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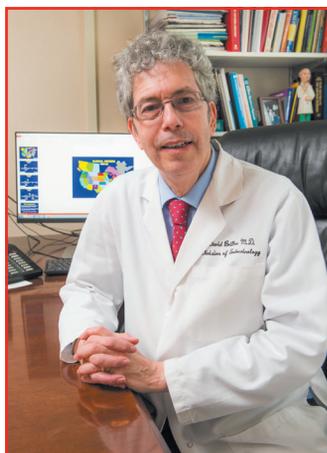
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Controlling Blood Sugar Lengthens Life in Patients with Type 1 Diabetes

Patients with type 1 diabetes who closely monitor and control their blood sugar live longer than those patients who do not, according to results of a nearly 30-year study by the National Institutes of Health. Published January 6 in the *Journal of the American Medical Association*, the two-part multi-site trial followed some 1,500 patients with type 1 diabetes. The findings provide physicians and their patients with clear evidence showing that intensively maintaining near-normal blood sugar levels translates into improved overall health outcomes.

David J. Brillon, MD, an endocrinologist in the Division of Endocrinology, Diabetes, and Metabolism at NewYork-Presbyterian/Weill Cornell



Dr. David J. Brillon

Medical Center, has led the Diabetes Control and Complications Trial (DCCT) at Weill Cornell since the late 1980s.

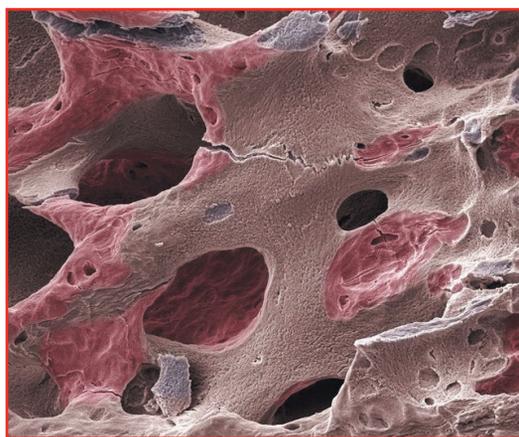
While aggressively controlling blood sugar is the accepted treatment for type 1 diabetes today, at the inception of the DCCT there were two schools of thought about whether hyperglycemia was the main reason that individuals with type 1 diabetes developed microvascular disease and complications, such as retinopathy, neuropathy, and nephropathy. “Some investigators

and experts in the field thought that high blood sugar was the main problem that would lead to these complications over time,” says Dr. Brillon.

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Raising the Red Flag on Osteoporosis

Watching both of her parents suffer the painful and disabling effects of fractures in their later years was a major factor in the decision of endocrinologist Ethel S. Siris, MD, to seek help for people with metabolic bone diseases.



Colored scanning electron micrograph showing osteoporotic bone.

“Having seen that in my own family, I care deeply about bone health,” says Dr. Siris, Director of the Toni Stabile Osteoporosis Center at NewYork-Presbyterian/Columbia University Medical Center, the largest such program of its kind in the Tri-state area.

At the Toni Stabile Osteoporosis Center, Dr. Siris and her colleagues are trying to prevent the burden of fractures that is so common in older people. “We’d rather not wait until somebody breaks a bone to figure out if he or she is at risk of breaking a bone,” says Dr. Siris. “It’s like waiting for a stroke before you decide to take your blood pressure. It’s not good practice. The problem is that in the United States this disease remains significantly underdiagnosed and undertreated.”

Tools, such as bone mineral density measurements and also the FRAX Risk Assessment developed by the World Health

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“Others thought there might be some other metabolic defect independent of glucose levels that was causing the microvascular complications to occur years later and after onset of diabetes.”

It was not known whether or not changing glucose levels would result in benefits to the patients in terms of decreasing microvascular disease, explains Dr. Brillon. “Indeed, some short studies that occurred before the DCCT did not find any effects in terms of retinal disease and at least one actually showed worsening.”

The randomized DCCT began with a feasibility phase in 1983, followed by the full cohort trial with investigators at Weill Cornell and at 28 other sites in the United States and Canada enrolling 1,441 people between the ages of 13 and 39 with type 1 diabetes. “The conventional group – comprised of half the patients – checked their blood glucose levels daily and administered insulin once or twice a day, which is the protocol that was in place and used by most physicians at that time,” says Dr. Brillon. The other half monitored their glucose levels four or more times a day, particularly before and after meals and overnight. Those in the

“If someone with type 1 diabetes is able to attain glucose levels closer to the normal range, I think that imparts positive effects for the patient in general. In addition to less eye, kidney, nerve and heart disease, these patients come away with a reduction in overall mortality.”

— Dr. David J. Brillon

intensive monitoring group also utilized more advanced insulin delivery protocols, administering insulin three or more times a day. In some cases, intensive treatment included insulin pumps, which had become commercially available in the mid-80s.

“Nowadays, these types of multiple insulin injection regimens and use of insulin pumps are fairly universal, but at the time this was considered a more intensive treatment,” notes Dr. Brillon.

All of the participants worked closely with nutritionists and certified diabetes educators (CDE) throughout the course of the study. “This was on an as-needed basis for the conventional group and more frequently for the intensive group to make sure that they were following appropriate nutritional recommendations and learning intensive management, which, obviously, would allow for optimal glucose levels,” says Dr. Brillon.

According to Dr. Brillon, the main reason for the success of the trial was the dedication and interest of the DCCT study participants in wanting to find the answer to the study question. Participation of trial coordinators was critical to its success and longevity. The DCCT study coordinators were also crucial to the success of the DCCT. “Coordinators, including **Mary Ellen Lackaye, RN, MPH**, here at Weill Cornell, actually see the patients, perform the procedures, and act as liaisons,” he says. “Along with the investigators, the coordinators have been participating in the trial for decades. That continuity of having a coordinator in the study from day one has been integral to the remarkably high participant retention and data completion rates. By optimizing their organizational and scientific contributions to

the overall research endeavor, study coordinators have made major contributions to the unprecedented success of the study.”

Enter the EDIC Study

The DCCT prematurely ended in 1993 when the Data Safety Monitoring Board recognized that patients in the intensive glucose monitoring group had substantially less eye, nerve, and kidney disease than their peers in the conventional treatment group. Investigators found that participants in the intensive monitoring group had a 33 percent lower risk of dying compared to those in the conventional group. While 22 percent of patients died from cardiovascular diseases and 18 percent from acute diabetes complications characterized by dangerously high or low blood glucose, not all deaths were attributable to diabetes.

“The intensive glucose monitoring resulted in improvements in terms of microvascular disease where it was demonstrated for the first time that reductions in glucose levels would translate into decreased complications,” says Dr. Brillon.

All of the DCCT study patients were advised to follow the intensive blood glucose monitoring, and nearly all enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study that allowed physicians to monitor their long-term health outcomes. Dr. Brillon also served as PI for EDIC at Weill Cornell, an observational multi-center study that continues today. EDIC found that the effects of the 6.5 years of intensive control in reducing the rate of progression of microvascular disease persist for up to 8 years after cessation of intensive therapy. EDIC has also demonstrated reductions in cardiovascular disease outcomes with the use of intensive therapy.

In the ensuing years since the start of the DCCT, there have been continuing advancements in insulin delivery systems and sensors that monitor glucose levels. “There are many, many innovations that have occurred over the last 20 years that have increased the ability of patients to attain levels that will reduce complications,” says Dr. Brillon. “I think the DCCT and EDIC have been instrumental in giving the impetus for these advances.”

Dr. Brillon notes that to date less than one percent of study participants has had any significant visual impairment and kidney failure or amputations. “If someone with type 1 diabetes is able to attain glucose levels closer to the normal range, I think that imparts positive effects for the patient in general,” says Dr. Brillon. “In addition to less eye, kidney, nerve and heart disease, these patients come away with a reduction in overall mortality. These are dramatic differences from what had been the case before the DCCT and EDIC. There’s been a wealth of scientific information coming from these studies over the past 30 years that have significantly demonstrated benefits to patients with type 1 diabetes.”

Reference Article

Writing Group for the DCCT/EDIC Research Group, Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, Lachin JM. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *Journal of the American Medical Association*. 2015 Jan 6;313(1):45-53.

For More Information

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Raising the Red Flag on Osteoporosis *(continued from page 1)*

Organization and the National Osteoporosis Foundation, are available to estimate risk for fractures. “The clinicians in our program are all highly trained in bone metabolism and osteoporosis management,” notes Dr. Siris. “We’re endocrinologists and we are highly focused in the area of osteoporosis. Our Center has four bone density units with dedicated technicians. Testing is very easy, safe, takes only about 15 minutes, and is reimbursable. Yet, we know very well that the great majority of people who are 65 and older are not having the test done.”

The Toni Stabile Osteoporosis Center is part of a larger effort, the Metabolic Bone Diseases Program, that includes Dr. Siris’s colleagues: Drs. John P. Bilezikian, Elizabeth Shane, Shonni Silverberg, Mishaela Rubin, Marcella Walker, Adi Cohen, Emily Stein, Angela Carrelli, John Ausiello, and Natalie Cusano. Together they oversee a large program of research into osteoporosis and other metabolic bone diseases, as well as provide first rate care in this area. The unit also features state-of-the-art evaluation tools, such as Xtreme CT, a high resolution peripheral CT scanner that permits, in a non-invasive way, detailed evaluation of skeletal microstructure.

The U.S. Preventive Services Task Force recommends screening for osteoporosis for women age 65 years or older, and earlier screening for women age 50 to 64 years with certain risk factors. For example, a 55-year-old white woman whose parent has had a hip fracture should consider getting screened early because her 10-year risk of fracture is at least as great as a 65-year-old white woman who has no additional risk factors. Family history of osteoporosis can be due to a combination of genetic, environmental, and behavioral factors. Studies in recent years have identified over 60 genetic markers associated with bone density and susceptibility to fractures due to osteoporosis.

“One of the most powerful clinical risk factors for future fractures is having had a fracture after the age of 50,” says Dr. Siris. “That should require a workup that includes a bone density test and an assessment for low bone mass as the explanation for the fracture.” Additional subgroups of individuals at risk include certain women who have had breast cancer after menopause, including women whose menopause was precipitated by breast cancer chemotherapy. Aromatase inhibitors, which are commonly used to manage breast cancer, are associated with heightened fracture risk. Similarly, older men who have had prostate cancer that was treated by ablating their ability to produce testosterone are going to have bone loss and may also need an assessment.”

Meeting the Challenge of Delivering Treatment

Dr. Siris stresses that even when osteoporosis is identified, there are still many patients who are not getting treatment. “Those individuals who have low bone mass may turn out to be at high risk in the setting of their unique clinical risk factors associated



Dr. Ethel S. Siris

with that low bone mass,” she says. “They should be treated, but they are not being treated. For example, we know that in the U.S. when an older woman or man comes into the ER with a major fracture – a hip fracture, a new spine fracture, a broken shoulder, or broken pelvis – many of these patients are admitted to an orthopedic service. The orthopedic surgeons in this country do a great job fixing the fracture and then the patient is discharged. Nobody says, ‘Hey, this patient is 82 with a broken hip. This is probably osteoporosis.’”

According to Dr. Siris, only about 20 percent of older patients with major fractures admitted to an orthopedic service receive treatment to prevent the next fracture for which they are at very high risk. Currently there are few systems in place to identify and capture individuals after a fragility fracture to ensure

appropriate assessment and treatment to reduce future fracture risk and adverse health outcomes. To that end, Dr. Siris and her Center colleagues – in collaboration with the Department of Orthopedics – have initiated a Fracture Liaison Service at New York-Presbyterian/Columbia.

“Our coordinator visits the orthopedic inpatient service five days a week to meet with newly admitted patients who are over 50 and have had a low impact fracture. The patient is educated about osteoporosis; it’s a teachable moment since they’ve just fractured. After discharge the patient is connected to the Toni Stabile Center for further evaluation. If we think this was an osteoporosis-associated fracture, he or she will get treated to prevent the next fracture. The bottom line is that we make every effort to make sure that as many of these patients with osteoporotic fractures, who would clearly benefit from treatment to minimize the likelihood of another osteoporotic fracture, get that treatment. We encourage them to stay the course, to take their calcium and vitamin D, to take their prescription medication, and to remember how to minimize their fall risk.”

Throughout her career, Dr. Siris has consulted on the earliest bisphosphonates used in the medical management of osteoporosis. She and her colleagues have extensive clinical experience with virtually all of the drugs approved for osteoporosis, including the bisphosphonate compounds, as well as selective estrogen receptor modulators (SERMs), a class of compounds that acts on the estrogen receptor. Dr. Siris was also on the steering committee for the FREEDOM Trial testing denosumab, a monoclonal antibody and the newest FDA-approved medication for the prevention of fractures in postmenopausal women with osteoporosis. The results of this study were published in *The New England Journal of Medicine*.

“There are new medications on the horizon, and my colleagues and I have also consulted on most of those drugs that are evolving,” says Dr. Siris. “We are frequently asked by scientists at the drug

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Advances in Diabetes and Endocrinology

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companies to help reflect on some of the data as it comes forward. It allows us to be very aware of data early on from the clinical trials and, perhaps, will give us greater insight once these medications are approved. We want to use the right drug for the right person.”

Leading the Charge Nationally

Dr. Siris, who is past president of the National Osteoporosis Foundation, also serves as a member of the Executive Committee of the National Bone Health Alliance, a public-private partnership launched in 2010 that brings together the expertise and resources of its member organizations to collectively promote bone health and prevent disease; improve diagnosis and treatment of bone disease; and enhance bone research, surveillance, and evaluation. The Alliance’s 52 member organizations, along with liaisons representing the Centers for Disease Control and Prevention, National Aeronautics and Space Administration, National Institutes of Health, and the U.S. Food and Drug Administration, work together to improve the overall health and quality of life of all Americans by enhancing their bone health.

Dr. Siris’s own research is public policy-based involving treatment adherence to therapy and on how to better communicate the identification, management, and prevention of osteoporosis. “The biggest issue in bone health in America is osteoporosis. Lowering this terrible toll of two million fractures every year at a cost of some \$19 billion annually is where we have to do a better job,” says Dr. Siris. “Ironically, there has been a lack of excitement about osteoporosis. People assume it’s for older people,

therefore, it doesn’t matter. But it does matter because a lot of these older people can be helped to prevent the next fracture. Half the people who break a hip in America had previously broken some other bone. However, that red flag never got raised and the patient was never treated to prevent the likelihood of the next fracture.”

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For More Information

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