PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

DECEMBER   2005

**HIGH PREVALENCE OF LOW CARDIORESPIRATORY FITNESS IN ADOLESCENTS AND
ADULTS—A Risk Factor for Later Cardiovascular Disease**

PERIODONTAL DISEASES—A Possible Risk Factor For Cardiovascular Disease.

**A COMPARISON OF LETROZOLE (An Aromatase Inhibitor) WITH TAMOXIFEN IN POST
MENOPAUSAL WOMEN WITH EARLY BREAST CANCER**

AROMATASE INHIBITORS—A TRIUMPH OF TRANSLATIONAL ONCOLOGY

**THE METABOLIC SYNDROME AS A PREDICTOR OF NON-ALCOHOLIC FATTY LIVER DISEASE
THE MYRIAD USES OF BOTULINUM TOXIN**

**USE OF GASTRIC ACID-SUPPRESSIVE AGENTS AND THE RISK OF COMMUNITY-ACQUIRED
Clostridium difficile-ASSOCIATED DISEASE**

THE NEW VIRULENT *CLOSTRIDIUM DIFFICILE*

**INTENSIVE DIABETES TREATMENT LOWERS RISK OF CARDIOVASCULAR DISEASE IN
PATIENTS WITH TYPE 1 DIABETES**

This document is divided into two parts

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

> **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 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 5
years can be accessed at www.practicalpointers.org

Richard T. James Jr, M.D.

Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS*   DECEMBER 2005

"Low Cardiorespiratory Fitness Affects Approximately 1 Out Of 5 Persons Aged 12 Through 49 In The US"

12-1   PREVALENCE, AND CARDIOVASCULAR DISEASE CORRELATES, OF LOW
CARDIORESPIRATORY FITNESS IN ADOLESCENTS AND ADULTS

The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional,
nationally representative sampling of the non-institutionalized civilian US population. This report covers years
1999-2002.

Participants were adolescents age 12-19, and adults age 20-49. All were free of CVD.

All underwent submaximal graded treadmill testing to achieve 75% to 90% of age-predicted maximum heart
rate. Estimated maximal oxygen consumption (**VO2max**) by comparing heart rate response to reference levels of
submaximal work. (Higher VO2max indicates more favorable fitness.) Cutpoints for fitness were defined as low
(< 20th percentile); moderate (20th -59th percentiles); and high (60th and higher).

Thirty three % of adolescents and 14% of adults had low fitness. (This represents 7.5 million adolescents in
the US, and 8.5 million adults.)

More than 25% of adults reported *no* moderate or vigorous physical activity in the past month.

Adults mean body mass index (**BMI**) = 27. About 20% had the metabolic syndrome.

Low fitness persons were 2 to 4 times more likely to be obese compared with those in the moderate-high
fitness groups.

The strong association between obesity and CVD risk factors is the most striking indication of the health
burden of low fitness. BMI and waist circumference demonstrated the most consistent association with fitness.

Mean values decreased in a nearly graded fashion with increasing fitness. The association is already present in adolescents and young adults.

The relationship between low fitness and cardiovascular mortality is proposed to be mediated by the development of CVD risk factors including hypertension, diabetes, dyslipidemia, and the metabolic syndrome.

Physical activity training in efforts to improve fitness has been shown to lower the likelihood of developing risk factors, independent of changes in weight.

As primary care clinicians follow patients, they should watch for any increase in BMI and abdominal girth. A change may present an opportunity to ask about the patient's physical activity and to encourage intervention..

Clinician must first be able to point to their own fitness as an example.

"Could Have A Role In The Initiation Or Progression Of Coronary Artery Disease And Stroke."

12-2   PERIODONTAL DISEASES

The term periodontal disease usually refers to the common inflammatory disorders (gingivitis and periodontitis) that are caused by pathogenic microflora in the biofilm (dental plaque) that forms adjacent to the teeth every day.

Inflammation that extends deep into the tissues and causes loss of supporting connective tissue and alveolar bone is termed *periodontitis*. The result is formation of soft tissue pockets, or deepened crevices between the gum and the tooth root. Severe periodontitis results in loosening of teeth, occasional pain and discomfort, impaired mastication, and eventually tooth loss. An estimated 13% of US adults have moderate to severe periodontitis.

The clinical diagnosis is based on visual and radiographic assessment.

Causes include

1. Oral microorganisms:

The mouth contains hundreds of species of aerobic and anaerobic bacteria (many uncharacterized) living in symbiosis with a healthy host. These organisms grow on tooth surfaces in biofilms. They are attached to, and densely packed, against the tooth.

2. Tobacco:

Smokers are much more likely to develop periodontitis. Smokeless tobacco may also lead to gingivitis, loss of tooth support, and precancerous leucoplakia at the site of quid placement.

"In the USA, about half of the risk of periodontitis can be attributable to tobacco use.

3. Osteoporosis:

Osteoporosis raises susceptibility to periodontal break down. The risk could be attenuated by estrogen replacement therapy.

Association with cardiovascular disease and stroke:

Inflammation has been implicated in the cause and pathogenesis of atherosclerosis. "Periodontal disease could have a role in the initiation or progression of coronary artery disease and stroke."

Periodontitis is associated with raised systemic concentrations of C-reactive protein, fibrinogen, and cytokines, all of which have been causally linked to atherosclerotic-induced diseases. Periodontitis treatment has been shown to reduce serum inflammatory markers and C-reactive protein.

In animals, periodontal bacteria can promote platelet aggregation.

One study reported that severe periodontitis was associated with increased intima-media thickening.

Severe periodontal bone loss was associated with a nearly four-fold increase in risk for presence of carotid artery plaques.

A meta-analysis concluded that periodontal disease was associated with a 19% increase in the risk of future cardiovascular disease. A 12-year study suggested that periodontal disease and fewer teeth could be associated with a raised risk of ischemic stroke.

Since periodontal disease is so common, even a modest increase in risk could have profound public-health effects.

I included this review mainly to comment on the putative relation of periodontitis with cardiovascular disease. Although tentative, I believe the relationship should be suspected.

Inspection of the teeth and gums should be routinely included in the physical examination. I believe many primary care clinicians do not regularly examine patients for periodontitis. They defer to the dentist.

Presence of periodontitis provides an opportunity to stress the importance of tobacco cessation.

Women may be told that osteoporosis may lead to tooth loss.

Letrozole Was Associated With Greater Reduction In Risk Of Recurrent Disease.

12-3 A COMPARISON OF LETROZOLE WITH TAMOXIFEN IN POST MENOPAUSAL WOMEN WITH EARLY BREAST CANCER

Tamoxifen inhibits activity of estrogen by competitively binding to the estrogen receptor. Aromatase inhibitors block the conversion of androgens to estrogen, and reduce estrogen levels in tissue and plasma.

Letrozole (*Femara)*, a third-generation aromatase inhibitor inhibits aromatase activity by over 99%.

This study compared letrozole with tamoxifen therapy in postmenopausal women with hormone-receptor-positive BC.

At five year follow-up	Letrozole (%)	Tamoxifen (%)
5-y Disease-free survival	84	81.4
Breast cancer recurrence	10.3	13.6
Node-positive BC survival	77.9	71.4
Node-negative BC survival	88.7	88.7
Distant recurrence	4.4	5.8

The absolute % differences in favor of letrozole ranged from 1.4% to 6.2%. The number needed to treat with letrozole vs tamoxifen to benefit one patient ranged from 15 to 71. Patients who were node positive benefited more from letrozole.

"Our study confirms the positive results reported in other trials of letrozole as adjuvant treatment for hormone-receptor positive breast cancer in postmenopausal women."

Of particular interest was the finding of a significant reduction in the risk of recurrences at distant sites. (Difference = 1.4% favoring letrozole).

In postmenopausal women with endocrine-responsive BC, adjuvant treatment with letrozole, as compared with tamoxifen, reduced risk of recurrent disease, especially at distant sites

12-4   AROMATASE INHIBITORS—A TRIUMPH OF TRANSLATIONAL ONCOLOGY

"All evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes, and who are at substantial risk of recurrent disease. "

A Major Cause Of Liver-Related Morbidity And Mortality

12-5   THE METABOLIC SYNDROME AS A PREDICTOR OF NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease **(NAFLD)** is a major cause of liver-related morbidity and mortality. It has the potential to progress to cirrhosis and liver failure. Non-alcoholic steatohepatitis (**NASH)** is an intermediate stage of NAFLD. NASH is characterized by hepatic steatosis, liver cell injury, hepatic inflammation, fibrosis, and necrosis.

NAFLD is often associated with obesity, type 2 diabetes, dyslipidemia, and hypertension. Each of these abnormalities carries a cardiovascular disease risk. Together they are often categorized as the insulin-resistance syndrome, or the metabolic syndrome (**The MS).** The MS is an emerging problem worldwide. Its prevalence is increasing.

This study characterized the longitudinal relationship between The MS and NAFLD.

Prospective observational study followed over 4400 apparently healthy Japanese men and women age 21 to 80 who attended routine medical checkups. None abused alcohol. None were taking drugs. None had hepatitis B or C.

The examination included an abdominal ultrasound. The diagnosis of NAFLD was based on ultrasound using hepato-renal contrast and liver brightness as markers.

At baseline, 18% of the 4000 participants had NAFLD.

NAFLD was more common in men than in women (25% vs 10%).

During a follow-up of 14 months, 241 men who did *not* have NAFLD at baseline developed NAFLD. These men had gained weight. About 10% of men who *had* NAFLD at baseline had normal ultrasound on follow-up. These men had lost weight.

The term NAFLD refers to a spectrum of liver disease in the absence of significant alcohol consumption. At the "benign" end of the spectrum, most patients with NAFLD have simple steatosis. About 10% have features of liver cell injury or fibrosis (non-alcoholic steatohepatitis—**NASH**).

The distinction between simple steatosis and NASH is important because their natural history differs. Patients with simple steatosis have a benign prognosis, at least from the standpoint of liver disease. Up to 20% of patients with NASH may ultimately develop advanced liver disease.

The prognosis of NASH-related cirrhosis is poor. About 1/3 develop liver failure or liver-related death. Hepatocellular cancer is a complication of NASH-related cirrhosis.

Although only a minority of patients with NAFLD develops advanced liver disease, it is causing alarm because of its high prevalence.

The adverse effects of The MS extend beyond the cardiovascular system.

An important recommendation to patients with NAFLD—even small amounts of weight loss (and loss of abdominal girth) can reverse NAFLD. Conversely, small gains in weight can induce NAFLD.

I believe abstinence from alcohol may also be an important recommendation. In patients with hepatitis C, abstinence has been recommended. In addition to possible toxic effects, the tendency of alcohol to increase caloric intake adds to risk of The MS.

If geese can be force-fed to produce fatty livers, why cannot humans? Why not call NAFLD the "Foie Gras syndrome"?

Abdominal obesity (more specifically intra-abdominal obesity) is emerging as a serious risk factor for cardiovascular disease. Abdominal girth, a marker of intra-abdominal obesity, had been considered the major criterion (of the 5) for The MS. Is the lesser risk of NAFLD in women due to their tendency to add weight to the hips and lower extremities rather than the abdomen? .

The "Big Belly" syndrome is a major risk factor for both cardiovascular and liver disease.

An Important Therapeutic Agent With Widespread Applications.

12-6 THE MYRIAD USES OF BOTULINUM TOXIN

Botulinum toxin (**BTx**) is an important therapeutic agent with widespread applications. It is one of the most potent neurotoxins known. BTx derives its name from the Latin word *botulus*, "sausage". This refers to poisoning from badly preserved meat observed in the early 19th century. BTx is a protein produced by *Clostridium botulinum.*

BTx targets peripheral cholinergic systems and prevents the release of acetylcholine, blocking synaptic transmission.

Over the past 24 years, it has proved to be remarkably successful in relieving spasms, unwanted movements, abnormal postures, and pain associated with many disorders. It has made it possible to control some neurological conditions that once required systemic therapy. Double-blind placebo-controlled clinical trials have shown that it safely and effectively resolves excessive muscle contraction in dystonia (a condition characterized by sustained twisting and posturing movements); hemifacial spasm; and spasticity from stroke, cerebral palsy, brain trauma, and multiple sclerosis. It has also been successful in patients with hyperhidrosis due to autonomic disorders. More recently, BTx has attracted interest in headache and pain disorders, and for cosmetic uses.

This issue of *Annals* reports effectiveness in treatment of the pain of lateral epicondylitis ("tennis elbow").

C. difficile *Infection Is Becoming An Important Public Health Issue. It May Occur Without Prior Antibiotic Use.*

12-7   USE OF GASTRIC ACID-SUPPRESSIVE AGENTS AND THE RISK OF COMMUNITY-ACQUIRED *Clostridium difficile*-ASSOCIATED DISEASE

C. difficile is an important cause of nosocomial diarrhea. *C. difficile*-associated disease (**CDAD**) is also a cause of diarrhea in the community. It has been reported that it is the 3rd most common cause of infectious diarrhea in persons over age 75. The absolute number of CDAD cases in the community could be significant.

Gastric acid constitutes a major defense mechanism against ingested pathogens. Loss of stomach acid has been associated with colonization of the normally sterile upper gastrointestinal tract.

Suppression of stomach acid production by proton-pump inhibitors (**PPI**) and histamine2-receptor blockers (**H2RB)** may lead to increased likelihood of CDAD.

This case-control compared:

> 1) Cases of community-acquired CDAD (n = 1233; mean age 72—no hospitalization in the prior year), with
>
> 2) Ten matched controls without CDAD (n = 12 330—also not hospitalized in the prior year).
>
> 3) Determined current use of PPI and H2-RB in both groups.

Cases were 3 times more likely than controls to have received antibiotics; 3 times more likely to have received PPI; and 2 times more likely to have received H2RB.

Between 1994 and 2004, antibiotic prescriptions per outpatient per year declined by about 1/3 while prescriptions for PPI increased. Community cases of *C. difficile* per year rose dramatically from less than 1 case per 100 000 patients to 22 per 100 000 patients.

Antibiotic exposure has, in the past, been considered almost a prerequisite for the diagnosis of

CDAD. In this study, only 37% cases had received antibiotics within the preceding 90 days. "The belief that prior antibiotic exposure is practically a prerequisite for *C. difficile* infection needs to be reevaluated."

"C. difficile -associated disease is becoming an important public health issue."

Primary care clinicians should consider that C. difficile infection can occur without prior antibiotic use. And that users of PPI, especially the elderly, may be at increased risk.

Case-control studies are not definitive. This requires confirmation.

A New Very Virulent Strain Resistant To Fluoroquinolones.

12-8   THE NEW *CLOSTRIDIUM DIFFICILE*

Old pathogens can emerge with increased virulence and challenge scientists to explain their rebirth, and clinicians to care for patients, and infection-control personnel to prevent their spread.

C. difficile appears to illustrate these challenges. It already has some distinctive features. It causes disease almost exclusively in the presence of exposure to antibiotics.[1]

Two articles in this issue of NEJM describe new gene-variant strains of *C. difficile* isolated from patients with *C. difficile*-associated disease (**CDAD**). The variant types were resistant to fluoroquinolones. They produced up to 23 times more toxins A and B than some other strains. One of the studies reported hospital incidence of CDAD of 2 per 100 admissions and a high mortality rate, especially in the elderly. In the majority of cases, fluoroquinolones were the inducing agent.

"A more virulent strain of *C. difficile* is causing epidemic disease."

Treatment consists of prompt discontinuation of the implicated offending agent, and administration of oral metronoidazole (*Flagyl*). Oral vancomycin should be considered in patients who do not have a prompt response.

"Particularly important is antibiotic stewardship, with restraint in the use of implicated antimicrobial agents."

[1]*See the previous article. It suggests that community-acquired* C. difficile-*associated disease may occur without prior antibiotic use.*

Intensive Glycemic-Control Had Long-Term Beneficial Effects In Reducing Risk Of Cardiovascular Disease.
12-9   INTENSIVE DIABETES TREATMENT AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 1 DIABETES The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)

This study assessed whether more intensive therapy, as compared with conventional therapy, would affect long-term incidence of *macro*-vascular complications (cardiovascular disease). Type 1 diabetes (**DM-1**) is associated with at least a 10-fold increase in cardiovascular disease.

The Diabetes Control and Complications Trial (**DCCT 1983-93**) randomized 1441 patients with DM-1 to: 1) intensive therapy, or 2) conventional therapy. Mean duration of 6.5 years. Mean baseline age = 27. At baseline, subjects had no, or minimal, microvascular disease; no hypertension; no hypercholesterolemia (by standards at the time); and no clinical evidence of cardiovascular disease.

At the end of 6 years, all participants were returned to their own health care providers and the Epidemiology of Diabetes Interventions and Complications study (**EDIC**) began. Ninety three % of the subjects were subsequently followed until 2005 (11 more years; total of 17 years). In the EDIC study, patients in both treatment group then received intensive therapy, During the subsequent 11 years, there were non-significant differences in the use of 3 or more daily injections of insulin.

(Ie, this report compares 6 years of intensive therapy + 11 years of continued intensive therapy with 6 years of conventional therapy + 11 years of intensive therapy.)

During the mean of 17 years, 46 cardiovascular events occurred in 31 patients in the 17-year intensive group

vs 98 events in 52 patients in those originally assigned to conventional therapy. (0.38 vs 0.80 events per 100 patient-years.)

At baseline, mean HbA1c was 9.1 % in both groups. At the end of DCCT (6 years), it was 7.4% in the intensive group *vs* 9.1% in the conventional group. At the end of the 17 years, mean levels were about equal in both groups (7.9% vs 7.8%).   The intensive group maintained HbA1c at a lower level; the HbA1c of those originally in the conventional group were subsequently treated intensively and their HbA1c fell to comparable levels.

Seventeen continuous years of intensive therapy resulted in greater sustained benefit on subsequent risk of cardiovascular event than the period of 6 years of conventional therapy followed by 11 years of intensive therapy. The original 6-years of intensive therapy, begun at a younger age, produced a sustained benefit.

The same glycemic mechanisms related to development of micro-vascular disease may also apply to the development of arteriosclerosis. Epidemiological evidence suggests that any elevation in glycemia, even within the subdiabetic range, increases risk of cardiovascular disease. This may be mediated by formation of advanced glycemic end-products

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The mean age at end of 17 years was 44. I would judge the benefits would continue to accrue over a more extended period of time.

The atherosclerotic process in patients with DM-1 begins at an early age. The earlier you start intensive treatment, the better.

The results could easily be extrapolated to patients with DM-2

The patients in the study did not meet the American Diabetes Association goal of a HbA1c 7.0% and under. Achieving this goal is difficult. Newer insulins would likely make achieving the goal easier.

Of course, treatment should include other interventions to reduce risk of cardiovascular disease (aspirin, statins, BP control, weight and abdominal girth control, increased physical activity, and especially tobacco cessation. (11% to 20% of subjects continued to smoke.)

"Low Cardiorespiratory Fitness Affects Approximately 1 Out Of 5 Persons Aged 12 Through 49 In The US"

12-1   PREVALENCE, AND CARDIOVASCULAR DISEASE CORRELATES, OF LOW CARDIORESPIRATORY FITNESS IN ADOLESCENTS AND ADULTS

Physical inactivity and poor cardiorespiratory fitness (ie, fitness) are associated with higher morbidity and mortality from all causes, including cardiovascular disease (**CVD**) and cancer. A recent large case-control study attributed 12% of myocardial infarctions to physical inactivity.

Our society is becoming increasingly less physically active.

This study describes the prevalence of low fitness in the US population age 12 through 49, and relates it to CVD risk factors.

Conclusion: Low fitness was associated with increased prevalence of CVD risk factors.

STUDY

1. The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional, nationally representative sampling of the non-institutionalized civilian US population. This report covers years 1999-2002.

2. Participants were adolescents (n = 3110) age 12-19, and adults (n = 2205) age 20-49. All were free of CVD. None had existing medical conditions, physical limitations, or abnormal hemodynamic parameters.

3. All underwent submaximal graded treadmill testing to achieve 75% to 90% of age-predicted maximum heart rate. Estimated maximal oxygen consumption (**VO2max**) by correlating heart rate response to reference levels of submaximal work. (Higher VO2max indicates more favorable fitness.)

   (*The determination of fitness was objective [treadmill testing]. This is a strength of the study*.)

4. Cutpoints were defined as low (< 20th percentile); moderate (20th -59th percentiles); and high (60th and higher).

5. Main outcome measures: 1) low fitness (defined using percentile cut points of estimated VO2max). and 2) other CVD risk factors.

RESULTS

1.

	Adolescents	Adults
Low fitness	33%	14%

   (This represents 7.5 million adolescents in the US, and 8.5 million adults.)

2. More than 25% of adults reported *no* moderate or vigorous physical activity in the past month.

3. Adults mean BMI = 27. About 20% had the metabolic syndrome.

4. Low fitness persons were 2 to 4 times more likely to be obese compared with those in the moderate-high fitness groups

5. Prevalence of low fitness was higher in adult females, blacks, and Mexican-Americans.

6. In all age groups, BMI and waist circumference were inversely related to low fitness.

7. Total cholesterol and systolic BP were higher in the low fitness groups, and HDL-cholesterol was lower.

DISCUSSION

1. "Low cardiorespiratory fitness affects approximately 1 out of 5 persons aged 12 through 49 in the US population." There is a disproportionate impact on adolescents, adult females, and non-white minorities.

2. The most striking indication of the health burden of low fitness is the strong association between obesity and CVD risk factors. BMI and waist circumference demonstrated the most consistent association with fitness. Mean values decreased in a nearly graded fashion with increasing fitness. The association is already present in adolescents and young adults.

3. Although adolescents are not generally considered at risk for having clinical CVD events in the short term, the development of risk factors during adolescence and young adulthood sets the stage for heart disease in the middle and older ages.

4. The relationship between low fitness and cardiovascular mortality is proposed to be mediated by the development of CVD risk factors including hypertension, diabetes, dyslipidemia, and the metabolic syndrome.

5. Physical activity training in efforts to improve fitness has been shown to lower the likelihood of developing risk factors, independent of changes in weight.

6. "Obesity and overweight could be described as the seminal public health problem today." The burgeoning obesity epidemic is the first sign of the trend of increasing morbidity and mortality from chronic diseases.

7. These data likely represent an underestimate of the true prevalence of low fitness in the population.

8. Historical evidence from the campaign to educate about the dangers of cigarette smoking indicates that education efforts, particularly among youth, can retard and reverse negative health behaviors.

CONCLUSION

Low fitness is a prevalent and important public health problem. It is associated with increased prevalence of CVD risk factors.

"Could Have A Role In The Initiation Or Progression Of Coronary Artery Disease And Stroke."
12-2   PERIODONTAL DISEASES

The term periodontal disease usually refers to the common inflammatory disorders (gingivitis and periodontitis) that are caused by pathogenic microflora in the biofilm (dental plaque) that forms adjacent to the teeth every day.

Gingivitis is the mildest form of periodontal disease. It is highly prevalent and is readily reversible by simple effective oral hygiene. Inflammation that extends deep into the tissues and causes loss of supporting connective

tissue and alveolar bone is termed *periodontitis*. The result is formation of soft tissue pockets, or deepened crevices between the gum and the tooth root. Severe periodontitis results in loosening of teeth, occasional pain and discomfort, impaired mastication, and eventually tooth loss. An estimated 13% of US adults have moderate to severe periodontitis.

CAUSE:

1. Oral microorganisms:

   The mouth contains hundreds of species of aerobic and anaerobic bacteria (many uncharacterized) living in symbiosis with a healthy host. These organisms grow on tooth surfaces in biofilms. They are attached to, and densely packed, against the tooth.

2. Tobacco:

   Smokers are much more likely to develop periodontitis. Smokeless tobacco may also lead to gingivitis, loss of tooth support, and precancerous leucoplakia at the site of quid placement.

   "In the USA, about half of the risk of periodontitis can be attributable to tobacco use."

3. Nutrition:

   Extensive epidemiological studies have failed to show an effect of minor hypovitaminoses on periodontal disease.

4. Osteoporosis:

   Evidence indicates that osteoporosis raises susceptibility to periodontal break down. The risk could be attenuated by estrogen replacement therapy.

5. Diabetes:

   Patients with well-controlled diabetes do *not* seem to be at increased risk. Those with poorly controlled diabetes are at raised risk.

PATHOGENESIS:

   Although bacteria are necessary for periodontal disease to take place, a susceptible host is also needed.

   An immune response to the plaque bacteria results in destruction of the periodontium. The host response is essentially protective, but both hypo-responsiveness and hyper-responsiveness of certain pathways can result in enhanced tissue destruction. Both the host and the bacteria release proteolyic enzymes which break down tissue.

   After all oral hygiene procedures (including tooth brushing) are ceased, the biofilm begins to develop within 24 hours and causes gingivitis in 2 to 3 weeks. Thorough cleaning returns gums to a healthy condition within about 1 week.

   Once a periodontal pocket forms and becomes filled with bacteria, the situation becomes largely irreversible. Gingival epithelium proliferates to line the pocket and even if treatment resolves the inflammation and some bone and connective tissue are regenerated, complete restoration of the lost tooth support is impossible.

DIAGNOSIS:

   The clinical diagnosis is based on visual and radiographic assessment.

Mild bleeding during tooth brushing is often a result of chronic gingivitis. It is usually only a minor annoyance.

Chronic periodontitis is usually asymptomatic until so severe that teeth shift and loosen. Patients may have periodontal abscesses and halitosis.

ASSOCIATIONS WITH SYSTEMIC DISEASES:

A. Pregnancy:

Several prospective cohort studies have reported a link between poor periodontal health and increased risk of complications of pregnancy—preterm birth, low birth weight, and preeclampsia.

B. Cardiovascular disease and stroke:

Inflammation has been implicated in the cause and pathogenesis of atherosclerosis. "Periodontal disease could have a role in the initiation or progression of coronary artery disease and stroke."

Periodontitis is associated with raised systemic concentrations of C-reactive protein, fibrinogen, and cytokines, all of which have been causally linked to atherosclerotic-induced diseases. Periodontitis treatment has been shown to reduce serum inflammatory markers and C-reactive protein.
In animals, periodontal bacteria can promote platelet aggregation.

One study reported that severe periodontitis was associated with increased intima-media thickening. Severe periodontal bone loss was associated with a nearly four-fold increase in risk for presence of carotid artery plaques.

A meta-analysis concluded that periodontal disease was associated with a 19% increase in the risk of future cardiovascular disease. A 12-year study suggested that periodontal disease and fewer teeth could be associated with a raised risk of ischemic stroke.

Since periodontal disease is so common, even a modest increase in risk could have profound public-health effects.

C. Pulmonary disease:

Various pulmonary infections have been associated with periodontal disease. There are reports that potential respiratory pathogens that cause pneumonia colonize the mouth of high-risk patients in intensive care units.

Preliminary studies indicate that oral hygiene with mechanical or antiseptic rinses can reduce the rate of respiratory infections in patients living in institutions.

PREVENTION AND TREATMENT:

Regular tooth cleaning can maintain the biofilm mass at an amount compatible with gingival health. "Unfortunately, few individuals achieve this, and exhortations to the public to clean teeth more thoroughly are generally ineffective in public health care."

Control of the biofilm by professionally administered oral hygiene can slow or stop periodontitis and tooth loss by many years.

Tooth brushing and use of dental floss to remove plaque are the most common ways of removing biofilm. They are effective if used daily. They require motivation.

Mouthwashes and toothpastes containing antibacterial drugs have been used as adjuncts. They can reduce biofilm and are generally not associated with emergence of resistant microbes. Used as adjuncts to cleaning methods, they can reduce gingivitis. Their role in preventing or treating periodontitis has not been established.

Tobacco use should be stopped.

Antibiotics: There is insufficient evidence that microbial assessment can improve treatment outcomes. A wide variety of antibiotics has been used, either alone or in combination with standard therapy. Limited data exists regarding their effect when used alone. Use runs the risk of adverse drug reactions and increased selection of resistant organisms. "Systemic antibiotics should be used only in conjunction with mechanical debridement." They can provide the greatest benefit to patients who do not respond to debridement alone, or who have fever and lymphadenopathy.

Letrozole Was Associated With Greater Reduction In Risk Of Recurrent Disease.
12-3   A COMPARISON OF LETROZOLE WITH TAMOXIFEN IN POST MENOPAUSAL WOMEN WITH EARLY BREAST CANCER

Among women with hormone-receptor-positive breast cancer (**BC**), tamoxifen (*Nolvadex*) reduces risk of breast cancer **(BC)** recurrence by 47%, and the risk of death by 26% About half of the women relapse.

Tamoxifen inhibits activity of estrogen by competitively binding to the estrogen receptor. Aromatase inhibitors block the conversion of androgens to estrogen, and reduce estrogen levels in tissue and plasma.

Third generation aromatase inhibitors:

Letrozole (*Femara* a non-steroidal—inhibits aromatase activity by over 99%)

Anastrozole (non-steroidal—inhibits aromatase activity by 97%)

Exemestane (steroidal—inhibits aromatase activity by 98%)

This study compared letrozole with tamoxifen therapy in postmenopausal women with hormone-receptor-positive BC

Conclusion: Letrozole was associated with greater reduction in risk of recurrent disease.

STUDY

1. Randomized, double-blind study entered over 8000 postmenopausal women (mean age 61).

2. All had operable invasive BC positive for estrogen receptors, progesterone receptors, or both. In all, the primary surgery had clear margins. None had evidence of metastatic disease.

3. Nodal status: negative in 57%; positive in 41%.

4. Estrogen-receptor positive and progesterone + receptor positive (63%).

Estrogen-receptor positive and progesterone-receptor negative (20%);

Estrogen receptor negative and progesterone-receptor positive (2%).

5. Randomized to:

    A. Letrozole (2.5 mg daily) alone for 5 years.

       Letrozole alone for 2 years followed with tamoxifen alone for 3 years.

    B. Tamoxifen (20 mg daily) alone for 5 years.

       Tamoxifen alone for 2 years followed by letrozole alone for 3 years.

5. Primary end-points included: 1) disease-free survival—time from randomization to the first event ending disease-free survival: 2) recurrence at local, regional, or distant sites; and 3) a new invasive cancer in the opposite breast.

6. Follow-up for up to 5 years. Median follow-up = 26 months.

RESULTS

1. Five year follow-up

	Letrozole (%)	Tamoxifen (%)
both groups (n = 4003)	both groups (n = 4007)	
5-y Disease-free survival	84	81.4
Breast cancer recurrence	10.3	13.6
Node-positive BC survival	77.9	71.4
Node-negative BC survival	88.7	88.7
Distant recurrence	4.4	5.8

2. The absolute % differences in favor of letrozole ranged from 1.4% to 6.2%. The number needed to treat with letrozole vs tamoxifen to benefit one patient ranged from 15 to 71.

3. Benefit from letrozole-alone was also greater than benefit from tamoxifen alone. (Data not shown.)

4. Benefit from letrozole was as evident in patients with progesterone-receptor positive status as with estrogen-receptor positive status.

5. Safety:

    A. More patients in the letrozole groups reported at least one protocol-specified adverse event of any severity (73% vs 63%).

    B. The number of patients with life-threatening or fatal adverse events was similar in both groups (1.7%).

    C. Adverse effects

	Letrozole (%)	Tamoxifen (%)
Cardiac event	4.1	3.8
Vaginal bleeding	3.3	6.6
Hot flashes	33.5	38
Night sweats	13.9	16.2
Fracture	5.7	4.0
Arthralgia	20.3	12.3

    D. Cholesterol: Both groups were associated with reductions—letrozole -1.8%; tamoxifen -14%. Hypercholesterolemia more common in the letrozole groups (44% vs 19%).

DISCUSSION

1. "Our study confirms the positive results reported in other trials of letrozole as adjuvant treatment for hormone-receptor positive breast cancer in postmenopausal women."

2. Of particular interest was the finding of a significant reduction in the risk of recurrences at distant sites. (Difference = 1.4% favoring letrozole.)

3. Patients who were node positive benefited more from letrozole. Node negative patients did not benefit.

4. The American Society of Clinical Oncology states that information is insufficient to determine the effect of aromatase inhibitors of cardiovascular disease, especially coronary disease.

CONCLUSION

In postmenopausal women with endocrine-responsive BC, adjuvant treatment with letrozole, as compared with tamoxifen, reduced risk of recurrent disease, especially at distant sites.

NEJM December 29, 2005; 353: 2747-57 Original investigation by the Breast International Group (BIG) 1-98 Collaborative Groups, Coordinating Center Berne Switzerland.

Study supposed by Novartis.

12-4   AROMATASE INHIBITORS—A TRIUMPH OF TRANSLATIONAL ONCLOLGY

(This editorial comments and expands on the preceding study.)

Great strides have been made in the diagnosis and treatment of early-stage breast cancer **(BC).**

Both screening and adjuvant (postoperative) therapy have increased survival. The benefit occurs in all subgroups of patients, regardless of the presence or absence of tumor cells in the draining lymph nodes. Benefit extends to women who are premenopausal and postmenopausal, and to those with estrogen-receptor-negative as well as estrogen-receptor-positive tumors.

BC consists of a heterogeneous group of cancers. They are now being classified into subgroups in order to delineate distinct characteristics and targets that will lead to tailored therapies.

A randomized trial reported in this issue of NEJM concerned postmenopausal women with early-stage BC. The aromatase inhibitor letrozole (*Fermara*) was compared with the estrogen-receptor blocker tamoxifen (*Nolvadex*). The findings validated the results of previous studies—letrozole was associated with a greater reduction in the incidence of relapse.

The incidence of both distant recurrence and contralateral BC was reduced. The benefit of letrozole was greatest in women who had positive nodes.

Five other trials have evaluated aromatase inhibitors alone, or with various combinations of tamoxifen for various lengths of time. All have reported more favorable outcomes with letrozole.

Questions remain: What is the optimal duration of therapy? Should tamoxifen or aromatase inhibitor be given first? Is sequential treatment optimal? Which aromatase inhibitor is better? Are aromatase inhibitors beneficial for premenopausal women after ovarian ablation? Are they beneficial in women whose tumors are progesterone-receptor positive? Progesterone-receptor negative?

Estrogen is synthesized from androstenedione and testosterone. The enzyme aromatase facilitates the synthesis. Aromatase inhibitors block the conversion to estrogen almost completely.

Unlike tamoxifen, aromatase inhibitors are not associated with an increased risk of thromboembolism or uterine cancer. But the incidence of serious cardiac events was more common in women given letrozole.

"All evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes, and who are at substantial risk of recurrent disease. "

NEJM December 29, 2005; 353: 2807-09 Editorial by Sandra M Swain, National Cancer Center, Bethesda, MD

A Major Cause Of Liver-Related Morbidity And Mortality

12-5 THE METABOLIC SYNDROME AS A PREDICTOR OF NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disese **(NAFLD)** is a major cause of liver-related morbidity and mortality. It has the potential to progress to cirrhosis and liver failure. Non-alcoholic steatohepatitis (**NASH)** is an intermediate stage of NAFLD. NASH is characterized by hepatic steatosis, liver cell injury, hepatic inflammation, fibrosis, and necrosis. It resembles alcohol-induced liver disease, but it occurs in people who do not abuse alcohol.

NAFLD is often associated with obesity, type 2 diabetes, dyslipidemia, and hypertension. Each of these abnormalities carries a cardiovascular disease risk. Together they are often categorized as the insulin-resistance syndrome, or the metabolic syndrome (**The MS).** The MS is an emerging problem worldwide. Its prevalence is increasing.

The MS consists of 5 variables: 1) high waist circumference, 2) elevated serum triglycerides, 3) reduced HDL-cholesterol, 4) elevated BP, and 5) elevated fasting plasma glucose.

This study characterized the longitudinal relationship between The MS and NAFLD.

Conclusion: The MS is a strong predictor of NAFLD.

STUDY

1. Prospective observational study followed over 4400 apparently healthy Japanese men and women age 21 to 80 who attended routine medical checkups. None abused alcohol. None were taking drugs. None had hepatitis B or C.
2. The examination included an abdominal ultrasound. The diagnosis of NAFLD was based on ultrasound using hepato-renal contrast and liver brightness as markers.

3. Correlated NAFLD with prevalence of The MS (3, 4, or 5 indicators to be present to diagnose The MS):

    1) Abdominal obesity (circumference > 102 cm in men and > 88 cm in women).

    2) Triglycerides > 150 mg/dL.

    3) HDL-cholesterol < 40 for men and < 50 for women.

    4) BP > 130/85.

    5) Fasting glucose > 110 mg/dL.

    (Because waist measurement was not available for the entire cohort, the investigators substituted a BMI of 25 or more for all participants as an index of obesity. This cutpoint has been proposed to diagnose obesity in Asian people.)

RESULTS

1. At baseline, 18% of the 4000 participants had NAFLD.

    NAFLD was more common in men than in women (25% vs 10%).

    In men, the prevalence of 3 or more criteria for The MS was more common in those who had NAFLD *vs* those who did not have NAFLD (40% *vs* 8% in women).

2. During a follow-up of 14 months, 241 men who did *not* have NAFLD at baseline developed NAFLD. These men had gained weight. About 10% of men who *had* NAFLD at baseline had normal ultrasound on follow-up These men had lost weight.

3. Among subjects who did not have NAFLD at baseline, those who met the criteria for The MS were more likely to develop NAFLD during follow-up. (Odds ratio = 4.0)

DISCUSSION

1. The MS was a strong risk factor for nonalcoholic fatty liver disease in apparently healthy Japanese men and women.

2. The MS is highly predictive of insulin resistance. Insulin resistance may play a pivotal role in the pathophysiology of NAFLD.

3. The investigators state that ultrasonography of the liver may lead to an incorrect diagnosis of NAFLD in 10% to 30%. US cannot distinguish between steatohepatitis and simple steatosis.

4. Generalization to non-Japanese is uncertain.

CONCLUSION

    Japanese persons with The MS had increased risk of developing NAFLD.

    Development and regression of NAFLD may occur in a substantial number of people with modest weight changes.

An editorial in this issue of the Annals (pp 753-54), first author Elizabeth E Powell, University of Queensland, Brisbane, Australia, comments and expands on the study:

The term NAFLD refers to a spectrum of liver disease in the absence of significant alcohol consumption. At the "benign" end of the spectrum, most patients with NAFLD have simple steatosis. About 10% have features of liver cell injury or fibrosis (non-alcoholic steatohepatitis—**NASH**).

The distinction between simple steatosis and NASH is important because their natural history differs. Patients with simple steatosis have a benign prognosis, at least from the standpoint of liver disease. Up to 20% of patients with NASH may ultimately develop advanced liver disease.

The prognosis of NASH-related cirrhosis is poor. About 1/3 develop liver failure or liver-related death. Hepatocellular cancer is a complication of NASH-related cirrhosis.

Although only a minority of patients with NAFLD develops advanced liver disease, it is causing alarm because of the high prevalence of NAFLD.

NAFLD can develop with very small increases in body weight. Small decreases in weight can cause regression of NAFLD. Lifestyle modification is the principle management strategy.

Increased waist circumference (abdominal obesity) is more closely associated with The MS than is BMI.

Once cirrhosis develops, fat and other histological features of steatohepatitis may regress, leaving inactive micronodular cirrhosis. It has been suggested that many cases previously regarded as cryptogenic cirrhosis may represent "burnt out" NASH.

Abdominal ultrasound is an imperfect tool to diagnose NAFLD. Without biopsy, it cannot be determined which patients have NAFLD or which have NASH. Liver function tests have not been helpful for diagnosis. We rely mainly on clinical factors. Biopsy is the gold standard for diagnosis.

An Important Therapeutic Agent With Widespread Applications.

12-6 THE MYRIAD USES OF BOTULINUM TOXIN

Botulinum toxin (**BTx**) is an important therapeutic agent with widespread applications. It is one of the most potent neurotoxins known. BTx derives its name from the Latin word *botulus*, "sausage". This refers to poisoning from badly preserved meat observed in the early 19th century. BTx is a protein produced by *Clostridium botulinum.*

BTx targets peripheral cholinergic systems and prevents the release of acetylcholine, blocking synaptic transmission.

It was first used therapeutically in the 1970s to treat strabismus. Over the past 24 years, it has proved to be remarkably successful in relieving spasms, unwanted movements, abnormal postures, and pain associated with many disorders. It has made it possible to control some neurological conditions that once required systemic therapy. Double-blind placebo-controlled clinical trials have shown that it safely and effectively resolves excessive muscle contraction in dystonia (a condition characterized by sustained twisting and posturing movements); hemifacial spasm; and spasticity from stroke, cerebral palsy, brain trauma, and multiple sclerosis. It has also been successful in patients with hyperhidrosis due to autonomic disorders. More recently, BTx has attracted interest in headache and pain disorders, and for cosmetic uses.

Long-term studies report that it continues to be safe and effective after repeated use for 15 years.

The effect of one injection may last for several months, but it is self-limited. It has few side effects—the main one being unwanted weakness in the injected muscles or adjacent muscles. The effects on muscle tone and involuntary movements usually last longer than the weakness does.

Excessive weakness can be avoided by using low doses, and by electromyography-guided injections.

Electromyographic guidance is helpful for accurately localizing muscles, particularly for limb conditions such as writer's cramp.

BTx has also been reported to be useful to treat pain through yet unknown pain-relieving mechanisms. This issue of *Annals* reports effectiveness in treatment of the pain of lateral epicondylitis ("tennis elbow")[1]. Compared with placebo injections, BTx significantly relieved pain at 4 and 12 weeks. "These findings are promising because BTx injections are less harmful than other therapies for lateral epicondylitis, such as corticosteroids or surgery."

The number of applications is expanding. Currently, physicians should consider BTx of patients who have focused involuntary movements.

Annals Int Med December 6, 2005; 143: 838-39 Editorial by Seth L Pullman, Columbia University Medical Center, New York NY

[1] "Treatment of Lateral Epicondylitis with Botulinum Toxin" Annals Int Med December 6, 2005; 143: 793-97 original investigation, first author Shiu Man Wong, Chinese University of Hong Kong, China.

C. difficile *Infection Is Becoming An Important Public Health Issue. It May Occur Without Prior Antibiotic Use.*

12-7 USE OF GASTRIC ACID-SUPPRESSIVE AGENTS AND THE RISK OF COMMUNITY-ACQUIRED *Clostridium difficile*- ASSOCIATED DISEASE

C. difficile is an important cause of nosocomial diarrhea. *C. difficile*-associated disease (**CDAD**) is also a cause of diarrhea in the community. It has been reported as the 3rd most common cause of infectious diarrhea in persons over age 75. The absolute number of CDAD cases in the community could be significant.

Gastric acid constitutes a major defense mechanism against ingested pathogens. Loss of stomach acid has been associated with colonization of the normally sterile upper gastrointestinal tract.

Suppression of stomach acid production by proton-pump inhibitors (**PPI**) and histamine2-receptor blockers (**H2RB**) may lead to increased likelihood of CDAD.

This study determined whether gastric acid-suppressive agents increase risk of CDAD in the community.

Conclusion: These agents, especially PPI, were associated with increased risk of community-acquired CDAD.

STUDY

1. Case-control study compared:

1) Cases of community-acquired CDAD (n = 1233; mean age 72—no hospitalization in the prior year), with

2) Ten matched controls without CDAD (n = 12 330—also not hospitalized in the prior year).

2. Determined current use of antibiotics, PPI and H2-RB in both groups.

RESULTS

1. Comparison   Cases   Controls:

	Cases	Controls
Antibiotics	37%	13%
PPI	23%	8%
H2RB	8%	4%

3. Cases were 3 times more likely than controls to have received antibiotics; 3 times more likely to have received PPI; and 2 times more likely to have received H2RB.

4. An unexpected finding: cases were 1.3 times more likely to have received NSAIDs excluding aspirin. *(The investigators state this requires further study.)*

5 Between 1994 and 2004:

A. Antibiotic prescriptions per outpatient per year declined by about 1/3 while prescriptions for PPI increased.

B. Community cases of *C. difficile* per year rose dramatically from less than 1 case per 100 000 patients to 22 per 100 000 patients.

DISCUSSION

1. This increased risk of CDAD associated with PPI (*vs* H2RB) may be related to the greater degree of gastric acid suppression by PPI.

2. Decreased gastric acidity is a risk factor for other infectious diarrheal diseases (traveler's diarrhea, salmonellosis, cholera).

3. Antibiotic exposure has, in the past, been considered almost a prerequisite for the diagnosis of CDAD. In this study, only 37% cases had received antibiotics within the preceding 90 days. "The belief that prior antibiotic exposure is practically a prerequisite for *C. difficile* infection needs to be reevaluated."

4. Acid-suppressive agents are among the most frequently prescribed medications. Their use by the public is increasing. While the overall rate of CDAD is lower than in hospital settings, incidence in the community appears to be increasing significantly. This has occurred in the face of data suggesting that outpatient antibiotic use is declining.

5. "*C. difficile* -associated disease is becoming an important public health issue."

CONCLUSION

Use of acid-suppressive drugs, particularly PPIs, is associated with increased risk of community-acquired *C. difficile*-associated diarrhea.

A New Very Virulent Strain Resistant To Fluoroquinolones.

12-8 THE NEW *CLOSTRIDIUM DIFFICILE*

Old pathogens can emerge with increased virulence and challenge scientists to explain their rebirth, and clinicians to care for patients, and infection-control personnel to prevent their spread.

C. difficile appears to illustrate these challenges. It already has some distinctive features: it causes disease almost exclusively in the presence of exposure to antibiotics[1]; it is the only anaerobe that poses a nosocomial risk; and it produces a toxin in vivo only in the colon.

About 3% of healthy adults and up to 40% of hospitalized patients are colonized with *C. difficile*. In healthy persons, the organism is inactive in the spore form. It is assumed that a perturbation of the competing flora promotes a conversion to the vegetative forms that then replicate and produce toxins.

The history of antibiotic-associated colitis (**AAC**) began with a multitude of reports early in the antibiotic era. At first, AAC was generally attributed to *S aureus*. *C. difficile* was reported as the cause in 1978. Within 3 years, toxins A and B were described and the cytotoxin assay became the standard diagnostic test.

The characteristic pathological finding is pseudomembranous colitis. Clinical studies indicate that almost any antibiotic with an antibacterial spectrum could cause this complication. Oral vancomycin became the standard treatment.

Over the past 2 decades, *C. difficile* has become the most commonly recognized microbial cause of nosocomial diarrhea. This reflects the high rates of antibiotic use in hospitals. The most commonly implicated agent in the 1970s was clindamycin; in the 1980s, cephalosporins. Recently, fluoroquinolones have played a prominent role.

A 13-year study of *C. difficile*-associated diarrhea reported the rate increased by a factor of 4 during this period. The disease became increasingly severe. Major risk factors were age over 65, and receipt of fluoroquinolones.

Two articles in this issue of NEJM[2,3] describe new gene-variant strains of *C. difficile* isolated from patients with *C. difficile*-associated disease (**CDAD**). The variant types were resistant to fluoroquinolones. They produced up to 23 times more toxins A and B than some other strains. One of the studies reported hospital incidence of CDAD of 2 per 100 admissions and a high mortality rate, especially in the elderly. In the majority of cases, fluoroquinolones were the inducing agent.

"A more virulent strain of *C. difficile* is causing epidemic disease at selected locations, and is associated with more frequent and more severe disease, as indicated by higher rates of toxic megacolon, leukemoid reaction, shock, requirement for colectomy, and death."

Treatment consists of prompt discontinuation of the implicated offending agent, and administration of oral metronoidazole (*Flagyl*) Oral vancomycin should be considered in patients who do not have a prompt response.

"Particularly important is antibiotic stewardship, with restraint in the use of implicated antimicrobial agents."

[1] See the previous article. It suggests that community-acquired C. difficile-associated disease may occur without prior antibiotic use.

[2] "An Epidemic, Toxin Gene-Variant Strain of *Clostridium difficile*" (pp 2433-41), first author L Clifford McDonald, Centers for Disease Control and Prevention, Atlanta GA

[3] "A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*-Associated Diarrhea with High Morbidity and Mortality." (pp 2422-41) first author Vivian G Loo, McGill University Health Center, Montreal, Canada.

Intensive Glycemic-Control Had Long-Term Beneficial Effects In Reducing Risk Of Cardiovascular Disease.

12-9   INTENSIVE DIABETES TREATMENT AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 1 DIABETES The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)

Hyperglycemia appears to play a central role in the pathophysiology of diabetes complications.

Intensive diabetes therapy aimed at near normoglycemia reduces risk of *micro*-vascular complications of type 1 diabetes (**DM-1**)—retinopathy, nephropathy, and neuropathy..

This study assessed whether more intensive therapy, as compared with conventional therapy, would affect long-term incidence of *macro*-vascular complications (cardiovascular disease). DM-1 is associated with at least a 10-fold increase in cardiovascular disease.

Conclusion: Intensive glycemic-control had long-term beneficial effects in reducing risk of cardiovascular disease.

STUDY

1. The Diabetes Control and Complications Trial (DCCT 1983-93) randomized 1441 patients with DM-1 to: 1) intensive therapy, or 2) conventional therapy. Mean duration of 6.5 years. Mean baseline age = 27. At baseline, subjects had no, or minimal, microvascular disease; no hypertension; no hypercholesterolemia (by standards at the time); and no clinical evidence of cardiovascular disease.

2. Intensive therapy consisted of 3 or more daily insulin injections, or treatment with an insulin pump. Doses were adjusted based on at least 4 daily self-monitored blood glucose measurements. Glucose goals were 70 to 120 mg/dL before meals, and less than 180 after meals. The goal for HbA1c was less than 6.05%.

3. Conventional therapy had no glucose goals beyond those needed to prevent symptoms of hyperglycemia and hypoglycemia, and consisted of 1 or 2 daily injections of insulin.

4. During the 6-years of the DCCT trial, fewer cardiovascular events (non-fatal myocardial infarction, stroke, death from cardiovascular disease, angina, need for coronary revascularization) occurred in the intensive group. The numbers of events were small in this relatively young cohort. This precluded definitive conclusions. Consequently, the trial was extended.

5. At the end of 6 years, all participants were returned to their own health-care providers, and the EDIC study began. Ninety three % of the subjects were subsequently followed until 2005 (11 more years; total of 17 years). Patients in both treatment groups then received intensive therapy. During the subsequent 11 years, there were non-significant differences in the use of 3 or more daily injections of insulin.
(Ie, this report compares 6 years of intensive therapy + 11 years of continued intensive therapy with 6 years of conventional therapy + 11 years of intensive therapy.)

RESULTS

1. During the mean of 17 years, 46 cardiovascular events occurred in 31 patients in the 17 year intensive group vs 98 events in 52 patients in those originally assigned to conventional therapy. (0.38 vs 0.80 events per 100 patient-years.)

2. At baseline mean HbA1c was 9.1 % in both groups. At the end of DCCT (6 years), it was 7.4% in the intensive group *vs* 9.1% in the conventional group. At the end of the 17 years, mean levels were about equal in both groups (7.9% vs 7.8%). The intensive group maintained HbA1c at a lower level. The HbA1c of those originally in the conventional group, after being referred back to their original health-care providers were treated intensively and their HbA1c fell to comparable levels.

DISCUSSION

1. Seventeen continuous years of intensive therapy resulted in greater sustained benefit on risk of cardiovascular event than the period of 6 years of conventional therapy followed by 11 years of intensive therapy. (The 6 years of intensive therapy, begun at a younger age, had a sustained benefit.) The pathophysiological mechanisms for the prolonged effects of early intervention are not clear. The authors refer to it as "metabolic memory".

2. The same glycemic mechanisms related to development of micro-vascular disease may also apply to the development of arteriosclerosis. Epidemiological evidence suggests that any elevation in glycemia, even within the subdiabetic range, increases risk of cardiovascular disease. This may be mediated by formation of advanced glycemic end-products

3. Intensive therapy should be implemented as early as possible.

CONCLUSION

Intensive diabetes therapy has long-term benefits on the risk of cardiovascular disease in patients with type 1 diabetes.