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DIAGNOSIS AND MANAGEMENT OF VITAMIN D DEFICIENCY [1-1]
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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 20-year publication of *Practical Pointers*.

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

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

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

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“Association Does Not Prove Causality”

1-1 DIAGNOSIS AND MANAGEMENT OF VITAMIN D DEFICIENCY

In recent years, non-musculoskeletal conditions have been found to be associated with low vitamin D (D) levels: cancer, metabolic syndrome, infections, and autoimmune disorders.

D deficiency is widespread. Rickets represents a small proportion of individuals with suboptimal D status. A recent nationwide survey in the UK showed that more than 50% of adults have insufficient levels and 16% have severe deficiency in winter and spring. Greatest deficiencies are in more northern latitudes, in the elderly, obese individuals, and blacks,

This review is based on evidence from descriptive and observational studies, randomized trials, and meta-analyses. It discusses:

- Sources of D
- How can D deficiency and insufficiency be determined?
- Who is at risk of D deficiency and insufficiency?
- How do patients with D deficiency present?
- What investigations are necessary?
- How should osteomalacia be treated?
- How should moderate deficiency be managed?

Conclusion

D deficiency and insufficiency is common. Health professionals have been slow to respond. Rickets and osteomalacia are entirely preventable. Deficiency now seems unequivocally linked to several other common and morbid conditions.

“We have some way to go.” A change in public health policy in the UK is overdue.

Please read the full abstract.

Practical Pointers has abstracted a number of articles about vitamin D. I enjoyed this overview. The various diseases putatively related to D need strict verification. Does deficiency really cause them? Association does not prove causality. If it turns out that deficiency is causal this would be a major advance.

Would it not be refreshing to have a major advance in therapeutics, which costs pennies, and is harmless?

The usual protocol in medicine is to test for deficiencies, then treat those who are deficient. When large numbers of the population are afflicted, is there not a good argument to treat everyone without
checking for deficiency, provided the therapy is low-cost and low-harm. We do not check patients for deficiency of antibodies to flu, tetanus and other infections before giving vaccines.

I grew up in the cod-liver-oil generation (1920-30). The reason was to prevent rickets. In hindsight, it probably brought more benefits.

**D Alone Does Not Reduce Risk Of Fracture. Add Calcium**

1-2 PATIENT LEVEL POOLED ANALYSIS OF 68 000 PATIENTS FROM SEVEN MAJOR VITAMIN D FRACTURE TRIALS IN US AND EUROPE

This study used individual patient data in a meta-analysis of randomized, controlled trials of D--with and without calcium-- in preventing fractures.

Literature search from 1966 to 2008 found 7 major randomized trials comparing D + calcium vs placebo, and D alone vs placebo, yielding a total of over 68 000 participants (mean age 70; 85% women). Analysis was at the level of individual patients according to intention-to-treat principle.

Effect of D (with and without calcium):

A. Any fracture (n = 7202; 170 000 person-years) hazard ratios (HR) vs placebo:

<table>
<thead>
<tr>
<th></th>
<th>HR (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D alone</td>
<td>1.01 (No effect)</td>
</tr>
<tr>
<td>D + calcium</td>
<td>0.92</td>
</tr>
<tr>
<td>Injected D</td>
<td>1.11 (No effect)</td>
</tr>
<tr>
<td>Oral D</td>
<td>0.92</td>
</tr>
</tbody>
</table>

B. Hip fracture (n = 978)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>D alone</td>
<td>1.09 (No effect)</td>
</tr>
<tr>
<td>Calcium + D</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Absolute risk reduction of fractures and number needed to treat over 3 years

(This was analyzed only for calcium + D, as D-alone provided no benefit.)

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fracture</td>
<td>0.5%</td>
<td>213</td>
</tr>
<tr>
<td>People over 70</td>
<td>0.9%</td>
<td>111</td>
</tr>
<tr>
<td>People with previous fracture</td>
<td>1.2%</td>
<td>82</td>
</tr>
<tr>
<td>Hip fracture (over age 70)</td>
<td>0.4%</td>
<td>255</td>
</tr>
</tbody>
</table>

Whether calcium is more important in preventing fracture than was previously recognized
remains to be determined. But calcium + D is more likely be more effective in attenuating secondary hyperparathyroidism and bone turnover than D alone.

“Our recommendation would be to use a vitamin D dose of at least 400 IU daily combined with 1000 mg calcium.” In high risk patients this should be supplemented by bisphosphonates or other anti-osteoporotic drugs.

Conclusion::

- Vitamin D alone was not effective in preventing fractures
- Calcium and vitamin D given together reduced hip fracture and total fractures irrespective of age, sex, or previous fractures.
- Daily calcium and vitamin D supplementation, even at doses as low as 400 IU + 1000 mg calcium daily, significantly reduced the risk of fracture. Incidence curves (vs placebo) deviated after about 15 months.

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I enjoyed this article. It presents an important intervention in primary care.
Primary care clinicians will appreciate the authors’ calculations of absolute risk reductions and the NNT. This will allow presentation of a clearer picture of benefits and costs to patients.

The benefit / harm-cost of D3 + calcium is very high. Fractures are costly and disabling, and sometimes fatal. The cost of daily calcium-D pills is very low (~ 7 cents). Harm is nil. This, I believe, will lead many patients to choose this intervention.

Benefit to society is also high.

I believe clinicians in the US often prescribe higher doses of D--1000 to 2000 IU daily.

“Weight Gain Experienced By A Typical American Must Be Caused By Repeated Changes In Diet, Physical Activity, or Both”

1-3 EXTRA CALORIES CAUSE WEIGHT GAIN--BUT HOW MUCH?

How much would an individual gain by eating an extra chocolate chip cookie every day for life?
One approach to answering this question is based on the assumption that a pound (454 g) of fat tissue has about 3500 kcal. Thus, a daily 60 kcal cookie would be expected to produce 0.5 lb weight gain a month, 6 lb in a year, 60 lb in a decade, and hundreds of pounds in a lifetime.

Of course, this does not happen.
This article reviews the physiology of weight gain and loss. And the amount of reduction in caloric intake necessary to avoid becoming overweight and obese.
WEIGHT CHANGE IS SELF-LIMITING

When energy intake increases above expenditure, the excess is used to build new tissue, and weight gain results. However, weight gain does not continue indefinitely. Calorie expenditure increases progressively because of the energetic costs of maintaining the newly created tissue. A person who consumes an extra cookie every day will initially gain weight, but over time an increasing proportion of the cookie’s calories will go into repairing, replacing, and carrying the extra body tissue. After a few years of daily cookie eating, weight gain will level off at approximately 6 lbs. Thus, a one-time step up in caloric intake will cause body weight to increase to a new stable level.

The converse occurs when an individual reduces food intake. As body size diminishes, so does the amount of fuel needed to maintain and move it. Weight settles to a new steady level.

1) To prevent weight gain as you age:
   As you age, physical activity lessens.
   If your weight is increasing, cut calories and/or increase physical activity
   As you later hit a weight plateau, you have to take a further step to reduce caloric intake and/or increase activity
   You may have to make several adjustments over the years to prevent gain.

2) To lose weight:
   Cut calories and increase physical activity
   When you hit a plateau, you may have to cut calories further and/or increase physical activity
   You may have to make several adjustments to continue losing weight.

Americans have the habit of overeating and gaining weight during holidays. They make no adjustment to subsequently lose the weight. Weight increases cumulatively.

"There Is Little Evidence To Suggest That ADM Produce Specific Pharmacological Benefit To The Majority Of Patients With Less Severe Acute Depression"

1-4 ANTIDEPRESSANT DRUG EFFECTS AND DEPRESSION SEVERITY: A Patient-Level Meta-analysis

The American Psychiatric Association rates the Hamilton Depression Rating Scale (HDRS) scores for severity of depression:

- 8-13 mild
- 14-18 moderate
- 19-22 severe
23 and above very severe

It is likely that many outpatients seeking treatment for depression have scores less than 22.

This meta-analysis estimated the relative benefit of medications vs placebo in patients with depression. It combined data from 6 large randomized, placebo-controlled trials of adult patients with a broad range of baseline symptom severity. The trials included patients with low as well as high HDRS--from the low teens to upper 30s.

Five trials included only patients with major depression (HDRS 20-24); one included only patients with minor depression (HDRS 14). Three trials used the tricyclic antidepressant imipramine (Generic); 3 used the selective serotonin reuptake inhibitor paroxetine (Generic; Paxil; GSK)

Duration = 6 to 11 weeks.

Differences between medication and placebo varied substantially as a function of baseline severity of depression. Among patients with HDRS score below 23 (this includes some of those classified as severe), differences in effect between medication and placebo were small.

Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity, and crossed the threshold defined by the National Institute for Clinical Excellence (NICE-UK) for a clinically significant difference at a baseline HDRS score of 25.

“True drug effects (an advantage of ADM over placebo) were nonexistent to negligible among depressed patients with mild, moderate, and even severe baseline symptoms.”

The authors estimated the number needed to treat (NNT) to produce a better outcome for one randomly selected depressed patient compared with placebo treatment:

Mild to moderate depression 16
Moderate depression 11
Severe depression 4.

There is little evidence to suggest that ADMs produce specific pharmacological benefit to the majority of patients with less severe acute depression.

For patients with very severe depression, the benefit of medications over placebo is substantial.

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How does this article apply to primary care medicine?

Depression is very common. Most patients with depression present to primary care and are treated in primary care.

Patients with severe depression should be referred if possible.

A. For diagnosis:

Many patients will self-diagnose depression.
Many primary care clinicians would depend on the 2-question screen:

1. During the past month how often have you been bothered by feeling down, depressed, or hopeless?

2. During the past month have you often been bothered by little interest or pleasure in doing things?

(This, of course, does not grade severity of the depression.)

3. For more detailed diagnostic tests, Google presents many references to the HDRS and the Beck depression scale. Self-scoring questionnaires are available.

Some primary care clinicians may use these.

B. For treatment:

I believe primary care clinicians would be liberal in prescribing ADMs. (Indeed, the NNT of 16 is not higher than for many other drugs.) They would likely not inform the patient that her depression is not severe enough to warrant prescription drugs.

Many patients with depression (including mild depression) are aware of drug treatments, and will request medication. (A tribute to the marketing ability of drug companies.) I believe most clinicians would comply with such requests.

The article did not deal with chronic depression.

Medicalization is prevalent in our society. Many patients will seek treatment for ills that are part of the normal ups and downs of living. “A pill for every ill.”--whether or not the “ill” is really a disease. I believe medication for depression is overused.

A Cautionary Note About Sulfonylureas Pioglitazone Outshines Rosiglitazone Metformin Still A First-Line Drug

1-5 RISK OF CARDIOVASCULAR DISEASE AND ALL CAUSE MORTALITY AMONG PATIENTS WITH TYPE-2 DIABETES PRESCRIBED ORAL ANTIDIABETES DRUGS

This phase IV retrospective cohort study investigated the risk of myocardial infarction (MI), congestive heart failure (CHF), and all-cause mortality (ACM) associated with different classes of antidiabetes drugs in a large general practice database in the UK.

The study comprised clinical and prescribing data based on clinical records of about 5 million people. Obtained data on patients (n = 91,521) age 35-90 (mean age = 65) with an episode of drug care for DM-2 from 1990 to 2005. Identified oral antidiabetes drugs in individual patients from prescription records. Drugs were identified as used alone or in combination.

Used intervals of drug treatment as the unit of observation, defined as the period from onset of
a drug treatment to onset of the next drug treatment, until censored, or until occurrence of the event of interest. There were a total of over 2.8 million intervals of treatment.

Compared the risks associated with each drug or drug combination with metformin monotherapy. (Metformin is advocated as first-line therapy.) Patients using insulin were excluded. Mean follow-up per individual was 7 years. During the study period there were: 3588 first events of MI, 6900 first events of CHF, 18 548 ACM.

Metformin monotherapy was the most commonly prescribed drug (75%) followed by second generation sulfonylurea monotherapy (64%)

Hazard ratios compared with metformin alone

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>CHF</th>
<th>ACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second generation sulfonylureas</td>
<td>1.31*</td>
<td>1.39*</td>
<td>1.55*</td>
</tr>
<tr>
<td>Rosiglitazone (combined)</td>
<td>1.08**</td>
<td>1.31*</td>
<td>0.80*</td>
</tr>
<tr>
<td>Pioglitazone (alone &amp; combined)</td>
<td>0.78**</td>
<td>1.18**</td>
<td>0.61*</td>
</tr>
<tr>
<td>Rosiglitazone vs pioglitazone</td>
<td>1.34**</td>
<td>1.05**</td>
<td>1.41*</td>
</tr>
</tbody>
</table>

(* significant  ** non-significant

“Our study of observational data in general practice allows assessment of the relative benefits and hazards of use of oral antidiabetes drugs in a ‘real world’ clinical setting.”

The study extends the evidence, suggesting higher mortality with sulfonylurea use than metformin among unselected patients attending general practice.

In this study, there was no evidence of excess MI associated with thiazolidinediones. Mortality associated with pioglitazone was lower than with rosiglitazone.

Conclusions

1. The finding of a relatively unfavorable risk profile of sulfonylureas vs metformin for all outcomes examined are consistent with ADA recommendations that favor metformin as the initial treatment of DM-2.
2. The previous reports of an excess risk of MI associated with rosiglitazone compared with metformin were not confirmed.
3. Pioglitazone was associated with reduced all-cause mortality and a favorable risk profile compared with rosiglitazone.

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This study is much more complex than I have outlined. I congratulate the investigators on their persistence in digging through such a mass of data.

The investigators calculated the data by 3 models using different possible confounding variables.
I have reported only #1.

For primary care the message is: Be guarded about use of sulfonylureas. Use pioglitazone instead of rosiglitazone. Metformin is still a standard first drug.

“All Begins With Excess Central Obesity”

1-6 THE METABOLIC SYNDROME

The metabolic syndrome (MS) has existed in various forms for more than 8 decades. Only in the past 5 years has real controversy about its definition and significance emerged.

The main controversy is that the syndrome has too many definitions, and there is a lack of clarity about its role and value in clinical practice.

The controversy drove the need for a single global definition.

Several prestigious organizations have combined to develop one unified definition, which has now been published.

The main difference between the NCEP ATP III and the new definition is the threshold value for waist circumference. Because the relation between waist circumference and cardiovascular disease and diabetes risk differs globally, national and regional cutpoints of waist circumference can be used.

Insulin resistance continues to explain most, if not all, of the MS. No other mechanisms have emerged that come close.

“Evidence now indicates that the metabolic syndrome all begins with excess central obesity”

When beta-cell function is responsive, hyperinsulinemia results and fasting and postprandial glucose often remains normal for years. In those genetically predisposed, defects in insulin secretion, and impaired fasting glucose and impaired glucose tolerance follow.

At present, however, drug therapy for the MS largely requires separate agents for treatment of dyslipidemia, dysglycemia, and hypertension.

“The metabolic syndrome is a widely accepted concept that identifies the centrally obese patient with increased risk for cardiovascular disease and diabetes.”

Lifestyle interventions remain the primary therapy. Drugs are used for residual risks for cardiovascular disease.

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The metabolic syndrome now defined:

1. Increased waist circumference Population-specific and country specific
2. Increased triglycerides 150 mg/dL and higher
3. Reduced HDL-cholesterol  Males under 40 mg/dL; females under 50
4. Increased BP  Greater or equal to 130/80
5. Increased fasting glucose  Greater than 100 mg/dL

\[ \text{a For many patients in the US, } < 102 \text{ cm (40’’) for males; } < 88 \text{ cm (35’’) for females} \]

\[ \text{b History of use of drugs to lower levels is an alternative} \]

Any combination of 3 will make the diagnosis.

A simple “eyeball test” can easily recognize patients with abdominal obesity and likelihood of the MS.

Extra-abdominal fat (outside the muscular abdominal wall) is not metabolically active. Intra-abdominal fat is the culprit, due to its drainage into the liver. This leads to other manifestations of the MS.

Do We Need Any More Risk Factors For Primary Prevention At This Time?

1-7 C-REACTIVE PROTEIN AND CARDIOVASCULAR RISK

Inflammation contributes to the pathogenesis of atherosclerosis.

The inflammatory marker C-reactive protein (CRP) can be used to predict cardiovascular events.

This month, Lancet presents a comprehensive meta-analysis on these issues. The analysis consisted of over 50 prospective studies in over 160 000 persons. It included nearly 28 000 fatal and non-fatal disease outcomes.

CRP concentrations were linearly associated with most established risk factors. And with several other inflammatory markers, including fibrinogen and interleukin 6 (the biological mediator of hepatic CRP production.)

CRP concentrations were also strongly associated with coronary heart disease, ischemic stroke, vascular mortality, and non-vascular mortality. The association with cardiovascular outcomes was confounded considerably by established risk factors.

What is the role of CRP for primary prevention?

Opponents believe that CRP, compared with established risk factors, provides little improvement in risk prediction. Proponents have argued that CRP does help to reclassify relevant risk categories.

Does CRP have a causal role in the development of cardiovascular disease?

CRP might have biological effects on endothelial function, coagulation, fibrinolysis, oxidation of LDL, and plaque stability. However, several studies have reported a lack of concordance between CRP concentrations and cardiovascular risk. This is an argument against causality.
In the meta-analysis, associations between CRP concentrations and various cardiovascular outcomes were attenuated on adjustment for known risk factors. The investigators interpret this as an argument against causality.

Even if CRP turns out not to be causal, it might be useful to identify individuals at risk and to quantify the efficacy of interventions.

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CRP has been a hot topic in the recent medical literature.

Do we need any more risk markers to guide primary prevention? In my view, we do not need any additional risk markers for primary care until we properly apply those we already know are established and valid. Thus far, we have failed miserably to do so.

“The Case Remains Open”

1-8 ANTIHYPERTENSIVE AGENTS AND PREVENTION OF DEMENTIA

Various studies have shown an association between mid-life hypertension (especially if untreated) and likelihood of developing dementia. This raises the possibility that antihypertension drugs might offer a form of prevention.

A prospective cohort study in this issue of BMJ reported the possible role of angiotensin receptor blocking (ARB) agents in reducing risk of dementia and in slowing its progression. The study followed over 800,000 male subjects older than age 65 with cardiovascular disease, and found significantly lower hazard ratios for incident dementia associated with ARBs than with the ACE inhibitor lisinopril (HR = 0.81) and with other cardiovascular drugs (HR = 0.76).

In patients with preexisting AD, ARBs were associated with a lower risk of admission to a nursing home.

Association does not prove causation.

Effects of combined ACE-inhibitors and ARB may be additive.

The public health implications of finding an effective way for preventing dementia are immense.

Further work is needed to verify the usefulness of antihypertensives in general and ARBs in particular.

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I abstracted this article as a provocative intervention to be aware of.

I will look for follow-ups.

We would expect some reduction in vascular dementia by control of BP.
“Association Does Not Prove Causality”

1-1 DIAGNOSIS AND MANAGEMENT OF VITAMIN D DEFICIENCY

In recent years, non-musculoskeletal conditions have been found to be associated with low vitamin D (D) levels: cancer, metabolic syndrome, infections, and autoimmune disorders.

D deficiency is widespread. Rickets represents a small proportion of individuals with suboptimal D status. A recent nationwide survey in the UK showed that more than 50% of adults have insufficient levels and 16% have severe deficiency in winter and spring. Greatest deficiencies are in more northern latitudes, in the elderly, obese individuals, and blacks,

This review is based on evidence from descriptive and observational studies, randomized trials, and meta-analyses.

Sources of D:

Two forms of vitamin D (ergocalciferol D2; cholecalciferol D3\(^a\)) are precursors of the active hormone 1,25 dihydroxyvitamin D3 (1, 25-OH2,D3; cacitriol)

The major natural source is photosynthesis in the skin following ultraviolet B solar irradiation.\(^b\) Food sources are limited. Twenty to 30 minutes of sunlight exposure produces the equivalent of 2000 IU of D. Several exposures a week are usually sufficient to achieve healthy levels in summer. For blacks, and to some extent the elderly, 2-fold to 10-fold exposures are necessary.

 Millions of people must rely on supplementation. Supplements in food are insufficient.

The recommended daily dose for adults in the UK is 400 IU/d (10 ug). For children, 280 IU. For infants, 340 IU. These doses provide only the amount needed to prevent rickets and osteomalacia and do not supply optimum D intake. Recently, there have been recommendations to increase these amounts.

(a Ergocalciferol (D2) is derived from plants. Unit-for-unit, it may be less effective in raising serum levels of 25OHD than D3. It is the only preparation available by prescription in the US for parenteral use.

(b Vitamin D is formed in the skin from precursor steroids. Some is supplied by the diet. Now, most is supplied by supplementation. D is hydroxylated first in the liver to form 25-OHD. The second OH is added in the kidney to form 1-21-OH2D.)

How can D deficiency and insufficiency be determined?

D status is most reliably determined by serum assay of serum 25-hydroxyvitamin D (25-OHD)
Deficiency: Less than 10 ug/L

Individuals with symptoms of osteomalacia and rickets have serum levels of 25-OHD less than 10 ug/L (25 nmol/L)--profound deficiency. (Equivalent to 400 IU/L)

Insufficiency: 10-20 ug/L

Levels between 10-20 ug/L (25 nmol/L -50 nmol/L) are common in the UK (about 50% of the population in the UK in spring). These levels denote insufficiency. Several observational studies have reported that insufficiency, although not enough to cause symptomatic bone and muscle disease, is associated with increased risk of mortality, cardiovascular disease, type 1 and type 2 diabetes, bowel cancer, breast cancer, and multiple sclerosis,

Optimum: 30 ug/L or more

Consensus is developing that optimum D, reflected by optimum calcium handling and best health, is 30 ug/L or more (75 nmol/L or more). Serum 25-OHD has a circulating half-life of 2 to 3 weeks. Circulating active D (1,25-dihydroxyvitamin D3; calcitriol) has a short half-life and is closely linked to parathyroid hormone production. Serum levels of calcitriol do not reflect D status.

Who is at risk of D deficiency and insufficiency?

In northern latitudes, pigmented skin is the major risk factor for deficiency and insufficiency at all ages, often in young people, immigrant children, and first generation offspring of immigrant parents who have dark skin. Sunscreen may block almost all of dermal synthesis. Elderly and institutionalized persons who spend much time indoors are at risk.

D deficiency may be present at birth. D status on infants depends on maternal D status. Multiple pregnancies, especially in women with dark skin, are a major risk factor. As breast milk does not meet D requirements, exclusively breast-fed infants are particularly susceptible.

The department of health in the UK recommends 400 IU/d for all infants and preschool children.

How do patients with D deficiency present?

Children:

Severe deficiency may cause hypocalcemic seizures and tetany during the rapid growth of infancy and adolescence. Children may present with rickets. Growth is impaired. They may be irritable and reluctant to bear weight. They are susceptible to respiratory infections-- “rachitic lung”.
Adults

Pain (rib, hip, pelvis, and foot) and proximal muscle weakness. More diffuse muscular aches and weakness (limbs and back), may be mislabeled as “fibromyalgia” or somatization or depression.

Low bone density on X-ray absorptiometry, or osteopenia on plain radiography.

What investigations are necessary?

Adults

The great majority of patients with osteomalacia have elevated alkaline phosphatase. Hypocalcemia and hypophosphatemia are less common.

Elevation of plasma parathyroid hormone (secondary hypoparathyroidism) is typical of osteomalacia, but is not found in 20% of those with deficiency.

(*In years past, we noted elevated alkaline phosphatase levels in many laboratory reports. Not knowing their significance, we tended to ignore them. It now appears likely that many were due to D deficiency.*)

How should osteomalacia be treated?

Adults

Calciferols (D2 and D3) have a high therapeutic index. A regular dose of 1000 IU daily raises serum 25-OHD by 10 ug/L.

Toxicity occurs at levels above 200 ug/L. *(Much higher than the optimum 30 + ug/L.)*

A daily dose of 10 000 IU will restore stores of body D in 8 to 12 weeks. Thereafter, a maintenance dose of 1000 to 2000 IU daily is adequate.

In patients with malabsorption, an intramuscular injection of 300 000 IU D2 monthly for 3 months followed by the same dose twice a year is an alternative.

Pathological lesions in bone may take months to heal. Serum alkaline phosphatase and parathyroid hormone will start to decline in the first 3 months, but may take a year to fall to normal.

Given that few adults have truly reversible risk factors for deficiency, supplementation will be needed life-long.
How should moderate deficiency be managed?

From a public health perspective, primary prevention of D deficiency is socially, as well as medically, justifiable.

“Given that clear and mounting evidence of the substantial disease burden associated with moderate vitamin D insufficiency information about appropriate sunlight exposure, use of vitamin D supplements, and eating oily fish should be made available to the whole population.

Children’s vitamin drops should be universally available.

A more robust approach to statutory food supplementation is needed in the UK.

(e Farm-fed fish may not contain much D.)

Conclusion

D deficiency and insufficiency are common.

Health professionals have been slow to respond.

Rickets and osteomalacia are entirely preventable.

Deficiency now seems unequivocally linked to several other common and morbid conditions.

“We have some way to go.” A change in public health policy in the UK is overdue.

BMJ January 16, 2010; 340: 142-47 “Clinical review” first author Simon H S Pearce, Newcastle University, Newcastle -upon-Tyne, UK

1 Table 2 in the article presents evidence for the association of low 25-OHD levels vs optimal levels, or D supplementation vs no supplementation with major health outcomes. (Relative risk, hazard ratios, or odds ratios.)

All-cause mortality (3 studies)

RR = 0.93

HR = 0.48 and 0.55

Cardiovascular mortality (2 studies)

HR 0.42 and 0.45

Diabetes (2 studies)

Type 1 OR 0.71.

Type 2 OR 0.36 Cancer

Colon cancer OR = 0.76
PATIENT LEVEL POOLED ANALYSIS OF 68 000 PATIENTS FROM SEVEN MAJOR VITAMIN D FRACTURE TRIALS IN US AND EUROPE

Vitamin D (D) insufficiency is common in older people, particularly in care homes. This may contribute to secondary hyperparathyroidism, bone loss, impaired neuromuscular function, and increased risk of falls and fractures.

This study used individual patient data in a meta-analysis of randomized, controlled trials of D—with and without calcium—in preventing fractures.

STUDY
1. Literature search from 1966 to 2008 found 7 major randomized trials comparing D + calcium vs placebo, and D alone vs placebo, yielding a total of over 68 000 participants (mean age 70; 85% women). Analysis was at the level of individual patients according to intention-to-treat principle.
2. All trials had two intervention arms: one arm with calcium + D vs placebo, and one arm with D alone + placebo. Trials included at least 1000 patients.
3. All trials reported incident hip fractures and other non-vertebral fractures. Six also reported clinical vertebral fractures.
4. Primary end-point = any fracture. Hip fracture and clinical vertebral fracture were secondary end-points.
5. Prespecified a subgroup analysis of D by dose (400 and 800 IU/d; 10ug and 20 ug/d)
6. Recent work suggests that D2 (ergocalciferol) has half the calcitrophic effect as D3 (cholecalciferol). The study regrouped 800 IU ergocalciferol studies with 400 IU cholecalciferol studies.

RESULTS
1. Effect of D (with and without calcium):
   A. Any fracture (n = 7202; 170 000 person-years) hazard ratios (HR) vs placebo:
      \[
      \begin{align*}
      \text{HR (vs placebo)} & \\
      \text{D alone} & 1.01 \quad \text{(No effect)} \\
      \text{D + calcium} & 0.92 \\
      \text{Injected D} & 1.11 \quad \text{(No effect)} \\
      \text{Oral D} & 0.92 
      \end{align*}
      \]
      Results were unaffected by exclusion of users of bisphosphonates and hormone replacement therapy.
Cumulative fractures per 1000 subjects over 3 years:

D alone ~130 (Same as placebo)
Calcium + D ~60
(My assessment of their figure 3 RTJ)

B. Hip fracture (n = 978)

HR
D alone 1.09 (No effect)
Calcium + D 0.84

Cumulative hip fractures per 1000 subjects over 3 years:

D alone ~ 40 (Same as placebo)
Calcium + D ~ 5
(My assessment of their figure 3 RTJ)

2. Clinical vertebral fracture(n = 542)

No significant treatment effect in calcium + D studies, or in vitamin D-alone studies.

3. Absolute risk reduction of fractures and number needed to treat over 3 years

(This was analyzed only for calcium + D, as D-alone provided no benefit.)

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fracture</td>
<td>0.5%</td>
<td>213</td>
</tr>
<tr>
<td>People over 70</td>
<td>0.9%</td>
<td>111</td>
</tr>
<tr>
<td>People with previous fracture</td>
<td>1.2%</td>
<td>82</td>
</tr>
<tr>
<td>Hip fracture (over age 70)</td>
<td>0.4%</td>
<td>255</td>
</tr>
</tbody>
</table>

DISCUSSION

1. Vitamin D + calcium reduced the risk of any fracture, and probably hip and vertebral fracture irrespective of sex and fracture history.

2. For hip fracture, the study was able to show a significant risk reduction in patients receiving 400 IU D + calcium.

3. Because the reduction in risk was small and the rates of fracture were low, the NNT to treat for 3 years ranged from more than 200 for those without previous fracture to 82 for those with previous fracture.

4. Whether calcium is more important in preventing fracture than was previously recognized remains to be determined. But calcium + D is more likely be more effective in attenuating secondary hyperparathyroidism and bone turnover than D alone.
5. “Our recommendation would be to use a vitamin D dose of at least 400 IU daily combined with 1000 mg calcium.” In high risk patients this should be supplemented by bisphosphonates or other anti-osteoporotic drugs.

CONCLUSIONS AND POLICY IMPLICATIONS

Vitamin D alone was not effective in preventing fractures

Calcium and vitamin D given together reduced hip fracture and total fractures irrespective of age, sex, or previous fractures.

Daily calcium and vitamin D supplementation, even at doses as low as 400 IU + 1000 mg calcium significantly reduced the risk of fracture. Incidence curves (vs placebo) deviated after about 15 months.

“We must emphasize that this analysis does not allow for a direct comparison of vitamin D against vitamin D given with calcium, but only comparisons between each intervention and no treatment.”

BMJ 2010;340"b5463  doi:10.1136/bmj.b5463  “Research ” article by the vitamin D Individual Patients Analysis of Randomized Trials (DEPART) Group, correspondence to B Abrahamsen Copenhagen University, Hellerup, Denmark
A condensed version was printed in BMJ January 16, 2010; 139

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“Weight Gain Experienced By A Typical American Must Be Caused By Repeated Changes In Diet, Physical Activity, or Both”

1-3 EXTRA CALORIES CAUSE WEIGHT GAIN--BUT HOW MUCH?

How much would an individual gain by eating an extra chocolate chip cookie every day for life?

One approach to answering this question is based on the assumption that a pound (454 g) of fat tissue has about 3500 kcal. Thus, a daily 60 kcal cookie would be expected to produce 0.5 lb weight gain a month, 6 lb in a year, 60 lb in a decade, and hundreds of pounds in a lifetime.

Of course, this does not happen.

This article reviews the physiology of weight gain and loss. And the amount of reduction in caloric intake necessary to avoid becoming overweight and obese.

WEIGHT CHANGE IS SELF-LIMITING

When energy intake increases above expenditure, the excess is used to build new tissue, and weight gain results. However, weight gain does not continue indefinitely. Calorie expenditure increases
progressively because of the energetic costs of maintaining the newly created tissue. A person who consumes an extra cookie every day will initially gain weight, but over time an increasing proportion of the cookie’s calories will go into repairing, replacing, and carrying the extra body tissue. After a few years of daily cookie eating, weight gain will level off at approximately 6 lbs. Thus, a one-time step up in caloric intake will cause body weight to increase to a new stable level.

The converse occurs when an individual reduces food intake. As body size diminishes, so does the amount of fuel needed to maintain and move it. Weight settles to a new steady level.

Weight loss produces changes in hormones, the autonomic nervous system, and the intrinsic efficiency of muscle that serve to conserve energy. Additional weight loss can be achieved only by a more severe diet, or more arduous physical activity. Most people do the opposite and weight gain recurs rapidly.

HOW MUCH ARE AMERICANS OVEREATING?
In the early 1970s, the first nationally representative study (NHANES) found that women age 20-29 had a mean BMI of 23. In the 2000 survey, women 50-59 (who were age 20-29 in 1970) had a mean BMI of 29. This represents a gain of about 35 lb in 28 years.

How much overeating is needed to gain this amount of weight?
A young adult woman must increase energy intake by 370 kcal per day to increase BMI from 23 to 29 (overweight). Adding one ounce of sugar-sweetened beverage and walking one minute less per day creates a temporary energy surplus of about 13 kcal/d, leading to a weight gain of 1.4 lb. Repeating changes in diet and physical activity of this magnitude on an annual basis for 28 years would produce the 370 kcal/d energy gap, and 35 lb weight gain.

To become obese, a much larger cumulative change in life-style would be required.
For a normal weight child age 6 to achieve a BMI at the 95th percentile at age 16, the child must over-consume 799 to 1000 kcal every day during this period.
Weight gain experienced by a typical American must be caused by repeated changes in diet, physical activity, or both.
Some studies suggest that energy intake per capita in the U.S. has increased by up to 500 kcal/d since 1970.

PREVENTING WEIGHT GAIN
What would it take for a lean young adult to stay that way, instead of gaining about 1 to 2 pounds every year?
A one-step change in energy balance initiated at age 25 would be sufficient to prevent overweight by middle age for most individuals. However, any single change in diet or physical activity, even if permanent, will elicit compensatory mechanisms that limit long-term effects on body weight. Since the weight gain experienced must be caused by repeated changes in diet, physical activity, or both, a small decrease in food intake or increase in physical activity will halt this increase only temporarily.

Small changes in lifestyle would have a minor effect on obesity prevention.

“An effective public health approach to obesity prevention will require fundamental changes in the food supply and the social infrastructure”

JAMA January 6 2010; 303: 65-66 “Commentary” first author Martjin B Katan, VU University, Amsterdam, Netherlands.

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“There Is Little Evidence To Suggest That ADMs Produce Specific Pharmacological Benefit To The Majority Of Patients With Less Severe Acute Depression”

1-4 ANTIDEPRESSANT DRUG EFFECTS AND DEPRESSION SEVERITY: A Patient-Level Meta-analysis

Antidepressant medication (ADM) is the current standard of treatment of major depressive disorder (MDD).

Baseline symptom severity is one dimension that may affect treatment outcome.

This meta-analysis estimated the relative benefit of medications vs placebo in patients with varying severity of depression.

STUDY
1. The American Psychiatric Association rates the Hamilton Depression Rating Scale (HDRS) scores for severity of depression:
   8-13 mild
   14-18 moderate
   19-22 severe
   23 and above very severe
2. It is likely that many outpatients seeking treatment for depression have scores less than 22.
3. This study combined data from 6 large randomized, placebo-controlled trials of adult patients with a
broad range of baseline symptom severity. The trials included patients with low as well as high HDRS--from the low teens to upper 30s.

4. Five trials included only patients with major depression (HDRS 20-24); one included only patients with minor depression (HDRS 14)

5. Three trials used the tricyclic antidepressant imipramine (Generic); 3 used the selective serotonin reuptake inhibitor paroxetine (Generic; Paxil; GSK)

6. Duration = 6 to 11 weeks.

RESULTS
1. Differences between medication vs placebo varied substantially as a function of baseline severity of depression.

2. Among patients with HDRS score below 23 (this includes some of those classified as severe), difference in effect between medication and placebo were small.

3. Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity, and crossed the threshold defined by the National Institute for Clinical Excellence (NICE-UK) for a clinically significant difference at a baseline HDRS score of 25.

4. The authors estimated the number needed to treat (NNT) to produce a better outcome for one randomly selected depressed patient compared with placebo treatment:

   Mild to moderate depression  16
   Moderate depression        11
   Severe depression          4.

5. A large benefit was evident for patients with a HDRS score of 27 or greater.

6. The two drugs produced approximately equal benefits in the severe depression group.

DISCUSSION
1. In this meta-analysis, the efficacy of ADM treatment varied considerably with symptom severity.

2. “True drug effects (an advantage of ADM over placebo) were nonexistent to negligible among depressed patients with mild, moderate, and even severe baseline symptoms.”

3. True drug effects were large for patients with very severe symptoms. Benefits were markedly superior to placebo in this group.

4. “These findings are consistent with an understanding that has informed the entry criteria used in
ADM registration trials, in which cutoff scores of 18 or greater typically have been imposed. Such cutoffs can be expected to exclude nearly half of all patients who meet diagnosis criteria for MDD.”

5. The results of this meta-analysis may not generalize to patients with scores of 13 and lower.

6. These results apply only to patients treated for short periods, not for continuing or maintenance treatment periods.

7. Several studies have demonstrated that ADM is superior to placebo for patients diagnosed with dysthymia, a condition partly defined by lower symptom levels relative to major depressive disorder. These studies indicate that ADM can produce a true drug effect in patients with mild to moderate depression. However, dysthymia is by definition a chronic condition, and chronicity is known to be associated with poor response to placebo.

8. “What makes our findings surprising is the high level of depression symptom severity that appears to be required for clinically meaningful drug/placebo differences to emerge, particularly given the evidence that the majority of patients receiving ADM in clinical practice present with scores below these levels.”

9. Prescribers and consumers may not be aware that the efficiency of antidepressants has been largely established on the basis of studies that have included only those individuals with more severe forms of depression. This important feature of the evidence base is not reflected in the implicit messages present in the marketing of these medications to clinicians and the public. There is little mention of the fact that efficacy data often come from studies that exclude precisely those patients who derive little specific pharmacological benefit for taking medications.

CONCLUSION

There is little evidence to suggest that ADMS produce specific pharmacological benefit to the majority of patients with less severe acute depression.

For patients with very severe depression, the benefit of medications over placebo is substantial.

JAMA January 6, 2010; 303: 47-53   Original investigation, first author Jay C Fournier, University of Pennsylvania, Philadelphia PA

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A Cautionary Note About Sulfonylureas  Pioglitazone Outshines Rosiglitazone  Metformin Still A First-Line Drug

1-5 RISK OF CARDIOVASCULAR DISEASE AND ALL CAUSE MORTALITY AMONG PATIENTS WITH TYPE-2 DIABETES PRESCRIBED ORAL ANTIDIABETES DRUGS

Type-2 diabetes (DM-2) is associated with at least a doubling of the risk of death, mainly due to cardiovascular disease (CVD).

Oral drugs are commonly prescribed. There is concern that some drugs may increase the risk of cardiovascular events.

Several clinical trials reported that rosiglitazone and pioglitazone are associated with increased risk of congestive heart failure (CHF), resulting in a black box warning against use in patients with preexisting CHF. The mortality associated with antidiabetes drugs and their net benefit on CVD is still hotly debated.

There is also uncertainty about cardiovascular safety of sulfonylureas.

This phase IV study investigated the risk of myocardial infarction (MI), CHF, and all-cause mortality (ACM) associated with different classes of antidiabetes drugs in a large general practice data base in the UK.

STUDY

1. This retrospective cohort study comprised clinical and prescribing data based on clinical records of about 5 million people.

2. Obtained data on patients (n = 91,521) age 35-90 (mean age = 65) with an episode of drug care for DM-2 from 1990 to 2005. Identified oral antidiabetes drugs in individual patients from prescription records. Drugs were identified as used alone or in combination.

3. Used intervals of drug treatment as the unit of observation, defined as the period from onset of a drug treatment to onset of the next drug treatment, until censored, or until occurrence of the event of interest. There were a total of over 2.8 million intervals of treatment.

4. Compared the risks associated with each drug or drug combination with metformin monotherapy. (Metformin is advocated as first-line therapy.) Patients using insulin were excluded.

5. Primary events were first occurrence of incident MI, CHF, and ACM.

RESULTS

1. Mean follow-up per individual was 7 years. During the study period there were:

   3588 first events of MI
6900 first events of CHF
18 548 ACM

2. Metformin monotherapy was the most commonly prescribed drug (75%) followed by second generation sulfonylurea monotherapy (64%)

3. Myocardial infarction compared with metformin monotherapy:
   A. Sulfonylureas (second generation all classes) -- significant excess risk
   B. Rosiglitazone (either alone or in combination) -- no significant association
   C. Pioglitazone (alone or combined) -- non-significant reduced risk.
   D. Rosiglitazone compared with pioglitazone -- non-significant higher risk.

4. Congestive heart failure compared with metformin monotherapy:
   A. Sulfonylureas (second generation) -- a significant excess risk
   B. Rosiglitazone (in combination) -- a significant excess risk
   C. Pioglitazone (alone or combined) -- non-significant excess risk

5. All-cause mortality compared with metformin monotherapy:
   A. Sulfonylureas (second generation) -- a significant excess risk
   B. Rosiglitazone (in combination) -- a significant reduced risk
   C. Pioglitazone (alone or combined) -- a significant reduced risk
   D. Rosiglitazone compared with pioglitazone: a non-significant 34% higher risk

6. Hazard ratios compared with metformin alone

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>CHF</th>
<th>ACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second generation sulfonylureas</td>
<td>1.31*</td>
<td>1.39*</td>
<td>1.55*</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>0.94**</td>
<td>1.31*</td>
<td>0.80*</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.78**</td>
<td>1.18**</td>
<td>0.61*</td>
</tr>
<tr>
<td>Rosiglitazone vs pioglitazone</td>
<td>1.34**</td>
<td>1.05**</td>
<td>1.41*</td>
</tr>
</tbody>
</table>

(* significant    ** non-significant

7. Fractures: (n = 2123)

Thiazolidinediones are associated with excess risk of non-hip fracture.

Hazard ratios compared with metformin alone:

Rosiglitazone 1.53*
Pioglitazone 1.28**

DISCUSSION
1. “Our study of observational data in general practice allows assessment of the relative benefits
and hazards of use of oral antidiabetes drugs in a ‘real world’ clinical setting.”

2. The analysis involved about 3 million intervals of drug treatment with ascertainment of drug co-prescriptions and covariates at the beginning of each interval.

3. As with any observational study, the possibility of residual confounding cannot be excluded.

4. Both sulfonylureas and metformin were routinely prescribed during the study period.

5. Results in context:

   A. Sulfonylureas

       In this study, monotherapy with a sulfonylurea was associated with excessive risk of mortality.

       Concerns about the safety of sulfonylureas were first raised by the University Group Diabetes Study (1970), which showed increased numbers of deaths from cardiovascular disease among users of tolbutamide.

       In contrast, the UKPDS (1999) reported no increase cardiovascular events or death with sulfonylurea use compared with a conventional diet. However, among a group of obese participants, the group randomized to metformin (vs those randomized to sulfonylurea) had a significantly lower all-cause mortality.

       “Our study extends the evidence, suggesting higher mortality with sulfonylurea use than metformin use, among unselected patients attending general practice.”

       The mechanism by which commonly prescribed sulfonylureas may adversely affect cardiovascular risk and mortality is speculative.

   B. Thiazolidinediones

       In this study, there was no evidence of excess MI associated with thiazolidinediones.

       “Overall, to date, there is no clear or consistent evidence on the possible cardiovascular benefits or harms of rosiglitazone therapy.” The observed excess risk of CHF associated with rosiglitazone or pioglitazone use compared with metformin alone accords with previous evidence from clinical trials and observational studies.

       In the present study, pioglitazone was associated with lower all-cause mortality than metformin.

       (This suggests a possible cardiovascular protective effect of pioglitazone despite increased risk of CHF.)

       In this study, mortality associated with pioglitazone was less than with rosiglitazone. It has been suggested that pioglitazone has more favorable effects on lipids than rosiglitazone. Pioglitazone has also been shown to decrease the rate of progression of carotid media
thickness and of coronary atherosclerosis, suggesting a possible role in slowing the development of atherosclerotic plaque.

CONCLUSIONS
1. The finding of a relatively unfavorable risk profile of sulfonylureas vs metformin for all outcomes examined are consistent with ADA recommendations that favor metformin as the initial treatment of DM-2.
2. The previous reports of an excess risk of MI associated with rosiglitazone compared with metformin were not confirmed.
3. Pioglitazone was associated with reduced all-cause mortality and a favorable risk profile compared with rosiglitazone.

BMJ 2009;339:b4731 “Research” first author Ioanna Tzoulaki, Imperial College London, London UK
A condensed version was printed in BMJ January 2 2010; 340: 35
1 Second generation sulfonylureas:
   Glipizide, gliclazide, glimepride, glibenclamide, gliclazide

“All Begins With Excess Central Obesity”
1-6 THE METABOLIC SYNDROME
The metabolic syndrome (MS) has existed in various forms for more than 8 decades. Only in the past 5 years has real controversy about its definition and significance emerged.

The main controversy is that the syndrome has too many definitions, and there is a lack of clarity about its role and value in clinical practice.

The controversy drove the need for a single global definition.

Several prestigious organizations have combined to develop one unified definition, which has now been published.

The main difference between the NCEP ATP III and the new definition is the threshold value for waist circumference. Because the relation between waist circumference and cardiovascular disease and diabetes risk differs globally, national and regional cutpoints of waist circumference can be used.

Insulin resistance continues to explain most, if not all, of the MS. No other mechanisms have emerged that come close.

“Evidence now indicates that the metabolic syndrome all begins with excess central obesity”
When beta-cell function is responsive, hyperinsulinemia results and fasting and postprandial glucose often remains normal for years. In those genetically predisposed, defects in insulin secretion, and impaired fasting glucose and impaired glucose tolerance follow.

How is insulin resistance related to hypertension? This has been controversial. The effects of insulin on sodium resorption and the sympathetic nervous system are maintained despite insulin resistance. Insulin resistance is also closely associated with abnormalities in nitric oxide bioavailability. Insulin resistance itself results in structural or functional damage to the endothelium.

Genetic predisposition also relates to the MS.

Another area of recent interest is vitamin D. Increasing evidence indicates that deficiency of D is associated with risk of cardiovascular disease. A study of over 3500 U.S. adolescents in the 2001-04 NHANES survey found the low D levels were associated with the MS.

The hypothesis that the MS is related to insulin resistance provides a strategy for management. Weight loss reduces insulin resistance. Caloric restriction and bariatric surgery are proven to be effective. In one study, a weight loss of 25% after surgery improved the MS. Even in the absence of weight loss, long-term physical activity prevents the MS, reduces cancer incidence, and all-cause mortality.

Thiazolidinediones reduce insulin resistance and many of the components of the MS. They act mainly on adipose tissue to favorably modify free fatty acids and adipocytokines, which contribute to the pathophysiology of the MS. Their major effect is on dysglycemia, yet the class as a whole has anti-inflammatory effects.

At present, however, drug therapy for the MS largely requires separate agents for treatment of dyslipidemia, dysglycemia, and hypertension.

“The metabolic syndrome is a widely accepted concept that identifies the centrally obese patient with increased risk for cardiovascular disease and diabetes.”

Lifestyle interventions remain the primary therapy. Drugs are used for residual risks for cardiovascular disease.


The metabolic syndrome now defined:

1. Increased waist circumference  
   Population-specific and country specific

2. Increased triglycerides  
   150 mg/dL and higher
3. Reduced HDL-cholesterol  Males under 40 mg/dL; females under 50b
4. Increased BP  Greater or equal to 130/80b
5. Increased fasting glucose  Greater than 100 mg/dL
   a  For many patients in the US, < 102 cm (40”) for males; < 88 cm (35”) for females
   b  Use of drugs to lower levels is an alternative
Any combination of 3 will make the diagnosis.

1  International Diabetes Foundation
   American Heart Association
   National Heart, Lung and Blood Institute
   World Heart Association
   International Atherosclerosis Society
   International Association for the Study of Obesity
2  National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of
   High Blood Cholesterol in Adults

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**Do We Need Any More Risk Factors For Primary Prevention At This Time?**

1-7  **C-REACTIVE PROTEIN AND CARDIOVASCULAR RISK**

Inflammation contributes to the pathogenesis of atherosclerosis.

The inflammatory marker C-reactive protein (CRP) can be used to predict cardiovascular events.

This was first reported in 1994.

We need proper documentation on the strength and shape of the association between CRP
concentrations and established CVD risk factors.

This month, *Lancet* presents a comprehensive meta-analysis on these issues1 The analysis consisted
of over 50 prospective studies in over 160 000 persons. It included nearly 28 000 fatal and non-fatal
disease outcomes.

CRP concentrations were linearly associated with most established risk factors. And with several
other inflammatory markers, including fibrinogen and interleukin 6 (the biological mediator of hepatic
CRP production.)
CRP concentrations were also strongly associated with coronary heart disease, ischemic stroke, vascular mortality, and non-vascular mortality. The associations with cardiovascular outcomes were confounded considerably by established risk factors.

“These observations will fuel the ongoing debate about the relevance of CRP in clinical practice.”

What is the role of CRP for primary prevention?

Current guidelines advise the use of established risk factors to quantify an individual’s risk. On this basis, people at high risk should be treated. For people at intermediate risk, additional information should be obtained to guide decision-making. CRP might be valuable to fine-tune the choice of treatment this group. Unfortunately, most studies do not focus on people at intermediate risk. The predictive role of inflammatory biomarkers differs substantially between the entire risk spectrum and the subgroup at intermediate risk. The role of CRP in clinical decision-making needs further analysis.

Opponents believe that CRP, compared with established risk factors, provides little improvement in risk prediction. Proponents have argued that CRP does help to reclassify relevant risk categories.

Does CRP have a causal role in the development of cardiovascular disease?

CRP might have biological effects on endothelial function, coagulation, fibrinolysis, oxidation of LDL, and plaque stability. Several studies, however, have reported a lack of concordance between CRP concentrations and cardiovascular risk. This is an argument against causality.

In the meta-analysis, associations between CRP concentrations and various cardiovascular outcomes were attenuated on adjustment for known risk factors. The investigators interpret this as an argument against causality.

The debate can be resolved only by randomized trials of agents that specifically target CRP.

Even if CRP turns out not to be causal, it might be useful to identify individuals at risk and to quantify the efficacy of interventions.

Lancet January 9, 2010; 375: 95-96 “Comment”, first author S Matthijs Boekholdt, Academic Medical Center, Amsterdam, Netherlands.

1 “C-reactive Protein Concentration and Risk of Coronary Heart Disease, Stoke, and Mortality” A Meta-analysis by the European Risk Factors Collaboration (ERFC). Correspondence to Emerging Risk Factors Collaboration, University of Cambridge, UK.

CRP concentration has continuous associations with the risk of coronary heart disease, ischemic stroke,
vascular mortality, and death from several cancers and lung disease. The relevance of CRP to such a range of disorders is not clear. Associations with ischemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.

Guidelines advise preventive treatment for those at high risk of an event over the ensuing 10 years (e.g., Framingham score over 20%). There is doubt about intermediate risk patients (score 10% to 20%). Additional risk markers may help to reclassify intermediate patients into lower or into higher risk categories, thereby guiding need for primary prevention.

I believe, however, that primary care clinicians do not regularly classify patients using risk scores such as Framingham. They treat individual risks (hypertension, dyslipidemia, smoking, and BMI) as they occur.

“The Case Remains Open”

1.8 ANTIHYPERTENSIVE AGENTS AND PREVENTION OF DEMENTIA

In the search for interventions to delay or prevent dementia, vascular risk factors have attracted attention. Various studies have shown an association between mid-life hypertension (especially if untreated) and likelihood of developing dementia. This raises the possibility that antihypertension drugs might offer a form of prevention.

Several prospective cohort studies show an association between pharmacotherapy for hypertension and a lower risk of cognitive decline or incident dementia in people under age 75.

Patients with Alzheimer’s disease (AD) treated with antihypertension drugs seem to have better cognitive outcomes.

But these observational studies assessed only baseline drug exposure and did not examine the duration of treatment. Failure to have a long enough latency period before the diagnosis of dementia when assessing drug exposure can lead to bias.

Several biological mechanisms by which antihypertensives might be neuro-protective have been suggested. In addition to lowering BP, certain agents may have an effect on the neuropathology of AD. It is not clear whether a protective effect is a result of a reduction in BP or some other mechanism. If the first is true, we should focus on lowering BP. If the second is true, we should be careful about the choice of agent.

Only the Systolic Hypertension in Europe (SYST-EUR) study showed a significantly lower incidence of dementia with active treatment. Meta-analyses have yielded equivocal results.
Two randomized controlled trials showed no significant benefit on either the rate of cognitive decline or incident dementia with ARBs.

The case remains open.

A prospective cohort study in this issue of BMJ\(^1\) reported the possible role of angiotensin receptor blocking (ARB) agents in reducing risk of dementia and in slowing its progression. The study followed over 800 000 male subjects older than age 65 who had cardiovascular disease. and found significantly lower hazard ratios for incident dementia associated with ARBs than with the ACE inhibitor lisinopril. (HR = 0.81) and with other cardiovascular drugs (HR = 0.76).

In patients with preexisting AD, ARBs were associated with a lower risk of admission to a nursing home.

Association does not prove causation.

Effects of combined ACE-inhibitors and ARB may be additive.

ACE inhibitions and ARB have complex and non-identical mechanisms of action. They act differently on angiotensin receptors type 1 and type 2 in the brain:

1) Stimulation of type 1 causes vasoconstriction. Blocking stimulation causes vasodilation.

2) Stimulation of type 2 receptors reportedly leads to vasodilation, neuronal differentiation, and axonal regeneration.

3) ACE inhibitors inhibit both receptors.

4) ARBs selectively inhibit only type 1 receptors. This could lead to improved cerebral blood flow and an enhanced neuroprotective effect.

The study duration was relatively short (4 years). The absence of changes in BP during follow-up clouds the issue.

The public health implications of finding an effective way for preventing dementia are immense.

Further work is needed to verify the usefulness of antihypertensives in general, and in ARBs in particular.

BMJ 2010;340:b5409  doi:10.1136/bmj.b5409  Editorial, first author Colleen J Maxwell, University of Calgary, Calgary, Alberta, Canada


1 “Use Of Angiotensin Receptor Blockers And Risks Of Dementia In A Predominantly Male Population” BMJ 2010;340:b5465  doi:10.1336/bmj.b5465 “Research” article, first author Nien-Chen Li, Boston University School of Public Health, Boston, MA