sugar response curve is constructed based on the average glucose response.
4) The area under the curve (AUC) is determined.
5) A food containing 50 grams of carbohydrate is tested in the same manner.
6) The two AUCs are compared to determine the GI of the food. (Expressed as a %).

**Glycemic load:**

Is the most practical way to apply the GI to dieting. It is calculated by multiplying a food’s glycemic index (as a %) times the number of net carbohydrate in a given serving.

\[ \text{GL} = \frac{\text{GI} \times \text{net carbohydrate(grams) in a serving}}{100} \]

For example, a baked potato has a glycemic index of 76 relative to 50 grams of glucose. (Relative to 100)

One medium baked potato contains 30 grams of carbohydrate. The glycemic load is 23

\[ L = 76 \times 30 = 2280 \div 100 = 23. \]

<table>
<thead>
<tr>
<th>Food</th>
<th>GI</th>
<th>Serving</th>
<th>Carbs per serving</th>
<th>GL per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaghetti</td>
<td>44</td>
<td>1 cup</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Orange</td>
<td>2</td>
<td>1 medium</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Skim milk</td>
<td>32</td>
<td>8 oz</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Peanuts</td>
<td>14</td>
<td>1 oz</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Potatoes, white rice, white bread, and high fructose carbonated beverages, high GI and GL foods, are most consistently associated with increased risk of DM-2

Low GI and low GL foods include whole grains, nuts, legumes, fruits and non-starchy vegetables.

Source: Linus Pauling Institute, Oregon State University,

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**Improves Blood Lipid Levels in A Dose-Related Manner**

**5-3 NUT CONSUMPTION AND BLOOD LIPID LEVELS**

Consumption of nuts has been the focus of intense research because of their potential to lower blood lipid levels and to reduce risk of CHD.

Nuts are rich in plant protein and fat, mostly unsaturated fat. They are a rich source of additional nutrients: dietary fiber, minerals and vitamins, as well as antioxidants and phytosterols.
Epidemiological studies consistently show that frequent nut consumption lowers risk of CHD—up to 37% lower in subjects who consume 4 or more servings of nuts per week, compared with those who seldom eat nuts.

In 2003, the US Food and Drug Administration issued a qualified statement that daily consumption of 1.5 oz of almonds, cashews, hazelnuts, macadamias, pecans, pistachios, walnuts, pine nuts, hazelnuts, or peanuts may reduce CHD risk.

This study examined the effect of nut consumption on blood lipids, and further examined whether these effects were consistent when stratified by different population groups and variables such as age, type of nut, and body mass index (BMI). The study pooled data from 25 intervention trials.

STUDY
1. Comprehensive MEDLINE search (1992-2004) identified 25 nut-consumption trials in which the dietary intervention was exclusively nuts. No subject had recently received lipid-lowering medications.
2. There were no body weight changes between diets at the end of the intervention. (Maximum 8 weeks)
3. Final data set contained 1284 observations contributed by 583 unique subjects.

RESULTS
1. Daily nut consumption ranged from 0.8 to 4.9 oz / day (mean 2.4 oz).
2. Effects of nut consumption were similar in men and women, across all age groups, and were independent of the specific type of nut consumed.
3. Estimated changes from baseline (nut consumers vs controls):

<table>
<thead>
<tr>
<th>Overall</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL</td>
<td></td>
</tr>
<tr>
<td>A. Total-c</td>
<td>-11</td>
</tr>
<tr>
<td>LDL-c</td>
<td>-10</td>
</tr>
<tr>
<td></td>
<td>&lt; 130</td>
</tr>
<tr>
<td></td>
<td>130-160</td>
</tr>
<tr>
<td></td>
<td>&gt;160</td>
</tr>
<tr>
<td>HDL-c</td>
<td>+0.1</td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 150</td>
</tr>
<tr>
<td></td>
<td>&gt; 150</td>
</tr>
</tbody>
</table>

B. Changes varied with baseline BMI
<table>
<thead>
<tr>
<th>BMI</th>
<th>Total-c</th>
<th>LDL-c</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>-12%</td>
<td>-12%</td>
<td>-6%</td>
</tr>
<tr>
<td>25-30</td>
<td>-11</td>
<td>-9</td>
<td>-1</td>
</tr>
<tr>
<td>&gt;30</td>
<td>-9</td>
<td>-7</td>
<td>-2</td>
</tr>
</tbody>
</table>

(As BMI increased, benefits decreased.)

4. Nut consumption had no significant effect on HDL-c. It had an effect on TG only in those with levels > 150 mg/dL.

5. When assessed against a Western control diet, nut consumption had a greater relative effect in reducing Total-c (7%) and LDL-c (10%) than when assessed against a Mediterranean diet (-4% and -6%).

6. The estimated effects of nut consumption on lipids were dose-related:
   - At 20% energy from nuts
     - 2.5 oz in a 2000 kcal diet: -4.5% for TG and -6.5% for LDL-c
   - At 12% of energy from nuts
     - 1.5 oz in a 2000 kcal diet: -3.2% for TG and -4.9% for LDL-c

   (1.5 oz is recommended by the US Food and Drug Administration.)

DISCUSSION

1. Incorporating nuts into the diet lowered TG and LDL-c.

2. “Most important, is the finding that the cholesterol-lowering effects of nut consumption are dose related and are most pronounced in subjects with higher baseline LDL-c or lower BMI.”

3. Nuts lowered the ratio of LDL-c to HDL-c and the ratio of TG to HDL-c.

4. The estimated reductions are almost identical to those obtained in a recent meta-analysis of walnut consumption.

5. Nuts are rich in plant sterols, which interfere with cholesterol absorption.

6. Effects are dose-related.

7. The estimated overall reduction in LDL-c (7.4%) is modest compared with the effects of statins.

   The effect of frequent nut consumption is likely due to other factors as well. Epidemiological studies have reported a summary 37% reduction in risk of CHD, which is double that attributable to lowering LDL-c by 7.4%. Other beneficial effects of nuts include improved endothelial function, and lowering lipoprotein (a) levels. In addition, nut consumption is associated with a lower risk of developing type-2 diabetes.

8. “Research has shown that frequent nut consumption does not lead to weight gain.”

9. The greatest lipid-lowering effect of nuts occurs when nuts replace saturated fats than when olive oil
is replaced. Thus, there is a lesser effect when taken by persons who are consuming the Mediterranean diet as compared with the usual Western diet.

10 “Our findings confirm the results of epidemiological studies showing that nut consumption lowers CHD risk and support the inclusion of nuts in therapeutic dietary interventions.”

CONCLUSION

Nut consumption improves blood lipid levels in a dose-related manner, particularly among subjects with higher LDL-c or with lower BMI.

Archives Internal Medicine  May 10, 2010; 170: 821-27  original investigation, first author Joan Sabate, Loma Linda University, Loma Linda, CA

1 Peanuts are members of the legume family. They were included because of their comparable nutrient profile to nuts, and their common identification as part of the nut food group.

2 This is too broad a statement. Weight change depends on whether the individual replaces calories with nuts, or eats them in addition to the usual diet.

The length of life of the 7th Day Adventists of California, a remarkable group, is significantly longer than most American groups. They maintain a healthy lifestyle, including consumption of nuts. The Loma Linda group has written other studies regarding nuts, especially walnuts, which are grown abundantly in California.

Significantly Reduced Incidence and Mortality from CRC

5-4  ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN PREVENTION OF COLORECTAL CANCER

Survival from colorectal cancer (CRC) is strongly related to stage at diagnosis, with survival rates of 90% for localized cases.

Three randomized-controlled trials have shown that biennial screening with the fecal occult blood test, which detects early cases, reduces mortality of CRC by about 25%. Many countries have introduced screening programs based on this test.

Screening can potentially prevent CRC because most arise from adenomas, predominantly symptomless growths that develop in 20-30% of the population.

Two thirds of CRCs and adenomas are located in the rectum and sigmoid.
Flexible sigmoidoscopy (FS) is well accepted, safe, and quick. It may be a suitable method for population screening.

This randomized trial examined the hypothesis that only one FS screen between ages 55-64 is cost effective, acceptable, and reduces CRC incidence and mortality. This is based on observations suggesting that most people who develop a distal colon cancer will have developed an adenoma by age 60, and removal of adenomas by sigmoidoscopy offers protection against distal CRC.

STUDY
1. Randomized, controlled trial entered (1994-1999) 170 432 men and women, age 55-64 (mean age 60) from multiple centers in the UK. All had previously indicated a willingness to accept a screening sigmoidoscopy. None had a history of adenomas or CRC, or had received a sigmoidoscopy within the previous 3 years. Those with a family history of CRC or symptoms of CRC were managed outside the trial because randomization would not have been in their interest.
2. Randomized (ratio of 1:2) to: 1) intervention group (offered a flexible sigmoidoscopy), or 2) controls (not contacted).
3. The sigmoidoscopies were done in hospital endoscopy clinics. All adenomas were removed. Those with adenomas larger than 10 cm, 3 or more adenomas, tubulovillous or severe dysplasia, or malignant disease were referred for colonoscopy.
4. Primary outcome = incidence of CRC, including prevalent cases detected at screening, and mortality from CRC.
5. Followed 112 939 controls and 57 099 intervention subjects for a median of 11 years, (of the intervention group, 40 621 were actually screened; 16 428 not screened).

RESULTS
1. Of the subjects actually screened, 95% were discharged because there were no polyps, or only low-risk polyps. 5% were referred for colonoscopy.
2. CRC incidence and mortality over a mean of 11 years:
   A. Controls (n = 112 939)
<table>
<thead>
<tr>
<th>Incidence of CRC</th>
<th>Cases</th>
<th>Rate per 100 000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>1192</td>
<td>98</td>
</tr>
<tr>
<td>Proximal</td>
<td>628</td>
<td>51</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>538</td>
<td>44</td>
</tr>
</tbody>
</table>
B. Screened (n - 40 621)    Cases  Rate per 100 000 person-years

<table>
<thead>
<tr>
<th>Incidence of CRC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>215</td>
<td>48</td>
</tr>
<tr>
<td>Proximal</td>
<td>224</td>
<td>50</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>111</td>
<td>25</td>
</tr>
</tbody>
</table>

C. Hazard ratio  (Screened vs controls):

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum and sigmoid</td>
<td>0.50</td>
</tr>
<tr>
<td>Proximal</td>
<td>0.97</td>
</tr>
<tr>
<td>CRC mortality</td>
<td>0.57</td>
</tr>
</tbody>
</table>

3. For the first 4 years, the cumulative incidence of all CRC and distal cancers was higher in the
screened group. This was because of early detection of prevalent cancers. After 4 years, the
 cumulative rates became higher in the controls.

4. The estimated number of people needed to be screened to prevent one death due to CRC = 489.

5. There was no difference between men and women, or between different age groups, in the effect
of screening on any outcome.

DISCUSSION

1. Both incidence and mortality from CRC are significantly reduced in people undergoing a single
   flexible sigmoidoscopy between ages 55-64.

2. CRC incidence was reduced by one third, and mortality from CRC by more than 40%.

3. Of the 215 distal cancers diagnosed in the screened group, 126 (58%) were detected at
   screening. Although the incidence of CRC thereafter was low, the protective effect of screening
   persisted.

4. There was no effect of screening on incidence of CRC in the proximal colon. Only 5% of
   screened subjects were referred for colonoscopy. In two ongoing trials of flexible sigmoidoscopy, all
   subjects with any adenoma or any abnormality are referred for colonoscopy. Whether there is any
   reduction in incidence of proximal CRC awaits conclusion of the studies.

5. Rates of all-cause mortality, excluding CRC deaths were slightly (not significantly) lower in the
   screened group. This suggests that screening did not have unexpected harms.

6. Economic analysis suggests that screening is cost-effective.

7. Adequately trained nurses can undertake flexible sigmoidoscopy as competently as can
   gastroenterologists, and public acceptance of nurse-led sigmoidoscopy screening is high.

8. CRC in the control group was 149 per 100 000 person-years, Almost exactly as expected in
persons age 55-64 followed up for 10 years.

CONCLUSION

Flexible sigmoidoscopy is a safe and practical test, and when offered only once to people between ages 55-64, confers a substantial and long-lasting protection from CRC.


=========================================================================  

Metformin Induces B-12 Malabsorption And Low Serum Levels

5-5 LONG TERM TREATMENT WITH METFORMIN IN PATIENTS WITH TYPE-2 DIABETES AND RISK OF VITAMIN B-12 DEFICIENCY

There are few disadvantages to use of metformin. Metformin, however, does induce B-12 malabsorption, which may increase risk of deficiency.

No long-term placebo-controlled studies concerning relation between metformin and B-12 have thus far been reported. All studies have been short term.

This placebo-controlled trial examined the long-term effects of metformin on serum concentrations of B-12, folate, and homocysteine in patients with type-2 diabetes (DM-2).

STUDY

1. This study is part of the Hyperinsulinaemia: the Outcome of the Metabolic Effects (HOME) randomized trial investigating the effects of metformin on macrovascular and microvascular disease in DM-2.

2. The trial included 390 outpatients with DM-2, aged 30-80. All patients were receiving insulin.

3. Patients were randomized to: 1) insulin+ metformin 850 mg 3 times per day, or

4. Serum levels of B-12, folate, and homocysteine were checked at 4, 17, 30, 42, and 52 months.

5. Defined deficiency of B-12 as below 150 pmol/L, and low levels as between 150 and 220 pmol/L

6. The end point of interest was the percentage change in each variable.

RESULTS

1. At baseline, 3 patients in the metformin group and 4 in the placebo group had B-12 deficiency
and 14 patients in each group had low concentrations.

2. Over the 52 months, mean B-12 in the placebo group remained stable. In the metformin group, mean levels fell in 4 months from a mean of 355 pmol/L to 300 pmol/L. Over the remainder of the study, mean B-12 levels continued to fall in the metformin group to a mean of about 280.

3. Change at 52 months:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-12 concentration (pmol/L)</td>
<td>+ 0.2 (0%)</td>
<td>- 90 (-19%)</td>
</tr>
<tr>
<td>Folate (nmol/L)</td>
<td>+ 1.01</td>
<td>+ 0.21 (Not statistically significant)</td>
</tr>
<tr>
<td>Homocysteine (umol/L)</td>
<td>+ 1.60</td>
<td>+ 3.28</td>
</tr>
</tbody>
</table>

At the end of the study:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency of B-12 (%)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>to cause deficiency (NNH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio for B-12 deficiency</td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>caused by metformin (vs placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low level of B-12 (%)</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Homocysteine levels (umol/L)</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

4. Compared with placebo, metformin was associated with a 19% decrease in B-12, and a 5% increase in homocysteine.

DISCUSSION

1. Main findings:

1) Metformin significantly reduced concentrations of B-12. The decrease persisted and grew over time.

2) A small significant decrease in folate concentrations was found in the metformin group compared with the placebo group. However, it was not significant after adjustments for BMI and smoking.

3) Homocysteine levels increased in individuals in whom B-12 levels decreased below 150 pmol/L, a level generally considered to indicate clinical deficiency.

2. The finding of a decrease in B-12 during metformin treatment is not a novel finding. That the decrease is progressive is novel.

3. Concentrations in some patients drop to the level at which most authorities agree that substitution is required.

4. Metformin is thought to induce malabsorption of B-12 and intrinsic factor in the ileum, an
effect that can be reversed by increased calcium intake.1

5. Treatment of B-12 deficiency is relatively easy, cheap, safe, and effective, in effect arguing in favor of treatment on the basis that treatment can do no harm. However, there is no consensus on the issue of whether “asymptomatic” deficiency should be treated.

6. It is reasonable to assume that harm will eventually occur in some patients with metformin-induced B-12 deficiency.

7. As treatment with metformin continues, B-12 levels will continue to decrease, associated with inevitable increases in homocysteine.

8. One strength of the study is its setting in the community, making generalization reasonable.

CONCLUSION

In patients with DM-2 treated with insulin, those additionally treated with metformin had a seven percentage point greater absolute risk of B-12 deficiency than those treated with placebo during a 4.3 year follow-up. “Our data provide a strong case for routine assessment of vitamin B-12 levels during long-term treatment with metformin.”

First author Jolien de Jager, Academic Medical Center, Amsterdam, Netherlands.

1 Ionic calcium is obligatory for the B-12-intrinsic factor complex to attach to the ileal cell surface receptors. Metformin competes with calcium for the mucosal cell membrane. This form of vitamin B-12 malabsorption was reversible with an oral calcium supplement. Personal communication from Prof dr. Coen Stehouwer, Maastricht University Medical Center quoting Victor Herbert, Diabetes Care 2000; 23: 1227

Both Are Associated With Improvement Over 2 Years

5-6 PIOGLITAZONE, VITAMIN E, OR PLACEBO FOR NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (NASH) is a common liver disease characterized histologically by hepatic steatosis, lobular inflammation, and hepatocellular ballooning. It progresses to cirrhosis in up to 15% of patients. It is closely associated with features of the metabolic syndrome: insulin resistance, obesity, hypertriglyceridemia, and type-2 diabetes.
Oxidative stress has been implicated as a key factor contributing to hepatic injury. Thus, both insulin resistance and oxidative stress are attractive targets for therapy.

This phase 3 study investigated whether either pioglitazone (to ameliorate insulin resistance) and vitamin E (to ameliorate oxidative stress) would improve NASH.

STUDY

1. Multicenter, randomized, placebo-controlled, double-blind clinical trial assigned 247 adults with NASH to: 1) pioglitazone (Actos; Takeda) 30 mg daily, or 2) vitamin E 800 IU daily, or 3) placebo. No patient had diabetes. No subject consumed alcohol more than 20 g per day for women, and 30 g per day for men. None had other liver diseases or heart failure. All subjects were given a standardized set of pragmatic recommendations about lifestyle and diet.

2. An activity score was based on a standardized grading system: steatosis (0 to 3); lobular inflammation (0 to 3); and hepatocellular ballooning (0 to 2) with higher scores indicating increased severity.

3. The specific inclusion criteria were definite or possible steatohepatitis with an activity score of 5 or more. A score of at least 1 for hepatocellular ballooning was required in all cases.

4. A repeat liver biopsy was done at 96 weeks, and the trial drugs were discontinued. Subjects were then followed for an additional 24 weeks.

5. Primary outcome = improvement in histological features of NASH assessed by use of a composite of standardized scores for steatohepatitis: lobular inflammation; hepatocellular ballooning; and fibrosis. “Improvement in histologic findings, which required an improvement by 1 or more points in the hepatocellular ballooning score, no increase in the fibrosis score, and either a decrease in the activity score of nonalcoholic fatty liver disease to a score of 3 or less, or a decrease in the activity score of at least 2 points, with at least 1 point decrease in either the lobular inflammation or steatosis score.”

6. Primary analysis by intention-to-treat.

RESULTS

1. Baseline: (mean)
   Age 46; Body mass index 34; Waist circumference 108 cm; body fat composition 39%; fasting glucose 84 mg/dL
   Histological findings: (mean)
   Total NASH activity score 4.9
2. A total of 90% underwent a liver biopsy at 96 weeks.

3. Outcomes: Improvement (%)  NNT to benefit one subject
   Vitamin E vs placebo  43 vs 19  4
   Pioglitazone vs placebo  34 vs 19  7  (Not statistically significant)

4. As compared with placebo, both treatment groups had a significant reduction in steatosis, lobular inflammation, ballooning, and activity score. Fibrosis was not improved.

5. Primary outcome Placebo (n = 83) Vitamin E (n = 84) Pioglitazone (n = 80)
   % with improvement 19  43  34

6. Improvements (% of subjects)
   Steatosis 31  54  69
   Lobular inflammation 35  54  60
   Ballooning 29  50  44

7. Resolution of NASH (%) 21  36  47

8. There was an early and highly significant sustained decrease in liver enzymes in both treatment groups.

9. There was a significant improvement in insulin resistance in the pioglitazone group, despite weight gain of 5 kg at week 96.

10. In the 24 weeks after active treatment ended, liver enzymes and insulin resistance increased. The weight gain in the pioglitazone group persisted. There was no weight loss in the other groups.

11. There were 10 severe adverse effects in the placebo group; 7 in the vitamin E group and 2 in the pioglitazone group. Four cases of diabetes developed in the vitamin E group.

DISCUSSION
1. The assessment of therapeutic agents for NASH is a complex process. There are no validated biomarkers of response to treatment. One must rely on histological assessment.

2. The activity score quantifies the severity of the steatosis.

3. To develop an outcome that was both quantifiable and clinically relevant, the requirement of an improvement in ballooning and no worsening of fibrosis were added to the requirements of a decrease in the activity score for the primary outcome. This makes it likely that the observed
improvements with vitamin E are both statistically and clinically significant. These data cannot be
generalized to patients with diabetes, or those with cirrhosis.

4. Although pioglitazone did not meet the pre-specified requirements for the primary outcome, it
was associated with highly significant reductions in steatosis, inflammation, and ballooning, as well
as improvements in insulin resistance and liver enzyme levels.

5. It is important not to overinterpret the data on adverse events because the study was not
powered to test any safety-related hypothesis.

6. Enthusiasm for the potential benefits of pioglitazone and vitamin E must be tempered by the
finding that there was an improvement of only 34% of the pioglitazone subjects and only 43% of the
vitamin E subjects.

7. Neither agent was associated with significant improvement in fibrosis.

8. Given that relapse occurred after discontinuation of the drugs, it is likely that they will have to
be taken indefinitely. The weight gain with pioglitazone did not resolve after discontinuation. This
also detracts from its long-term usefulness.

9. The unknown potential for adverse effects of the drugs must be factored into the decision about
whether to use these drugs.

10. The study was not designed to compare pioglitazone with vitamin E. No conclusions about
relative efficacy can be drawn.

11. Preliminary studies also provide a rationale for treatment by lifestyle intervention, bariatric
surgery, phlebotomy, and a variety of drugs.

CONCLUSION

Vitamin E was superior to pioglitazone for treatment of NASH in adults without diabetes.
Significant benefits of pioglitazone were observed in some of the secondary outcomes.

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Research Network (NASH CRN), first author Arun J Sanyal, Virginia Commonwealth University,
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At Present, “Genomics Are More Closely Aligned With Modern Science than With Modern Medicine”

5-7  TEN YEARS ON--THE HUMAN GENOME AND MEDICINE

Ten years ago, the teams deciphering the human genome announced that a draft sequence had been completed. The occasion was rich with promises of new and more powerful ways to understand, diagnose, and treat disease.

Two years later, readers of the NEJM were reminded that “the full potential of a DNA-based transformation of medicine will be realized only gradually, over a couple of decades”.

Now, after the first decade of a postgenomic world, only a handful of major changes have entered routine medical practice: some gene-specific treatments of a few cancers; some novel therapies for a few mendelian traits; and some strong genetic markers for assessing drug responsiveness, risk of disease, or risk of disease progression. Most of these can be traced to discoveries that preceded the unveiling of the human genome.

Francis Collins recently commented “the consequences for clinical medicine . . . have thus far been modest . . . the Human Genome Project has not yet directly affected the health care of most individuals”.

The NEJM is now beginning a series of articles on genomic medicine. Is this appropriate? It is because:

1) Readers want to know about the dramatic expansion of knowledge of genes and proteins.
2) About the extent to which such knowledge is affecting the prevention and treatment of disease.

Detailed maps of genetic markers, mostly single-nucleotide polymorphisms (SNP) have led to associations of disease predisposition. But his approach has usually failed to reveal strongly influential haplotypes. Implicated haplotypes collectively account for only a small fraction of the apparent heritable risk. More than one decade of genomics will be required to understand the inborn risks of most common disorders, such as diabetes and hypertension.

Despite remarkably rapid advances, genomics are more closely aligned with modern science than with modern medicine. Only a few selected items of that new information are widely used as guides to risk, diagnosis, or therapy.

“Physicians are still a long way from submitting their patients’ full genomes for sequencing . . . because the data are difficult to interpret.”

Even when genomics do yield findings of practical merit, adoption of new practices is often exasperatingly slow.
Changes in the worlds of commerce, law, regulation, ethics, health insurance, and information technology are intersecting with the expanded role of genetics in medicine.

The practice of direct-to-consumer marketing of geno-types, mainly identification of SNPs as putative markers of disease risk, has been among the most visible manifestations of genomics. Yet this practice is not regulated, lacks external standards for accuracy, has not demonstrated economic viability or clinical benefit, and has the potential to mislead consumers.

NEJM May 27, 2010; 362: 2028 -09  Editorial by Harold Varmus, Memorial Sloan-Kettering Cancer Center, New York. This editorial and the Genomic Medicine series will be available without charge at NEJM-org.