PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

A Free Public-service Publication

JUNE 2012

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

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26th YEAR OF PUBLICATION

This document is divided into two parts

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

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

   EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term reviews of the current literature and his 26-year publication of Practical Pointers.

2) The **FULL 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 10 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2012

Do The Right Thing For The Patient—Make Health Care More Patient-Centered

6-1 GOAL-ORIENTED PATIENT CARE: An Alternative Health Outcome Paradigm

The Center for Medicare and Medicaid Services has launched major efforts to make care more patient-centered, defined as "respectful of, and responsive to, individual patient needs, and values, and ensuring that patient values guide all clinical decisions".

At present, measures of quality address preventive and disease-specific care processes (eg, smoking cessation counseling and initiation of appropriate medications after myocardial infarction). The focus has been on condition-specific indicators, both short-term (HbA1c levels and hypertension control) and longer-term (disease-free survival) as well as overall motility. These process and outcome measures work well for relatively healthy patients with a single disease. They may be inappropriate for patients with multiple conditions, severe disability, or short life-expectancy. For such patients, the overall quality of care depends on more than disease-specific care processes. It should be considered in the context of the individual patient's goals and preferences.

An alternative approach to providing better care would be to focus on patient's individual health goals within a variety of dimensions (eg, symptoms; physical functional status; and social functioning) and determining how well these goals are being met.

The goal-oriented approach to making health care decisions, assessing outcomes, and measuring success has several advantages:

1) Frames the discussion in terms of individually desired rather than universally applied health status. For example, a new therapy may extend life for a patient with metastatic prostate cancer for several months. But the patient may not perceive this small gain as worthwhile.

2) Simplifies decision making for patients with multiple conditions by focusing on outcomes that span conditions, and aligning treatment toward common goals. Choices to deescalate treatment for one condition in order to optimize treatment for another can be made in the context of whatever therapy is most likely to achieve the patient's goals. Success or failure in attaining these individualized outcomes is easily determined. It is feasible to use goal attainment to assess treatment effectiveness and quality of care for patients with multiple clinical conditions.

Multiple potential competing disease-specific outcomes can be replaced by ascertaining whether individual health goals were elicited and attained.

3) Prompts patients to articulate which health states are important to them, and their relative priorities. Patients can be in control when treatment options require trade-offs (eg, better symptom control at the expense of potentially shortening life span). Such trade-offs are currently being made (eg, when patients choose to receive hospice care and decline aggressive treatment).

4) Allows for effective shared decision-making, with the patient selecting the health outcome of highest priority and the clinician determining what treatment strategies are most likely to achieve that outcome.

Not all patient goals may be realistically attainable. A patient with a dense hemorrhagic stroke may not be able to live alone even if doing so is a major personal goal. Clinicians need to explain what is possible and negotiate potentially achievable goals with the patient. The clinician should then provide a treatment plan, encouragement, and advocacy to meet the agreed goals. And readdress them if the situation changes over time.

Some goal decisions may be associated with adverse effects (eg, a family of a patient with dementia who has behavioral problems may elect to use an antipsychotic drug, in spite of the increased risk of death from CVD, because the drug controls behavior well enough to allow the patient to remain at home). In such a case, a positive outcome from the perspective of the individual could contribute negatively to the perceived quality of the clinician's care.

The most important barrier to goal-oriented care in medicine is the deep-rooted disease- outcome based paradigm. Rather than asking what patients want, the culture has valued managing each disease as well as possible according to guidelines.

Ultimately, good medicine is about doing the right thing for the patient. For patients with multiple diseases, severe disability, or limited life-expectancy, any accounting of how well we are succeeding in providing care must above all consider the patient's preferred outcomes.

NEJM March 1, 2012; 366: 777-79 "Perspective", first author David B Reuben, David Geffen School of Medicine, UCLA, Los Angeles

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As the editorials suggest, goal oriented patient care is a high expression of autonomy and beneficence.

Some elderly patients may not be aware that they have a choice. They may simply rely on the doctor's advice. Clinicians should make it clear that they do have a choice, and may suggest a goal.

Our present practice, treating symptoms and diseases, leads to extreme polypharmacy, a result of the clinician's habit of automatically reaching for the prescription pad.

Some patients take 10 or 12 different drugs, leading to a complex daily routine or utter confusion. There is absolutely no way that benefit or harm can be ascertained from such a mixture. We do know that costs will be high.

The editorial focuses on the patient. Dealing with families maybe entirely different. Again, be sure your patient has designated a valid power of health-care power of attorney.

End-of-life presents special opportunities for goal-oriented patient care. Most would rather die at home. During the last few months of life, hospitalization is often associated with intrusive tests and interventions. Compassionate clinicians may suggest to the family that home care is a goal and help facilitate it.

Incidence Of CRC Was Reduced By 21% And Mortality By 26%

6-2 COLO-RECTAL CANCER INCIDENCE AND MORTALITY WITH FLEXIBLE SIGMOIDOSCOPY

This trial studied the effect of screening flexible sigmoidoscopy (**FS**) on the incidence of distal and proximal colo-rectal cancers (**CRC**) and related mortality.

Enrolled 154 900 men and women age 55 to 74 from 1993 through 2001. None had previous cancers. Most participants were offered FS every 5 years. An examination was considered positive if a polyp or mass was found. Biopsies were not routinely performed. Participants with a polyp or mass were referred to their primary care physician for decisions about diagnostic follow-up, a diagnosis of cancer, and cancer complications.

Death from CRC was the primary endpoint. Mean follow-up = 11 years

CRC incidence and CRC mortality according to study group.

	FS (N = 77 445)		Usual care (N = 77 455)		RR[a]
	No.	Rate per 10 000 Person-years	No.	Rate per 10 000 Person-years	
Incidence					
Total CRC	1012	11.9	1287	15.2	0.79
Mortality					
Total CRC	252	2.9	341	3.9	0.74

(a Relative Risk [RR])

In absolute terms: (*My estimates from their data. Ed..)*

Mortality from CRC decreased by about 1 per 1000 persons screened by FS.

Incidence of CRC decreased by 3 per 1000 screened by FS .

The number needed to invite for screening in order to prevent one CRC death was 871.

Among patients with screening-detected CRC, 83% were distal. Among those who were never screened, 53% of CRCs were distal.

Participants with screen-detected CRC were more likely to have earlier stage cancers (stage I or II) than participants who were never screened.

Mortality related to distal CRC was reduced by 50% and the incidence was reduced by 29%.

The investigators estimated that colonoscopy screening (vs. FS) would have increased the number of screen detected CRCs by about 16%.

Conclusion: Screening with FS, in conjunction with colonoscopy was associated with clinically important decreases in CRC incidence and mortality. A significant reduction in mortality was observed only for CRC in the distal colon. The incidence of CRC was reduced in both the distal and proximal colon

(See the full abstract for details and the citation Ed.)

Any screening that reduces mortality by 1 in 1000 over 10 years is noteworthy.

The trial was "contaminated". Ie, there were many protocol violations. Many participants in the usual care group crossed-over and received FS and colonoscopies. Many of those randomized to the intervention group did not undergo FS. Only about half received a second FS. Some with positive FS findings did not go on to receive colonoscopy.

I believe more strict compliance with a screening protocol would result in more lives saved.

What should the frequency of FS be? "Choosing wisely" in an effort to reduce medical costs and improve patient care, suggested every 10 years after a completely normal colonoscopy in average risk patients. And every 5 years after complete removal of one or two small adenomas without high grade dysplasia. The same should apply to FS. However, if these adenomas were discovered by FS, the protocol of this trial calls for colonoscopy.

The greatest advantage of screening FS vs screening colonoscopy is population acceptance, lower costs and wider availability. Many more patients would be willing to undergo a FS and would refuse colonoscopy.

Preparation for FS is less intrusive, usually enemas and dulcolax. Sometimes magnesium citrate. No sedation was used. (Personal communication Dr. Robert Schoen.)

6-3 PREDIABETES: A High-Risk State For Diabetes Development

Prediabetes (**PD**; pre-type-2 diabetes) is a high risk state for diabetes mellitus type-2 (**DM-2**). PD is defined as higher than "normal" fasting plasma glucose, but lower than the threshold for diabetes.

Diagnostic criteria for PD have changed over time and vary depending on the institute of origin. The ADA defined PD:

1) Fasting plasma glucose (FPG) of 100-125 mg/dL. (126 and higher is DM-2.)
2) Or an impaired glucose tolerance: Plasma glucose, 2-hours after 75 g oral glucose, between 140- 200 mg/dL. (Over 200 = DM-2)
3) Or Hemoglobin A1c of 5.7% -6.4%

The NHANES suggested that 35% of US adults older than 20 years and 50% of those over 65 had PD in 2008.

According to the ADA, up to 70% of individuals with PD will eventually develop DM--2.

Risk predictors include: age, BMI, waist circumference, high systolic pressure, hypertension, family history, smoking, physical inactivity, blood levels of glucose at the high end of the PD range, and triglycerides, uric acid, lipid levels.

A proposed model of progress from normo-glycemia to diabetes:

1) A long period of insulin resistance accompanied by a compensatory increased rate of insulin secretion and increased beta-cell mass.
2) A stable adaptation period when beta-cells are no longer fully compensating for increased insulin resistance. Fasting and post-load glucose are not completely maintained. This period probably starts when fasting and post-load glucose levels are still in the normal range, and is usually accompanied by a decrease in acute insulin secretion at FBG concentrations of about 100 mg/dL.
   (The first and second stages occur before the PD phase.)
3) During the unstable early PD period beta-cells become unable to compensate for insulin resistance. Blood glucose levels rise above normal.
4. Manifest DM-2
   A. Stable decompensation
   B. Severe decompensation

In DM-2 patients, body glucose disposal is decreased, mainly related to muscle insulin resistance. If insulin secretion was able to compensate for insulin resistance, no change in glucose concentrations would occur. This means that, by definition, beta-cell dysfunction is already present in PD, and insulin secretion is decreased.

Numerous observational studies have reported evidence of associations between PD and neuropathy, nephropathy, retinopathy, and macrovascular events.

Lifestyle interventions: PD should be treated to prevent progression to DM-2. Lifestyle changes should be the cornerstone of treatment. Obesity and physical inactivity are the most important modifiable risk factors. Two large studies reported a 58% risk reduction after interventions aimed at weight reduction, dietary changes, and increased physical activity.

Drug therapy: Metformin is safe. No serious adverse effects (only mild GI effects) have been detected in the years of use. Its beneficial effect is greater in PD patients with higher baseline BMI and higher FBG.

Several trials support a long-term reduction in risk of DM-2 and a delay in onset of DM-2 as a result of lifestyle and drug interventions.

In view of its long-term safety, metformin could be given to people who cannot comply with lifestyle advice.

(See the full abstract for details and the citation. Ed)

I spent more time and effort abstracting this article than usual because of its importance as an application and opportunity for primary care.

DM-2 is preventable.

We need a better definitions for diabetes. It is now defined by blood levels, which are arbitrary and imprecise. Definitions differ and change over time. Diabetes type-2 is a state of insulin resistance leading to beta-cell stress and failure, increasing blood glucose levels, and organ damage. By this definition, some patients with PD actually have diabetes.

PD also requires a new definition. It is a very heterogeneous group. Differences in definition are still present after years of study.

Since DM-2 is defined by blood glucose levels, FBG must be determined by screening. Who should be screened? Certainly the high-risk groups of obese and sedentary patients. But, determination is so inexpensive and available, I believe most patients will be screened from time to time.

I believe metformin will delay incidence of DM-2 and may help to prevent it. Except for expense, trouble, and duration of therapy, I see no reason why it should not be prescribed in conjunction with lifestyle changes.

In the group of patients with PD, who are subject to develop DM-2, other risk factors for cardiovascular disease are likely present, and should be treated.

The challenge for prevention extends to physicians, some of whom are overweight and sedentary. We must be good role-models.

"Moving Away From Rigid Guidelines"

6-4 GUIDELINES EASE UP ON GLYCEMIC CONTROL IN SOME PATIENTS WITH DIABETES

Physicians are being told to loosen up on glycemic control when treating certain patients with type-2 diabetes mellitus (DM-2)

Aggressive glucose management has been a mainstay of treatment, intended to reduce microvascular risks The traditional goal is keeping the HbA1c below 7.0%. But recent trials have suggested that achieving these goal puts certain patients at risk for cardiovascular complications and death.

The ADA released a report in April 2012 calling for a more patient-centered treatment approach that takes into account patient needs, preferences, and tolerances. The report noted that lowering HbA1c below 7.0% is still recommended in most patients. Less stringent goals, between 7.0% to 8.0%, are appropriate for patients with a history of severe hypoglycemia, limited life-expectancy, advanced complications, extensive co-morbid conditions, and those that have difficulty attaining the 7.0% goal despite intensive self-management, education, repeated consultations, and effective doses of glucose-lowering agents, including insulin.

The report adds that the goal of 6.5% might be considered in select patients with short DM-2 duration, long life expectancy and no significant cardiovascular disease, if the goal can be achieved without significant hypoglycemia.

These multiple targets emerged from a 2010 study that found a U-shaped risk curve. Those with the lowest rates of all-cause mortality had a HbA1c of 7.5%. Those with higher and lower levels had increased risk for all-cause mortality and cardiovascular events.

The ACCORD trial (2008) found that patients randomized to intensive therapy of 6.0% or lower were 22% more likely to experience a non-fatal myocardial infarction, non-fatal stroke, or death from CVD than those randomized to standard therapy with a target of 7.0% to 7.9%.

The goal of 7.0% came from a study of type-1 diabetes that found a target of 7.0% seemed to balance benefits and risks of glycemic control. But no study says that the target should be 7.0% for everyone.

The report also notes that lifestyle interventions (weight management, diet, and exercise) are key factors for minimizing complications of diabetes.

Another important element of the report addresses the growing array of pharmacological agents available for treatment of diabetes and their possible adverse effects. Metformin remains the optimal first-line drug. The report cannot say with certainty which additional drugs are better because of a " distinct paucity of long-term comparative effectiveness trials".

The report should serve as one of the tools available to physicians and patients as they discuss treatment options. Moving away from rigid guidelines is probably best for individual patients. One of the problems of evidence-based medicine is that it can make physicians develop a one-size-fits-all approach. Less rigid guidelines allow flexibility to change treatment courses over a patient's lifetime. People are different and their perspectives change. A continuing dialogue is important. Determine goals and tailor therapy, but adjust over time.

JAMA June 6, 2012; 307: 2243-44 Medical News and Perspective by Mike Mitka, JAMA staff.

Another example of treating the patient with the disease, rather than the disease alone.
This applies especially to chronic co-morbid illnesses.

A benefit / harm-cost ratio applies to interventions in each individual patient at a given time. The ratio may change over time. Costs increase with age, not only in monetary terms, but also in inconvenience, bother, difficulty in understanding and following a treatment protocol, problems with transportation. The elderly have less to gain by a strict treatment protocol.
They have less time to benefit.

Individualism is a key point. Reaching goals must be tempered by good judgment.

FULL ABSTRACTS JUNE 2012

Incidence Of Crc Was Reduced By 21% And Mortality By 26%

6-2 COLO-RECTAL CANCER INCIDENCE AND MORTALITY WITH FLEXIBLE SIGMOIDOSCOPY

This trial studied the effect of screening flexible sigmoidoscopy (**FS**) on the incidence of distal and proximal colo-rectal cancers (**CRC**) and related mortality.

STUDY

1. A total of 154 900 men and women age 55 to 74 were enrolled from 1993 through 2001. None had previous cancers.
2. Randomized to 1) screening FS and 2) usual care.
3. Participants in the intervention group randomized before 1995 were offered FS at baseline and at 3 years; and at 5 years thereafter. An examination was considered positive if a polyp or mass was found. Biopsies were not routinely performed. Participants with a polyp or mass were referred to their primary care physician for decisions about diagnostic follow-up, a diagnosis of cancer, and cancer complications.
4. Cancers located in the rectum through the splenic flexure were defined as distal. Those in the transverse colon through the cecum were defined as proximal.
5. The primary analysis was an intention-to-screen comparison of CRC mortality between the 2 groups..
6. Death from CRC was the primary endpoint. Mean follow-up = 11 years

RESULTS

1. In the intervention group, 84% underwent baseline FS screening and 54% underwent subsequent screening.
2. In 28% of participants screened, at least one screening was positive for polyps or mass.
3. Of the participants with abnormal screening results, 80% underwent a diagnostic intervention within 1 year; 95% of these underwent colonoscopy.
4. The rate of colonoscopy performed as a direct effect of screening by FS was 22%.

5. CRC incidence and mortality according to study group.

CRC incidence and CRC mortality according to study group.

	FS (N = 77 445)		Usual care (N = 77 455)		RR[a]
	No.	Rate per 10 000 Person-years	No.	Rate per 10 000 Person-years	
Incidence					
Total CRC	1012	11.9	1287	15.2	0.79
Distal CRC	479	5.6	669	7.9	0.71
Proximal	512	6.0	595	7.0	0.86
Mortality					
All CRC	252	2.9	341	3.9	0.74
Distal	87	1.0	175	2.0	0.50
Proximal	143	1.6	147	1.7	0.97

(a Relative Risk [RR])

Incidence of CRC: The incidence of CRC was 11.9 cases per 10 000 person-years (N = 1012) in the intervention group vs. 15.2 cases per 10 000 person-years in the control group (N = 1287). This represents a 21% reduction in risk. (RR] = 0.79) Significant reductions were observed in the incidence of distal colon cancers in the intervention group vs. the usual care group (479 vs. 669; RR = 0.71 and proximal colon cancers (512 vs. 595; RR = 0.86). The reduction in incidence of CRC was similar for participants ages 55-64 as for ages 65-74. The number needed to screen to prevent 1 case of CRC was 282.

Mortality: Mortality related to CRC was 2.9 per 10 000 person-years in the intervention group and 3.9 per 10 000 person-years in the usual care group (252 deaths vs. 341 deaths, a 26% reduction; RR = 0.74). Mortality related the distal CRC was reduced by 50% (87 vs. 175 deaths; RR = 0.50). But mortality related to the proximal CRC (143 vs. 147; RR = 0.97) was unaffected. No difference in mortality related to proximal CRC was observed. The number of deaths from proximal CRC was similar in both groups. There were only 4 fewer deaths from proximal CRC in the intervention group.

6. The number needed to invite for screening in order to prevent one CRC death was 871.

7. Among patients with screening-detected CRC, 83% were distal. Among those who were never screened, 53% of CRCs were distal.

8. Participants with screen-detected CRC were more likely to have earlier stage cancers (stage I or II) than participants who were never screened.
9. There was a reduction in incidence of distal CRC in the intervention group for each cancer stage ranging from 20% for stage I to 62% for stage IV.
10. Adverse effects: There were 3 bowel perforations in the FS group; 19 perforations during follow-up colonoscopy.
11. False positive results (positive on FS but no neoplasm identified subsequently) occurred in 20% of men and 13% of women.

DISCUSSION

1. FS, as compared with usual care, was associated with a 26% reduction in overall CRC mortality and a 21% reduction in incidence of CRC.
2. Mortality related to distal CRC was reduced by 50% and the incidence was reduced by 29%.
3. A statistically significant 14% reduction in proximal CRC was observed, but there was no significant reduction in mortality related to proximal CRC.
4. A second screening increased the cumulative diagnostic yield of CRC or advanced adenoma by 26% in women and 34% in men.
5. There was substantial use of FS and colonoscopy in the usual care group. This probably reduced the difference in mortality and incidence between the two groups.
6. There was less protection against CRC in the proximal colon. However, the trial did find a statistically significant cancer reduction in the incidence of proximal CRC. This was achieved with a colonoscopy rate of 22% as a direct result of FS screening. But this did not result in a reduction in mortality from proximal CRC.
7. Mortality from stage IV CRC is much higher than for lower stages. In this trial, 79% of patients with stage IV CRC died of the CRC. In the distal colon, there was a reduction of more than 60% in incidence of stage IV CRC.
8. In the intervention group, tumors that were not detected by screening were more likely to be proximal and late stage.
9. As compared with the distal colon, the proximal colon presents a more difficult challenge for CRC control. The investigators estimated that colonoscopy screening (vs. FS) would have increased the number of screen detected CRCs by about 16%.
10. The effectiveness of FS in reducing mortality related to distal CRC reflects a

reduction in cancer incidence and the identification of earlier stage cancers, which are less likely to cause death. Tumors detected by FS were discovered predominately at an early stage.

11. Compared with the Minnesota trial of fecal occult blood screening: After 13 years of follow-up, with 6 rounds of screening and a 38% rate of colonoscopy, CRC was reduced by 12% and mortality by 33%. In the present trial of FS, incidence of CRC was reduced by 21% and mortality by 26%.

CONCLUSION

Screening with FS, in conjunction with colonoscopy was associated with clinically important decreases in CRC incidence and mortality.

A statically significant reduction in mortality was observed only for CRC in the distal colon.

The incidence of CRC was reduced in both the distal and proximal colon

NEJM June 27, 2012; 366: 2035-57 Original investigation by The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial, first author Robert E Schoen, University of Pittsburg Medical Center, Pittsburg, PA

Sponsored by the National Cancer Institute

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6-3 PREDIABETES: A High-Risk State For Diabetes Development

Prediabetes (**PD**; pre-type-2 diabetes) is a high risk state for diabetes (diabetes mellitus type-2; **DM-2**). PD is defined as higher than "normal" fasting plasma glucose, hut lower than the threshold for diabetes. Each year, 5% to 11% of persons with PD progress to DM-2. The same proportion reverts back to normoglycemia.

PD is associated with insulin resistance, and beta-cell dysfunction.

Observational evidence shows associations between PD and early forms of nephropathy, neuropathy, diabetic retinopathy, and increased risk of macrovascular disease.

Life modification is the cornerstone of DM-2 prevention. There is also evidence of benefits from drugs. (eg,, Metformin)

Introduction:

An expert committee of the American Diabetes Association (ADA prefers the term "high risk state of developing diabetes".

Diagnostic criteria for PD have changed over time and vary depending on the institute of origin. The ADA defined PD:

1) Fasting plasma glucose (FPG) of 100 mg/dL to 125 mg/dl (5.6 to 6.9 mmol/L);
   126 and higher is DM-2. The WHO definition is 110 to 125.
2) Or an impaired glucose tolerance:
   Plasma glucose, 2-hours after 75 g oral glucose, between 140 mg/dL and 200 mg/dL. (7.8 mmol/L and 11.0 mmol/L). Over 200 = DM-2.
3) Or Hemoglobin A1c of 5.7% -6.4%

Reproducibility of thresholds used to define PD is about 50%

Individual risk factors for DM-2 (history of gestational diabetes[1]; first degree relative with diabetes) and a combination of risk factors (eg, metabolic syndrome) can also be used to define populations at risk.

Epidemiology:

The NHANES suggested that 35% of US adults older than 20 years and 50% of those over 65 had prediabetes in 2008.

Progress from prediabetes to DM-2:

According to the ADA, up to 70% of individuals with PD will eventually develop DM--2.

Women with gestational diabetes have high risk of developing DM-2 in 5 to 10 years. In a meta-analysis of 20 studies, 13% of mothers with gestational diabetes[1] developed DM-2 after pregnancy compared with 1% of those without gestational diabetes.

Reversion to normality

Several trials have reported reductions in the risk of DM-2 development in prediabetic individuals after lifestyle and drug-based interventions.

In the DPP study, 19% of controls reverted to normal.

Risk predictors

Various diabetes risk models include:

Non invasive variables: Age, BMI, waist circumference, high systolic pressure, hypertension, family history, smoking, physical inactivity.

Laboratory variables: Blood levels of glucose at the high end of the PD range,

triglycerides, uric acid, lipid levels.

It is important to determine future risk of DM-2.

Pathophysiology of PD:

In healthy people, blood glucose is strictly regulated. FBG is maintained between 70 mg/dL and 100 mg/dL (3.9 and 5.6 mmol/L). Post meal increases rarely exceed 50 mg./dL (3 mmol/L).

During development of DM-2, homeostasis of fasting and post-load glucose becomes abnormal. Development of DM-2 from normal glucose tolerance is a continuing process, with decreased insulin sensitivity and decreased insulin secretion. DM-2 risk prediction might be more accurate if treated as continuous rather than categorical variables.

Blood glucose levels may gradually increase for several years (and remain "normal") before diagnosis of PD. Insulin sensitivity may be reduced and a compensatory increase in insulin secretion may be present for several years before diagnosis of PD.

Multi-stage model of diabetes development:

A proposed model is composed of several stages

1) A long period of insulin resistance accompanied by a compensatory increased rate of insulin secretion and increased beta-cell mass.
2) A stable adaptation period when beta-cells are no longer fully compensating for increased insulin resistance. Fasting blood glucose and post-load glucose levels are not completely maintained. This period probably starts when fasting and post-load glucose levels are still in the normal range, and is usually accompanied by a decrease in acute insulin secretion at FBG concentrations of around 100 mg/dL.
   (The first and second stages occur before the PD phase.)
3) During the unstable early period beta-cells become unable to compensate for insulin resistance. Blood glucose levels rise rapidly.
4. Manifest DM-2
   A. Stable decompensation
   B. Severe decompensation

Glucose dysregulation:

FBG values are maintained by endogenous glucose production (EGP) from the liver. EGP and fasting insulin are strongly related to FBG. During absorption of a glucose-containing meal, changes

in blood glucose are caused by intestinal absorption, suppression of EGP, and glucose uptake by the body. EGP is greatly suppressed in people with normal glucose tolerance after glucose ingestion. Suppression is less in PD.

In DM-2 patients, body glucose disposal is decreased, mainly related to muscle insulin resistance. If insulin secretion were able to compensate for insulin resistance, no change in glucose concentrations would occur. This means that, by definition, beta-cell dysfunction is already present in PD. In PD, beta-cell function and insulin secretion are markedly decreased.

Nephropathy and kidney disease in PD:

People with PD have concomitant end-organ damage: retina, kidneys, blood vessels, nerves, and macrovascular disease. These are traditionally thought to be complications of DM-2.

PD has been linked to urinary albumin secretion and decreased estimated glomerular filtration rate. Micro-albuminuria and macro-albuminuria increase as glycemia worsens. But micro-albuminuria can be indicative of hypertension, and therefore is an imprecise marker for diabetes-related early nephropathy. Some nephropathic changes may be present in PD before onset of diabetes. By contrast, decrease in estimated glomerular filtration rate is a late manifestation, and evidence for these changes in PD is mixed.

Neuropathy in PD:

The strongest supporting evidence is for the association between PD and autonomic neuropathy. PD is associated with decreased heart rate variability (a marker of parasympathetic function), decreased postural changes in heart rate, increased prevalence of erectile dysfunction.

Studies of PD and senso-motor neuropathy suggest that small demyelenated fibers might be implicated with IGT and early neuropathy.

Evidence is accumulating for increased prevalence of idiopathic polyneuropathy (idiopathic sensory or painful neuropathy) in individuals with PD.

Retinopathy:

In a study of over 5000 Pima Indians, retinopathy ascertained by direct ophthalmoscopy was associated with PD.

Macro-vascular disease:

Cross sectional studies provide evidence in favor of vascular risk from mild or moderate hyperglycemia. An excess prevalence of coronary disease is reported in people with fasting or post-load hyperglycemia lower than the diabetes threshold.

Pooled data from large European cohorts showed that IGT is associated with increased risk of coronary disease and total coronary death.

However, this increased risk may be confounded by various other risk factors in individuals with PD.

Evidence from prospective studies suggests that fasting hyperglycemia, post-load glucose, and HbA1c are all robust predictors of vascular mortality, and that these associations are independent of vascular risk factors such as obesity, BP, triglycerides and lipoproteins.

Treatment

Lifestyle interventions

PD should be treated to prevent progression to DM-2. Lifestyle changes should be the cornerstone of treatment. Obesity and physical inactivity are the most important modifiable risk factors. Two large studies reported a 58% risk reduction after interventions aimed at weight reduction, dietary changes, and increased physical activity. Benefits were dependent on the number of goals achieved (weight loss > 5%; fat intake < 30%; saturated fat < 10%; fiber intake > 15 g per 1000 kcal; exercise > 4 hours per week). Every weight loss of 1 kg reduced risk by 16%.

Drug therapy

Metformin is safe. No serious adverse effects (only mild GI effects) have been detected in the years of use. It reduces fasting blood glucose, mainly through its effect on output from the liver. In patients with IGT, it lowers risk of DM-2 by 45%.

Its beneficial effect is greater in PD patients with higher baseline BMI and higher FBG.

Other anti-diabetes drugs have been tested, with varying results and adverse effects.

A variety of non-antidiabetes drugs (ACE inhibitors, angiotensin II inhibitors, fenofibrate). All have had problems. The benefits are smaller than anti-diabetes dugs, and they are not recommended for treatment of PD.

Bariatric surgery reduces risk of PD. Benefits from other weight-loss programs have not been reported.

Long term effects of lifestyle and antidiabetes drugs:

Several trials support a long-term reduction in risk of DM-2 and a delay in onset of DM-2 as a result of lifestyle and drug interventions. One study of 20 years follow-up reported those receiving lifestyle interventions had a 43% reduction in risk of developing diabetes. This translated into a 3.6 year delay onset of DM-2. In the same study, lifestyle intervention was associated with a 50% reduction in relative risk of incident severe retinopathy. Rates of other microvascular complications were not affected.

Another trial found that reversal of PD to normoglycemia during the randomized phase, even if transient, was associated with a 56% reduced risk of future DM-2 during a 5.7 year follow-up.

In a 20-year follow-up of another study, evidence of a benefit on macrovascular events was not consistent.

In a recent meta-analysis of trials, lifestyle and drug-based interventions had no significant effect on the risk of all-cause mortality or cardiovascular deaths during a mean follow-up of 3.8 years except for borderline benefit on stroke.

Another study reported that diet and exercise were more beneficial in lowering all-cause mortality than in the control group during 12-years of follow-up.

Clinical and public health implications

People with PD comprise a heterogeneous group. PD is characterized by simultaneous presence of insulin resistance and beta-cell dysfunction.

Multifactorial risk scores promise to further improve identification of individuals at high risk of developing DM-2. But whether risk scores will help prevent DM-2 is not clear.

PD is not only related to development of diabetes and its complications, but also might cause damage to kidneys and nerves. Identification and treatment of individuals with PD is crucial. Randomized trials show that lifestyle interventions and metformin prevent development of DM-2.

Lifestyle interventions aimed at achieving more than 7% weight reduction and 150 minutes of moderate exercise per week are recommended for all people with PD.

In view of its long-term safety, metformin could be given to people who cannot comply with lifestyle advice. Treatment may be needed lifelong.

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1 Gestational diabetes (ADA target levels):

Fasting FBG before glucose load	90 mg/dL	
Oral glucose load 75 g		
	1 hour	180 mg/dL
	2 hour	153 mg/dL
	3 hour	not dose

(The American Congress of OB-GYN definition differs.)