

DIABETES MANAGEMENT™

The Complete Diabetes Disease State Management Resource

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Studies show exercise is crucial to keeping diabetic patients healthy

Programs can be developed for just about anyone

There are plenty of studies demonstrating how exercise helps patients control the risks associated with diabetes — chances are good you already are a believer. But your patients may not share your enthusiasm unless you explain why keeping active is worthwhile to them. If you talk about these exercise benefits with your patients, you may be able to entice the sedentary to become active:

- If they have diabetes, exercise can reduce or even eliminate the need for medication to control their disease.
- For patients at risk of developing Type 2 diabetes, exercise and weight control often can prevent or delay the disease from developing.
- Those who maintain a sedentary lifestyle face dramatically higher risks of dying from a heart attack.

For many diabetics, it comes down to realizing exercise, like their medication, is essential to preserving their quality of life and helping them stay as healthy as they can. “How well a diabetic does depends very much on exercise,” notes **Paul Thompson**, MD, president of the American College of Sports Medicine and cardiac director of preventive care at Hartford (CT) Hospital.

“I’d say anyone who wants to begin an intensive exercise program should see a doctor first. But a diabetic patient who is sedentary or obese should probably have a full cardiac evaluation first,” says endocrinologist **William Isley**, MD, an associate professor of medicine

KEY POINTS

- Exercise is a cornerstone of diabetes management.
- Patients and care teams should agree on what is needed and what patients will tolerate.
- Followed carefully, an exercise program can delay or even prevent the onset of Type 2 diabetes.
- For those with diabetes, exercise can reduce or even eliminate need for oral agents and/or insulin.

The Hard Facts

- About half of all diabetics have coronary artery disease (CAD).
- More than 50% of diabetics with CAD die from cardiovascular causes.
- The risk of cardiac death is three times higher in diabetics than in nondiabetic patients.

at the University of Missouri in Kansas City and director of the dyslipidemia clinic at the Lipid and Diabetes Research Center at St. Luke's Hospital, also in Kansas City.

Isley, a runner who has completed three marathons, urges clinicians and patients that persistence and moderation may produce better long-term results than an aggressive start that quickly fizzles out.

"While patients need to be active, being active in the usual daily activities may be better than joining a gym, being very diligent for 12 weeks, and then never going again," he says.

Isley says clinicians need to focus on exercise for patients of all age groups. Lately, the need to get patients moving is most apparent in what he calls an "epidemic" of Type 2 diabetes among teen-agers and children — whom he describes as "couch potatoes whose only exercise is the thumb on the remote."

Motivate, don't intimidate

The idea is not to use scare tactics or rigid routines. Isley recommends a practical approach to getting patients to stay active: "Find out what the patient is willing to do and what the patient will tolerate."

Then patients should see results. Not only does exercise improve insulin sensitivity, it also increases high-density lipoprotein (HDL) levels and helps patients lose weight and generally feel better and more motivated, says **Linda Haas**, RN, PhC, CDE, president for health care and education of the American Diabetes Association and a clinician at the VA Medical Center in Seattle.

Haas has two warnings for this group of patients:

- Diabetics with signs of retinopathy should not run or engage in weight training.
- Those taking insulin or sulfonylureas should

monitor their blood glucose carefully before and after exercise to determine if the activity is causing hypoglycemia.

Haas recommends individual assessments, including cardiac stress tests for all patients older than 35 who are planning to begin an exercise program, "since people with diabetes have a lot of asymptomatic cardiovascular disease."

She also supports the U.S. surgeon general's recommendation for 20 to 30 minutes of exercise every day, but not necessarily all at the same time. Five- or 10-minute exercise breaks can be just as effective, Haas says. "If we can get folks to increase what they're doing, that's good."

The amount of exercise necessary for fitness has been the subject of great controversy. "It is

Guidelines for Diabetics and Their Caregivers

- Achieve appropriate blood glucose control before starting an exercise program.
- Check blood glucose levels before and after exercise to understand how blood glucose responds to various types of exercise and intensities.
- Keep exercise programs moderate and consistent, using:
 - regular aerobic exercise (**see note about retinopathy near end of this box**);
 - strength training (weightlifting) if there are no signs of retinopathy;
 - flexibility and stretching.
- Understand that a regular exercise program may change medication needs over time. Patients' need regular follow-ups with their health care team so personal status can be assessed and tracked.
- Be aware that exercise may change a patient's nutritional and caloric needs.
- Remember that diabetics taking insulin should not inject it into the working muscle shortly before exercise. The abdomen is the best site.
- Avoid weightlifting and running if there are signs of retinopathy.
- Be sure to have frequent foot examinations after beginning an exercise program.

Getting a Big Bang for Your Exercise Buck

Activity	Cost
Mall walking	\$50 for decent pair of walking shoes. Ask salesperson for advice on proper fit and brand for your needs. Keep an eye out for sales and discounts, too.
Dancing	Free — if you do it at home.
Jumping rope	No need to get fancy here. A 50-cent section of soft nylon rope with knotted ends works well. Wear supportive shoes and gradually work on how long you can jump rope at one time.
Homemade weights	Free — if you use canned goods or other heavyweight items loaded into bags at home. Small hand or leg weights are fairly inexpensive, about \$10.
Stair climbing	Free — if you do it at home, at the mall, or in a public building.
Exercise videos	Free — Borrow them from the library and make copies.

extremely difficult to determine how much exercise is necessary to prevent the complications of diabetes in someone who is already diagnosed with the illness,” notes **Tedd Mitchell**, MD, director of internal and sports medicine at the Cooper Clinic Aerobics Centers in Dallas.

It’s easier to look at healthy patients and compare their risk of developing the disease according to how active they are. Mitchell and other researchers at Cooper found that inactive men over 30 face nearly four times the risk of developing Type 2 diabetes compared with fit, physically active men.

Mitchell has some caveats of his own for diabetics beginning an exercise program:

☐ Know your sugar.

“People who are diabetic need to appreciate that if their sugar is uncontrolled with the onset of exercise [greater than 250 mg/dL], blood glucose can actually rise rather than fall during exercise,” he says.

☐ Be aware of how you react to the time of day.

Hypoglycemia is more likely during night exercise than during daytime, Mitchell says, because of diurnal variation in growth hormone levels.

☐ Know the effects of insulin.

He also cautions that exercise performed shortly after taking a regular insulin injection can drop blood sugars dangerously because the exercise speeds up the absorption of insulin.

☐ Consider your body’s nutritional needs for longer workout sessions.

Mitchell also warns prolonged, intense exercise (activity lasting more than two hours such as marathons, triathlons, etc.) increase the need for supplemental food and should be accompanied by additional carbohydrate intake every 30 minutes.

While the Cooper study involved only men, Mitchell notes that it “would be our best guess” that the benefits would be seen in women and children as well.

Isley adds some studies suggests diabetes can cancel the hormonal protection that premenopausal women have from heart disease, so women should monitored as closely as men.

[William Isley can be reached at (816) 932-3100, Linda Haas at (206) 764-2721. Contact Tedd Mitchell at (972) 239-7223, Paul Thompson at (860) 545-5000, and Kathy Mullooly at (617) 732-2400.] ■

Lure patients with instant gratification

Kathy Mullooly, MS, CDE, director of exercise physiology at the Joslin Diabetes Center in Boston, has a few suggestions to encourage patients to exercise.

The one she's found most effective plays right into what she calls a cultural hunger for instant gratification: She takes blood sugars before and after an exercise session to show patients how quickly their sugars are affected.

"They see their sugars change after just 20 minutes of simply moving around the gym or riding the exercise bike or walking on the treadmill — something they consider easy. It's immediate, and it reinforces why activity is good, so they make an informed decision to continue it," Mullooly says.

She recommends moderate exercise with incremental increases in the activity levels. "If you tell people they're going to have to exercise every day for the rest of their lives, they'll run away," she says. "But if you get them from zero exercise to one day a week, they'll begin to see the improvement; they'll feel better, maybe even lose a little weight."

An exercise program can be as simple as encouraging patients to walk up stairs or park their cars at the outskirts of a parking lot so they have to walk farther. "Go with what they like to do. If somebody likes hunting or cycling, encourage that," Mullooly says. "Keep the level where it doesn't overwhelm them. Take a more reasonable approach."

Mullooly's clinic also offers small rewards for patients. Those who accumulate stars next to

Some exercise protection can last for years

A Japanese study shows that fitness early in life provides protection from diabetes decades later.

Researchers at the Juntendo University School of Medicine in Tokyo studied army officers between 30 and 39 years old who ran a 1,500-meter event. The ones who completed the course in about six minutes were three times more likely to go on to develop impaired glucose tolerance in their 50s than those who had completed the course in 5 minutes. ■

Literature Review

- ✓ Inactive men face nearly four times the risk of developing diabetes compared with fit, physically active men:
Wei M, Gibbons L, Mitchell T, et al. The association between cardiorespiratory fitness and impaired fasting glucose and Type 2 diabetes mellitus in men. *Ann Intern Med* 1999; 130:89-96.
- ✓ Men who maintain physical fitness during their 30s have a significantly reduced risk of impaired glucose tolerance during their 50s:
Takemura, et al. The protective effect of good physical fitness when young on the risk of impaired glucose tolerance when old. *Prev Med* 1999; 28:14-19.
- ✓ High-risk patients with Type 2 diabetes who cannot exercise for a variety of health reasons were seven times more likely to die from a heart attack than similar patients who were able to exercise:
Vanzetto G. Prediction of Cardiovascular Events in clinically selected high risk NIDDM patients. *Diabetes Care* 1999; 22: 19-26.

their names for 10 or 15 sessions at the gym are rewarded with a small gift to help them manage their condition, perhaps some lancets or a sharps disposal container. "They have a lot of fun with this," she says. "It can be adapted for people working at home, if they put a dollar in a jar every time they exercise and then at a certain point they treat themselves, perhaps with a new shirt or a night out at the movies."

A French study reported in the January issue of *Diabetes Care* showed that those who can't exercise due to medical conditions face a high risk of death from heart attacks.

The subjects at the University of Grenoble were all Type 2 diabetics with two or more of these cardiac risk factors:

- ✓ over 65 years of age;
- ✓ active smoking;
- ✓ high blood pressure;
- ✓ hypercholesterolemia;
- ✓ history of coronary artery disease;
- ✓ peripheral vascular disease;
- ✓ abnormal resting EKG or microalbuminuria.

A Widely Accepted Exercise Program

1. Aerobic exercise for 30 to 45 minutes at least three times a week — include gradual warm-up section, main exercise section, and winding-down (or warm-down) section.
2. Stretching for five to 10 minutes after exercise.
3. Resistance training at least three times a week, repetitive lifting of weights using major muscle groups. ■

Some patients had as many as six risk factors. About half the patients in the study couldn't exercise for a variety of reasons: extreme obesity, chronic fatigue, peripheral neuropathy, pulmonary disease, peripheral vascular disease, heart failure with exertional dyspnea, or previous cerebrovascular accident.

Those who could not exercise had a mortality rate seven times higher than those who exercised.

Most people, however, do not have clinical reasons to avoid exercise. Experts agree few people can use that excuse to keep them from doing some sort of medically recommended activity. "We are very much in favor of walking," says Thompson. "Anybody can do it anywhere, and it doesn't require any equipment."

[Contact Kathy Mullooly at (617) 732-2400.] ■

Physical activity and diabetes

Ralph Hall, MD

Emeritus Professor of Medicine
School of Medicine
University of Missouri-Kansas City

(Commentary from Diabetes Management Consulting Editor)

It has been conclusively demonstrated that exercise can delay the onset of arteriosclerotic vascular disease and reduce the morbidity and mortality from heart attack and stroke. It has also been demonstrated that physical activity can delay, and most likely prevent, the onset of Type 2 diabetes in some patients.

The benefits of physical activity have not been as conclusively documented for Type 1 diabetes. However, the favorable effects of exercise on cardiovascular risk factors such as blood pressure, lipoproteins, and clotting factors show that exercise may reduce cardiovascular morbidity and mortality in patients with Type 1 diabetes.

Hein et al¹ demonstrated that physical activity was a greater predictor of ischemic heart disease (IHD) than physical fitness and that the benefits were dose-related. The more frequent and more intense the exercise, the greater the reduction in IHD. Lee and Paffenbarger point out, "Physical activity is an optional activity, while physical fitness is an achieved condition.

Physical activity modifies physical fitness over time, whereas physical fitness limits the amount of physical activity that can be performed."² Thus, physical activity and physical fitness each may act independently to increase longevity and reduce morbidity.

The study by Hein's group involved 4,999 men ages 40 to 59 and lasted 17 years. This study removed one of the criticisms that physical fitness, which has a strong genetic component, made it difficult to conclude that physical activity decreased the occurrence of cardiovascular disease. Critics claimed that those who were genetically fit tended to exercise and benefited more from exercise. Hein's studies, however, showed that less fit men who exercised had less cardiovascular disease than fit men who were sedentary. In another report by Sandvik et al, it was also found that there was a dose-response relationship. It also pointed out that the dose-response relationship could not have been detected if the study had been carried out for fewer than 10 years.³

Blair and others,⁴ have demonstrated that moderate physical activity can markedly reduce the incidence of cardiovascular morbidity and mortality. This was true even though the exercise program was begun during middle age in unfit subjects.

When the guidelines for physical activity were released by the Centers for Disease Control and Prevention and The American College of Sports Medicine, a controversy immediately erupted.

The recommendations from these two organizations was for moderate exercise. Paul Williams of

The Lawrence Berkeley National Laboratory in Berkeley, CA, and Paul Thompson, MD, of Hartford (CT) Hospital, both noted authorities in the field of exercise science, were concerned that too little exercise was being recommended. A review in *Science*, in which they were quoted,⁵ noted the dilemma. "Recommend too vigorous a regimen and people may be scared off; Recommend easier goals and many may be deterred from getting the full benefits of exercise."

Two recent publications have demonstrated that there are many benefits to a program of moderate exercise, confirming the results of Blair et al.^{6,7}

Improvements in cardiovascular risk factors occurred in both structured programs and in people who increased their activity through lifestyle changes in physical activity such as walking, climbing stairs, etc. The use of moderate physical activity, in the opinion of many experts, is more likely to elicit greater overall benefit. Those who wish to do more, however, should be encouraged to do so.

Endurance exercise has been the principal activity emphasized in the past as having the greatest benefit. Recent research indicates, however, that there is much benefit to be gained from resistance exercise. Resistance exercise has been shown to favorably effect insulin resistance, weight gain, lipoproteins, bone density, and other cardiovascular risk factors. It will correct many of the effects of aging by improving balance, strength, and increased muscle mass. Those with the least strength have the greatest percentage increase in strength in only a few weeks.⁸

There is much to be gained using an exercise program that includes all three elements of exercise:

1. **resistance training;**
2. **aerobic exercise;**
3. **stretching.**

It is the responsibility of all of us who work with patients with diabetes to be current in our knowledge of the benefits of exercise, as well as the potential risks. This knowledge is especially important if we are to safely manage older Type 2 diabetics and diabetics with neurologic and cardiovascular complications.

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3. Sandvik L, Erikssen J, Thaulow E, et al. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med* 1993; 328:533-537.

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8. Evans WJ. Exercise training guidelines for the elderly. *Med Sci Sports Exerc* 1999; 31:12-16. ■

When patients tell 'the big lie'

Ways to build a relationship of trust

It happens all the time. Newly diagnosed diabetic patients come into the clinic with their first monthly diary, recording the daily readings of their glucose monitor. It looks beautiful. There are no high numbers.

Then the clinician hits the glucose monitor's memory button. When the instrument's list of recorded readings doesn't match the diary, the doctor knows a little creative writing has been done. The patients are either changing the numbers to make the diary look like the disease is under control or making up the numbers for the diary because they are not using the glucose meter at all.

"Many of them [patients] don't realize there is a memory button, and we can see that there are

KEY POINTS

- Many diabetic patients, fearful of condemnation from health care practitioners, fail to report symptoms of complications or high monitor readings.
- Individualized plans help patients over the hurdles of fear.
- There are creative ways for physicians and diabetic care teams to help patients feel confident in their ability to manage the disease.

no numbers at all or there are high numbers,” says **Mary O’Connor Root**, BSN, RN, CDE, manager of the diabetic patients self-management education program at Englewood Hospital and Medical Center in Englewood, NJ.

In the same way, a patient may feel tingling in the feet, an early indicator of diabetic neuropathy, but doesn’t tell the doctor. The fear that the condition is deteriorating and that insulin may be needed, or perhaps even more drastic treatment for the complication, keeps the patient quiet. A patient may even feel the doctor will be angry.

“As soon as he tells the physician he has this symptom, the physician will say, ‘If you were following everything I tell you, this wouldn’t be happening,’” says **Jim Nolan**, president and CEO of the Institute for Diabetic Discovery, an independent research facility in Brantford, CT.

Why do patients tell the big lie? Quite simply, experts say, it’s because they are caught in a web of guilt and fear that their health care providers don’t understand. They haven’t built a relationship of trust with their care team, says Nolan.

“They will tell us what they think we want to hear,” says Root. “They are afraid the doctor or nurse or educator will scream and yell at them for not doing what they should be doing.”

There is “layer upon layer of dysfunction” on the part of patient and practitioner, says **Stanley Feld**, MD, FACP, MACE, past president of the American Association of Clinical Endocrinologists (AACE) and an endocrinologist on staff at Presbyterian Hospital of Dallas. Patients don’t lie, he says. They just don’t have access to a system that gives them the information they need to control the disease themselves.

Don’t ask, don’t tell

Nolan says his long experience with endocrinologists and diabetologists shows that a patient almost never brings up his symptoms and doctors frequently don’t ask. “He wants to believe he is normal. Neither side wants to admit everything isn’t hunky-dory. Most physicians don’t realize that psychology is 98% of the job in treating a diabetic.”

The psychology is needed on the other side, too, Nolan says. When patients are not doing their part to control their diabetes, doctors don’t really want to admonish them. Physicians often fear if they sound like a police officer all the time, patients will not come to see them at all. So patients continue to mismanage themselves until

their condition reaches a crisis point.

Root starts by taking away the guilt. “I tell them there are no good or bad numbers, and if they do their monitoring, no matter what the numbers, I won’t scream and yell. I use everyday words. If you use big college words, they’ll look at you like it’s Greek.”

Most of all, she says, health care professionals need to look at their patients as individuals, “As Mary Smith who has diabetes, not ‘that diabetic patient.’”

That’s the beginning of a relationship of trust.

“You can’t beat people into compliance,” agrees Feld. Instead, he says, “You have to create an environment where there is enough education.”

People are often less than truthful in reporting their symptoms, he says, “but it’s not really a lie. People are embarrassed to admit they don’t comply or they don’t know what they should do.” These feelings are particularly common when patients are first diagnosed, Feld says. “Their minds are opening, but they are scared stiff.”

Also, he adds, physicians rarely deal with education and frequently are not really part of a diabetes care team. “They respond to sky-high HbA1cs by adding more medication. The patient feels like a truck ran over him. If I make you feel worse every time I see you, what happens is the patient comes back but doesn’t tell you he feels worse and maybe he even stops taking his medication.”

Feld helped design the AACE’s Patients First program, which distributed half a million brochures containing a patient-physician contract detailing the responsibilities of each and signed by the patient and the doctor. (**See brochure, inserted in this issue.**)

“What drives compliance is the sense of high responsibility on the part of both physician and patient,” Feld says.

Root explains that managing diabetes is an enormous task. A patient must deal with it every day for the rest of his life, “so we take it one step at a time. It’s virtually impossible for them to do everything 100% of the time.”

For many diabetics, there is a great fear of what the future holds for them. One of the biggest fears is the fear of the insulin needle. “We help get over their biggest fear first,” Root says. “So if it’s the needle, we help them give themselves the first shot. They find out it’s not very painful and then they can go on.”

She says another key is to be flexible, to individualize care and “to work with what the

patient will do.” She recalls a 12-year-old patient a few years ago who told her he wouldn’t do anything if he couldn’t have his two packaged cupcakes in the morning. “So we worked out his exchanges and his meal plans so he could do that. He came back recently. He’s now in his 20s, and he’s doing great. He just wanted to thank us for working with him in that way.”

Root also says it’s important to make diabetes education fun. She has devised a diabetic Jeopardy game to test the patients’ grasp of material. Her clinic has an adult diabetic support group, and she takes it slowly at the beginning.

The key is letting them have small successes so they are eager to tackle the next step, she says. “I give them one or two things to work on over the next month and set realistic goals that they tell me they can achieve. That’s what works.”

[Mary O’Connor Root can be reached at (201) 894-3495. Contact Jim Nolan at (203) 789-1872 and Stanley Feld at (972) 233-3057.] ■

Group calls for sweeping funding for research

Battle plans to reverse toll of diabetes

The congressionally mandated Diabetes Research Working Group (DRWG) unveiled its battle plans in late February and called on Congress to take up the challenge by allocating \$827 million toward the race for prevention and a cure.

The high price tag will pay off in the end if headway is made against the disease, which costs \$100 billion a year in health care and an untold toll in terms of human misery, says **C. Ronald Kahn**, MD, DRWG’s chairman and director of the Joslin Diabetes Center in Boston and the Mary K. Iacocca professor of medicine at Harvard Medical School.

“We are taking action now that will save many thousands of men, women, and children from the severe consequences of a dangerous and life-threatening illness, as well as save the nation billions of dollars in medical care and lost productivity,” he says.

The report points out that government-funded diabetes research represents less than 3% of the

research budget of the National Institutes of Health (NIH), even though diabetes is one of the most costly diseases our society encounters and mortality has increased by 30% since 1980.

Calling diabetes “a public health crisis,” Rep. **George Nethercutt** (R-WA), co-chairman of the bipartisan Congressional Diabetes Caucus pledged to fight for the funding. “Over the last two decades, funding for diabetes has not kept up with scientific opportunities or public needs,” Nethercutt says.

DRWG identified what it calls “five extraordinary opportunities for making significant progress toward understanding, more effectively treating, and ultimately preventing and curing diabetes.”

“The extraordinary opportunities we identified — genetics of diabetics, autoimmunity and the beta cell, cell signaling and regulation, obesity, and clinical research and trials — highlight areas

KEY POINTS

- Congressionally established Diabetes Research Working Group calls for \$827 million in funding for publicly funded diabetes research.
- Target areas of research are:
 - genetics of diabetes and its complications;
 - autoimmunity and the beta cell;
 - cell signaling and cell regulation;
 - obesity;
 - clinical research and human trials of critical importance.
- There is a special research focus on:
 - the micro- and macrovascular complications of the disease;
 - methods of optimizing glucose control;
 - studies of environmental factors that cause diabetes;
 - research on diabetes in women, children and the elderly;
 - research on the disease in minority populations;
 - genetic engineering;
 - behavioral and health services research;
 - resource and infrastructural needs;
 - strengthening research training and human resources development;
 - enhancement of Diabetes Research Centers program;
 - developing and harnessing new technologies;
 - animal models for the study of diabetes;
 - enhancing mechanisms for obtaining human materials for diabetes research.

where recent advances in technology and knowledge would have the most profound impact on people with diabetes,” says DRWG member **Christopher Newgard**, PhD, the holder of the Gifford O. Touchstone Jr. and Randolph G. Touchstone chair in diabetes research at the University of Texas Southwestern Medical Center in Dallas.

Among the DRWG’s recommendations are these goals:

- Establishing a national consortium of researchers with adequate expertise and resources to unlock the genetics of diabetes and its complications, an achievement Kahn thinks is possible in the “next two or three years.”
- Creating centers to intensify research on islet cell transplantation.
- Establishing research centers that focus on the failure of cells to communicate on a molecular and genetic level (an underlying cause of Type 2 diabetes).
- Increasing the size, scope, and number of NIH-sponsored obesity research centers.
- Creating Diabetes TrialNet, a network of clinical research facilities that would provide a stable, high-quality base for clinical trials.
- Intensify research on mechanical devices for insulin replacement.
- Enhancing the mechanism for obtaining human material for research, from pancreases to stem cells.

Kahn says DRWG does not advocate creating new physical facilities for research, but to develop a “hub-and-spoke” method of bringing together existing facilities and creating databases so participants in clinical trials can be assembled efficiently and other research efforts can be coordinated.

An emotionally loaded issue

Kahn says the “human material” needed for research is likely to continue to be an emotionally loaded issue as Congress takes up the proposal, “But it doesn’t need to be that way.”

While most of the stem cells currently used in research are fetal cells, largely the products of abortions, Kahn says there are other ways to obtain such cells. These methods include harvesting the umbilical cords and placentas of live births and obtaining stem cells that are found “in virtually every organ of an adult.”

The DRWG’s \$827-million request is \$385 million more than the current \$442-million NIH funding for diabetes research.

However, Kahn says it’s not a lot of wishful thinking, but he doesn’t expect the funds will be available immediately. “The estimates of needs are realistic and in some cases conservative. I don’t think it’s pie-in-the-sky. It’s the result of some extremely thoughtful consideration.”

[C. Ronald Kahn can be reached at (617) 732-2400. A summary of the DRWG’s reports can be obtained at the ADA Web site at www.diabetes.org.] ■

FDA moves on drugs that attack insulin resistance

Rezulin under fire again; Avandia on fast track

While the rosy glow around Warner-Lambert Parke-Davis’s Rezulin (troglitazone) has somewhat dimmed after reports of liver damage and deaths from the use of the drug that targets insulin resistance, a new generation of thiazolidinediones is on the federal Food and Drug Administration’s (FDA) fast track for approval.

The FDA’s advisory committee on Endocrinologic and Metabolic Drugs will meet March 26 to consider “adverse events” associated with Rezulin according to a spokeswoman for the FDA.

At about the same time, the FDA gave a six-month priority review to SmithKline Beecham’s Avandia (rosiglitazone).

The post-approval review of troglitazone is unusual, says **Richard Kahn**, PhD, chief scientific and medical officer of the American Diabetic Association in Alexandria, VA. But, he says, “It’s premature to think this is the end of Rezulin. I don’t think we have the data or anything that shows an increase in the numbers of deaths. What the FDA has, no one else knows.”

Rosiglitazone may have been put on the fast track, Kahn says, because “at the very least, it’s

KEY POINTS

- The FDA advisory committee on Endocrinologic and Metabolic Drugs Advisory Committee will meet March 26 to consider reports of adverse effects of Rezulin (troglitazone).
- The FDA grants six-month priority review for Avandia (rosiglitazone).

being considered as a substitute when there are two drugs in the same class.” So if troglitazone is pulled, rosiglitazone may be available as a substitute.

Reports of deaths from liver failure began to emerge shortly after Rezulin was approved in March 1997.

In July 1998, the U.S. consumer advocacy group Public Citizen petitioned the FDA to withdraw troglitazone from the market after 26 deaths from liver failure and three reported liver transplants among troglitazone users.

The FDA responded by issuing a “Dear Health Care Professional” letter recommending vigilance and monitoring liver functions of patients on Rezulin. Warner-Lambert Parke-Davis also issued new labeling.

In response to the Public Citizen’s petition, the manufacturer issued a statement and presented data supporting the benefits of Rezulin. The company said the report “offers statistics that verify an overall decline in the rate of severe liver events possibly associated with the therapy that is related to labeling revisions and increased patient monitoring.”

In a letter to the *Annals of Internal Medicine* on Feb. 16, two physicians and a pharmacist said the reports on troglitazone are “worrisome.”

Risk too high?

One of the writers, **William L. Isley, MD**, is an endocrinologist, and an associate professor of medicine at the University of Missouri in Kansas City, and director of the dyslipidemia clinic at the Lipid and Diabetes Research Center at St. Luke’s Hospital also in Kansas City.

“The risk/benefit ratio is too high,” he says, for troglitazone and, while he has had “miraculous” responses in lowering glucose in some patients who did not respond to other therapies, he says those gains may be temporary.

“Many of them gained 20 to 30 pounds, their low-density lipoprotein (LDL) cholesterols went up in the space of a year to 18 months,” Isley

says. “After that, I found myself scratching my head and wondering if I did anything for this patient.”

He says he “won’t be disappointed if Rezulin is taken off the market,” and adds he thinks the indications for troglitazone should be “reduced to patients poorly controlled on insulin” and the monotherapy indications for Rezulin should be eliminated.

The March 26 FDA advisory committee meeting was open to the public. Kahn says the ADA will make a statement, but the content of that statement had not yet been determined at press time.

Rezulin is currently being used by about 1 million Type 2 diabetics, with sales for Warner-Lambert approaching \$1 billion, according to a Dec. 7 article in the *Los Angeles Times*.

[Richard Kahn can be reached at (703) 549-1500. Contact William Isley at (816) 932-3100.] ■

Vegetarian diet may help with insulin resistance

Experts disagree about the mechanism

A vegetarian diet can produce dramatic results for diabetics having a tough time getting control of glucose levels, says one researcher, while another has her doubts about the underlying causes of diabetes cases that are difficult to control.

Steve Provonsha, MD, MPH, director of preventive medicine at Kaiser-Permanente Medical Center in Riverside, CA, ties the reductions in fasting blood glucose in numerous patients to the elimination of glucagon and cortisol in animal tissue from their diets.

He theorizes in articles in *Medical Hypotheses* in November 1998 and *Vegetarian Nutrition* in March 1998 that glucagon from animal tissue aggravates

COMING IN FUTURE MONTHS

■ Hypertension education: A neglected part of diabetes management

■ Management strategies for primary care physicians

■ Helping kids cope with dietary requirements

■ Prioritizing and managing comorbidities and complications

■ Age and diabetes: Pediatric, teen, adult, and geriatric issues

KEY POINTS

- A vegetarian diet may be helpful for patients with trouble controlling blood glucose.
- One researcher says ingestion of animal muscle protein promotes insulin resistance.
- Another says there is no evidence that meat promotes insulin resistance, but the high-fiber, low-calorie, low-fat vegetarian diet may be good for some patients.

insulin resistance.

Provonsha cites results on five patients who reduced sugars and reduced or even eliminated medications in a very short time after beginning vegetarian diets.

He says one patient, a 50-year-old white male, weighing 284 pounds with average blood glucose of 298 mg/dL, dropped his blood glucose 119 mg/dL over a 30-day period. He lost 38 pounds, and his HbA1c was 6.9%. The patient was able to discontinue his 55 units of insulin, and his left foot was saved because his severe osteomyelitis was alleviated.

Provonsha says he is uncertain of the exact cause of the response, but theorizes it is glucagon and cortisol in consumed animal tissue that trigger the catabolic injury response.

“It appears that there is something about dietary muscle protein that activates a catabolic response similar to starvation or injury. Since meat is muscle and fat — the two substances utilized for fuel in the fasting state — it seems necessary to verify that its digestion and absorption is not supplying too many of the redundant substances that create the chemical profile of starvation in the bloodstream,” Provonsha wrote in *Vegetarian Nutrition*.

He also notes that glucagon promotes central obesity, a risk factor for diabetes, and cortisol makes the liver less sensitive to insulin and reduces insulin receptors on skeletal muscle. In addition, Provonsha says, high-protein diets are associated with insulin resistance.

Hard-pressed for scientific proof?

A vegetarian diet may have its merits in terms of lower calories, lower fat, and higher fiber intake, says **Marion Franz, MS, RD, CDE**, director of nutrition and professional education at the International Diabetes Center in Minneapolis. But there is no proof that insulin problems are a

result of the body receiving mixed signals from eating meat.

“There is evidence of a relationship between fat content and insulin resistance,” she says. “But I think we’d be hard-pressed for evidence that glucagon in animal tissue causes the insulin resistance. [Provonsha is] making a lot of statements without much scientific evidence.”

If glucagon is ingested from meat, Franz says, “The effect shouldn’t last for more than a couple of hours.”

In her experience, Franz says, “Vegetarian diabetics have no real unique problems. I can’t say they do better or worse.”

She says most of her patients in Minnesota tend to be older adults who have followed a fairly traditional Midwestern meat-and-potatoes diet, so vegetarianism would be quite a stretch for them.

[Steve Provonsha can be reached at (909) 352-7039. Contact Marion Franz at (612) 993-3393.] ■

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Editor: **Kathleen Barnes**, (828) 883-5695, (wolfeagle@citcom.net).

Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).

Executive Editor: **Park Morgan**, (404) 262-5460, (park.morgan@medec.com).

Managing Editor: **Valerie Loner**, (404) 262-5536, (valerie.loner@medec.com).

Associate Managing Editor: **David Flegel**, (404) 262-5537, (david.flegel@medec.com).

Production Editor: **Ann Duncan**.

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Editorial Questions

For questions or comments, call **David Flegel** at (404) 262-5537.

Benefits of aspirin therapy are big for diabetics

Death rate is cut substantially with small dose

Aspirin therapy can cut the death rate among Type 2 diabetics with coronary artery disease (CAD) by a third, according to an Israeli study published in the *American Journal of Medicine* and independent statements from the American Diabetes Association in Alexandria, VA.

A dose as small as 81 mg per day — the amount contained in one baby aspirin or one-fourth of an adult aspirin — can have profound life-saving effects, says **Gerald Bernstein, MD**, president of the American Diabetes Association.

“When I was an intern in 1959, the chief of endocrinology said one aspirin per week prevented clotting,” Bernstein says. “Anybody with Type 2 diabetes should take the 81 mg dosage unless there are contraindications.”

The Israeli study, which used between 100 and 325 mg of aspirin daily, states, “The absolute benefit of aspirin was greater in diabetic patients than in those without diabetes.”

Participants who took aspirin had a 10.9% mortality risk from cardiac diseases compared to a 15.9% risk for nonusers. In addition, diabetics who took aspirin had an all-cause mortality rate of 18.2% compared to 26.2% for diabetics who did not take aspirin. By comparison, nondiabetic patients who used aspirin experienced a 4.8% mortality risk from cardiac diseases, and a 6.9% risk for those who did not take aspirin.

It's not really a surprise that aspirin helps diabetics; it's just that this is the first time anyone has specifically studied the effects in the diabetic population, says **David Vorchheimer, MD**, director of the cardiac care unit at the Mount Sinai Medical Center in New York.

He highly recommends a daily dose of 162 mg (one-half an adult-sized aspirin) as primary prevention in the presence of risk factors such as diabetes, high blood pressure, family history of CAD, and tobacco use (which should be stopped).

These “modest doses,” Vorchheimer says, can have “profound” preventive effects. For diabetics who have already had a heart attack, Vorchheimer recommends 325 mg or one adult-sized aspirin per day.

Bernstein warns that aspirin therapy should be discontinued if a patient experiences bleeding,

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excessive bruising, or heartburn. He also says aspirin therapy should be stopped before elective surgery.

[Gerald Bernstein can be reached at (703) 549-1500. Contact David Vorchheimer at (212) 241-8496.] ■

CE objectives

After reading this month's issue of *Diabetes Management*, the continuing education participant should be able to:

- Identify particular clinical, administrative, education, or managerial issues related to the disease management of diabetes patients.
- Describe how those issues affect diabetes patients, diabetes management programs, and diabetes costs.
- Cite practical solutions to disease management problems associated with diabetes, based on overall expert guidelines from the National Institutes of Health, the American Diabetes Association, the American Association of Diabetes Educators, or other authorities, or based on independent recommendations from clinicians at individual institutions. ■