

Exercise Benefits: New Research Evidence

The benefits of exercise have been proven in the treatment of diabetes. Participating in an exercise routine is a lifestyle habit that can help maintain good general health, prevent obesity, control diabetic symptoms and reduce the risks for other complications, such as high cholesterol and high blood pressure. Those who are living with diabetes should always check with their doctor before beginning an exercise program. They should engage in some type of physical activity, ideally for 30 minutes a day. Recent research results provide new evidence that helps us understand how exercise can positively impact health in people with diabetes.

Exercise, Diabetes and Depression

Coping with the rigors of diabetes management can cause a person to suffer from clinical depression. Clinical depression is a mental state characterized by low mood or a loss of interest in things a person commonly enjoys. This can be coupled with a lack of physical activity. New research indicates that diabetes and depression may be related and that exercise can be used to reverse symptoms.

In a recent article published in the June 18, 2008 issue of the *Journal of the American Medical Association*, researchers have established a bidirectional association between depression and diabetes. The study involved men and women between the ages of 45 and 84, from multi-ethnic backgrounds. Quantitative data to establish the existence of elevated depressive symptoms was collected using the Center for Epidemiologic Studies Depression Scale (CES-D) where scores range from 0 to 60, with higher scores indicating more depressive symptoms. Those who scored 16 or higher on the

CES-D and/or had other co-existing factors, such as taking anti-depressant medications, were defined as depressed.

Participants were also screened to determine their diabetes status. They were categorized as normal fasting glucose (< 100 mg/dl), impaired fasting glucose (IFG: 100 to 125 mg/dl) or type 2 diabetes (\geq to 126mg/dl). Those with diabetes were further divided into persons who were treated for diabetes and those who were untreated. All participants were then followed for three years.

The results of this study indicated that not only can depression lead to diabetes, but diabetes can lead to depression. Participants with depression at the onset of the study, but no diabetes, were at a higher risk for developing type 2 diabetes during the following three years. Those with higher levels of depression were almost 50% more likely to develop diabetes than those who were not depressed. Individuals who were the most depressed were most likely to become diabetic. Conversely,



those with IFG or diabetes at the onset of the study, but not depression, were followed for the subsequent three years. Interestingly, those with IFG or untreated diabetes were not at an increased risk to develop

depression, but those with treated type 2 diabetes had elevated depressive symptoms.

What are the possible reasons for these results? Depressive symptoms are associated with metabolic and behavioral risk factors for type 2 diabetes. Depressed individuals are less likely to comply with dietary and weight loss guidelines and more likely to be physically inactive, all contributing to development of obesity, a known risk factor for insulin resistance and type 2 diabetes. Depression might also lead to changes in physiological pathways leading to increases in stress hormones as well as

stimulation of pro-inflammatory compounds. The results indicating that treated, but not untreated individuals, with diabetes are at an increased risk for developing depression may be related to the psychological stress associated with their diabetes management. In addition, adults with treated type 2 diabetes may have a greater number of complications and comorbidities contributing to the development of

elevated depressive symptoms. Understanding that a relationship may exist between diabetes and depression means that improved treatment strategies can be developed for both conditions. Exercise could be utilized as one of these strategies for both depression and diabetes. According to a Mayo Clinic article on Depression and Anxiety¹, data indicates that exercise may help improve symptoms of depression. It may take at least 30 minutes a day of exercise for at least three to five weeks to see significant results; but mood can be improved by as little as 10 to 15 minutes of activity at a time.

The precise mechanism(s) of how exercise reduces symptoms is not fully understood but there are theories. Exercise may increase the levels of neurotransmitters, a



¹Depression and Anxiety: Exercise eases Symptoms. Mayo Clinic Staff. 23 October 2007. <http://www.mayoclinic.com/health/depression-and-exercise/MH0043>

chemical from a nerve that transmits nerve impulses. When released in the brain, neurotransmitters could excite nerves and enhance mood. A second theory is that engaging in exercise raises the level of endorphins which could increase moods by reducing muscle tension or reducing the stress hormone cortisol. Lastly, a rise in body temperature when working out could have a calming effect and improve depression symptoms.



The American Diabetes Association maintains that exercise is one treatment strategy that can be used to manage diabetes symptoms. While exercising, blood glucose levels are reduced. Exercise can increase the insulin receptors on the cells allowing more insulin to attach to the receptors. Glucose can more readily pass into the cells, reducing its level in the blood. Improvements in circulation could also be observed as a result of an exercise routine. Over time, the heart will pump blood more efficiently and the small vessels leading to extremities will open, allowing better blood flow. A reduction of the risks associated with heart disease and stroke are also benefits of an exercise routine.

In a December 2007 article published by *Science Daily News*, researchers may have identified a change in gene activity associated with exercise that influences antidepressant effects. Using mice models, researchers used microarray analysis to examine their gene activity. They focused on the hippocampus, a part of the brain that has been shown to influence mood regulation. After the mice were exercised for a week on a running wheel, they exhibited altered gene activity in a total of 33 genes. This was a previously undescribed profile of exercise-regulated genes. They performed further testing and infused the mice with a nerve growth factor, small proteins that are important to the development and maintenance of nerve cells. The nerve growth factor produced antidepressant effects in the mice that were placed in stressful situations.

Thus, using exercise to prevent and alleviate the symptoms of diabetes and depression along with proper medical care can help a person to cope with daily life and reduce the stressors and risks that diabetes brings.

Improvement of Insulin Resistance with Exercise

Insulin resistance is a main contributor to type 2 diabetes. A lack of exercise could contribute to the development of insulin resistance. Due to this inactivity, the muscle is unable to utilize insulin as efficiently, causing a rise in glucose circulating in the blood stream. People with insulin resistance may have fewer mitochondria or alteration of normal mitochondrial function in their skeletal muscle compared to people who are not insulin resistant. Mitochondria are the “powerhouses” for cells where energy is created. Current research aims to demonstrate that exercising could increase insulin sensitivity, reversing the effects of insulin resistance, perhaps by modulating mitochondrial number and/or function.



ADA-funded researcher Dr. Zhen Yan, PhD has a project entitled *“Exercise and Diet-induced Insulin Resistance”*. In his research, Dr. Yan conducted experiments on mice fed a high-fat diet. Once on this diet, they exhibited signs of obesity and diabetes.

To examine the effects of the high fat diet,

Dr. Yan performed

transmission electron microscopy analysis of skeletal muscles to determine if there was in fact a change in mitochondrial structure. Comparing the high fat diet mice to the control mice, he detected structural defects in the skeletal muscle mitochondria. Continuing his experiment, Dr. Yan exercised the mice to study the effects on the skeletal muscle mitochondria. From his research data, Dr. Yan concluded that the long-term exercise training program reduced the pathological effects on the mitochondria. The significance of his study results show that there may be a link between exercise and improving mitochondrial structure/function.

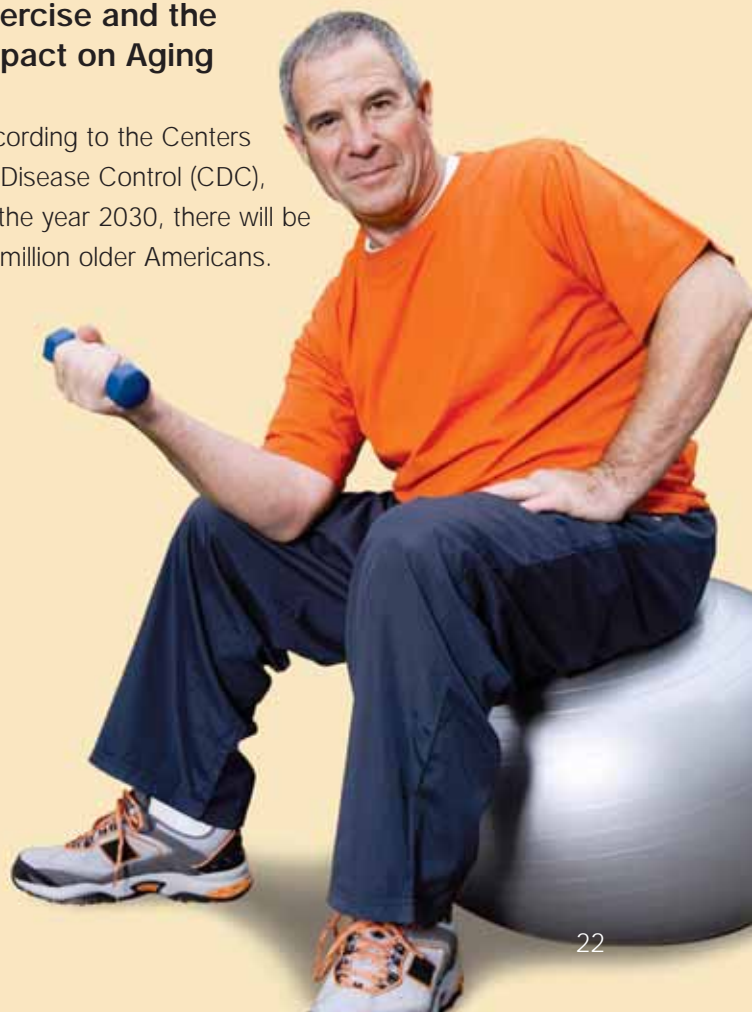
Dr. John Holloszy’s lab has also shown previously that exercise improves mitochondrial function in skeletal muscle. However, Dr. Holloszy and his ADA supported postdoctoral research fellow, Chad Hancock, PhD, suggest a different scenario for the effect of a high fat diet that causes insulin resistance on skeletal muscle mitochondria. In a paper entitled *“High fat diets cause insulin resistance despite an increase in muscle*

mitochondria” they report that rats given a high fat diet actually have an increase in muscle mitochondria. They conclude that raising free fatty acids with the high fat diet results in an increase in mitochondria by activating a factor called PPAR delta, which then mediates an increase in a protein PGC-1 alpha. Activation of PGC-1alpha has been previously shown to mediate the initial phase of the exercise-induced adaptive increase in muscle mitochondria.

Thus, the jury is still out. Insulin resistance can modulate muscular mitochondria and exercise appears to positively impact these changes. The exact hows and whys still need to be explored through further research. Understanding these processes will provide new insight into the benefits of exercise in the prevention or treatment of insulin resistance and diabetes.

Exercise and the Impact on Aging

According to the Centers for Disease Control (CDC), by the year 2030, there will be 70 million older Americans.



With age comes an increased risk for and development of chronic health problems. The latest CDC National diabetes fact sheet states that in 2007, 12.2 million people 60 years and older have diabetes. This is an increase from 10.3 million reported in 2005. As continuing reports of age-related health issues are released, the benefits of exercise could be seen as an effective means of alleviating these problems.

Older people may feel resistant to participating in physical activity. This resistance can stem from fears of becoming injured or getting sick or simply thinking it is too late to begin. But getting older does not have to mean succumbing to these fears. Although there may be a decline in health as we age, there is new research evidence that exercise could improve health complications that develop.

Annette Chang, MD and her colleagues at the University of Michigan have presented data that exercise can help improve the function of beta cells in older people at risk for diabetes. They have published their findings in the February 2008 *Journal of Clinical Endocrinology and Metabolism*.

As we age, our beta cells start to lose their ability to function properly and our cells also become less sensitive to insulin. Dr. Chang's research showed that after just one week of exercise, people age 60 and over (who were usually sedentary) had a significant increase in their beta-cell function (28 percent increase) and insulin sensitivity (53 percent increase on average).

Study participants exercised one hour per day at 60 – 70 percent of their heart rate capacity. There were no changes in levels of fat mass or fats in the bloodstream, which could have influenced the change in beta-cell function or insulin sensitivity. This led the authors to conclude, "Short-term exercise not only improved insulin resistance but also significantly

enhanced beta-cell function in older people with impaired glucose tolerance (IGT). These effects of short-term exercise on beta-cell function cannot be explained by changes in body weight or circulating levels of lipids, leptin, adiponectin, or catecholamines."

These research results provided the necessary data to allow Dr. Chang to successfully obtain an ADA Clinical Research Award ("*Beta-cell function and exercise in older people with impaired glucose tolerance*") where she is continuing her work on the effects of exercise in people over 60.



Dr. Chang explains that during her new ADA study, "Older people with IGT will be enrolled in supervised aerobic exercise programs for 3 months. Tests will be done before and after exercise to see how much insulin is made and how well the body uses insulin. This study may improve the understanding of how lifestyle changes such as exercise can prevent diabetes in older people who are at high risk of developing diabetes."

Aging can lead to development of other health complications such as arthritis. Arthritis, or joint inflammation, has recently been identified as a common health complication for those with diabetes. In a recent telephone survey conducted by the Centers for Disease Control Arthritis program², it was found that 52% of people who had arthritis also had a dual diagnosis of diabetes. However, this is not a problem just for older people, but for younger individuals as well. Arthritis prevalence among persons with diabetes was higher than in the general population for all age groups: age 18-45, 27.6% vs 11%; age 45-64, 51.8% vs 36.4%; 65 and older, 62.4% vs 56.2%.

The prevalence of self-reported physical inactivity in this survey was significantly higher among those with arthritis and diabetes compared to those with diabetes alone. This suggests that arthritis might be a barrier to being physically active in this population. However, being more physically active can benefit not only persons with arthritis or diabetes alone, but perhaps even more so in individuals with both conditions. In a May 8, 2008 press release from the CDC about the Arthritis study, Dr. Janet Collins of the CDC's National Center for Chronic Disease Prevention and Health Promotion, commented on the necessity of exercise. "We know it can be difficult, but regular physical activity helps in many ways. For people with diabetes, physical activity helps control blood glucose and risk factors for complications. For people with arthritis, physical activity reduces pain, and improves function." Accordingly, health-care providers interested in improving diabetes management of their patients might also need to consider arthritis-related barriers in those with diabetes and who are physically inactive.

The Alzheimer's - Diabetes Link

The link between Alzheimer's disease and diabetes is important. They are the sixth and seventh leading causes of death according to a recent report released by the Centers for Disease Control. Alzheimer's disease (AD) is defined as the most common form of dementia, caused by various



²MMWR weekly, May 9, 2008 / 57(18);486-489, Arthritis as a Potential Barrier to Physical Activity Among Adults with Diabetes --- United States, 2005 and 2007

diseases and conditions that result in damaged brain cells. This brain cell damage leads to decline in memory and can include decreased cognitive ability. AD is most common in people age 65 and older but can be seen at early ages as well. The links between diabetes and AD have been elucidated in recent research findings.

In the March 2008 online issue of *Neurobiology of Aging*, researchers tried to find the answer to the question, why does diabetes predispose people to Alzheimer's disease? Researchers induced diabetes in a young mouse model with a genetic predisposition to develop AD with old age. Results showed that the mice exhibited damage to the blood vessels in the brain even before they developed overt signs of AD. Researchers hypothesized a toxic interaction between amyloid naturally circulating in the blood and high blood glucose in the mice. The result of this interaction was the overproduction of free radicals resulting in oxidative damage to the cells lining the blood vessels of the brain. This study demonstrated basic mechanisms that could contribute to an increased risk for AD in people with diabetes.

In the April 9, 2008 online issue of *Neurology*, researchers discovered a link between men who develop diabetes in mid-life and their risk of developing AD. In this Swedish Study, 2,269 men at age 50 underwent glucose testing and were followed for 32 years. During this follow-up, 102 of the men were found to have developed AD, 57 had vascular dementia and 235 had other cognitive impairment. The men with low insulin secretion at age 50 were 1.5 times more likely to develop AD than those without a measured insulin problem. These results demonstrate that there could be a link between insulin levels and Alzheimer's development.

Uncovering the link between diabetes and Alzheimer's could help focus attention on prevention of these conditions with exercise. Doctors in Italy have determined that moderate exercise can help prevent vascular dementia. Study results were published in the December 21, 2007 issue of the *American Academy of Neurology*. Researchers followed 749 men and women who were 65 and older, and presented with no prior evidence of dementia, for four years. The study participants exercised weekly by walking or climbing stairs and participated in



moderate activities such as yard work and gardening. By the completion of the study, 54 participants had developed Alzheimer's and 27 had developed dementia. Doctors concluded that participants who exerted the most energy lowered their risk of developing vascular dementia by 29 percent. Including physical activity in their daily routine may have improved the circulation of blood to the brain and thus reduced the risk of dementia.

Polypill or Should it be Pol-e-Pill?

Clinicians and researchers have debated over the last decade whether a "polypill" could be developed as a measure to prevent the onset of metabolic diseases, diabetes being at the forefront of this discussion, or perhaps even obesity. This pill would have to be clinically effective, safe and affordable. It would act on multiple molecular pathways with little to no side-

effects. Of course, the likelihood of this pill being developed, let alone tested sufficiently in a large enough population and for long enough to prove safety and efficacy, is slim to none. James Levine and Ronald Davis recently presented a commentary in the July 2008 edition of *Diabetes*. They remind us of the issues regarding the polypill and propose a more realistic alternative for preventing and treating diabetes, obesity and most obesity-related complications: the Pol-e-pill. It meets all the criteria for effecting multiple molecular targets, has an excellent dose-response curve and superb safety profile. Side effects are minimal and it is affordable. What is this miracle cure and what does that "e" stand for? Exercise. As the authors implore, "We urge physicians to prescribe exercise just as they would a more costly tablet".

For more information on diabetes and exercise, look for the October issue of *Diabetes Forecast*. ■

