

Diabetes and cardiovascular outcomes



NEWS



Recent research suggests that maintaining intensively low blood sugar levels reduces heart attack and coronary heart disease risk in diabetics.

Researchers say that heart attack risk in diabetics can be reduced

INTERVIEW



RESEARCH HIGHLIGHTS



Researchers at the University of Cambridge were able to provide evidence that links intensive blood glucose control with fewer heart attacks. By carrying out a meta-analysis which collected data from five large trials, Dr Kausik Ray, lead author of the study, and his team pointed to a 17% reduction in heart attacks and a 15% reduction in coronary heart disease. Compared with some smaller studies, the current work did not report any adverse effects on deaths from any cause.

“Previous studies have been inconclusive, leaving diabetics and their doctors unsure as to whether maintaining lower blood sugar levels actually benefited the patients.” Explained Dr Ray, “Although additional research needs to be conducted, our findings provide insight into the importance of improving glucose levels, which should include lifestyle changes as well as medication.”

The five trials involved over 33,000 participants including 1497 heart attack cases, 2318 cases of coronary heart disease and 1227 stroke victims. The team examined data collected on the blood glucose levels of the participants, in particular a long-term glucose control marker, hemoglobin A1c (HbA1c). Levels of HbA1c in healthy subjects are usually 4–5%. In diabetics the levels are above 6.5%.

The present study demonstrated that those taking a standard treatment sustained a HbA1c level of 7.5%, whereas those who were submitted to intensive treatment to lower their blood glucose levels averaged at 6.6%, and subsequently had a dramatically reduced risk of disease in large blood vessels. The study also found a more modest trend that suggested

that there was a reduction in strokes using intensive glucose control compared with standard treatment.

“Although additional research needs to be conducted, our findings provide insight into the importance of improving glucose levels, which should include lifestyle changes as well as medication.”

Professor Peter Weissberg, Medical Director at the British Heart Foundation commented on the work, “It is well established that carefully controlling blood sugar in people with diabetes can help prevent disease in small blood vessels that leads to kidney failure and blindness. This collective analysis of several large clinical trials suggests that careful blood sugar control also protects against heart attacks and strokes, the major causes of death in people with diabetes.”

“These findings emphasize the importance of detecting and treating diabetes as early as possible, thus preventing the chances of developing heart and circulatory disease.”

Dr Ray concluded with the following message, “The present findings reinforce the need for diabetic patients to achieve and maintain better control of blood sugars long-term, as a means to reduce risk of heart disease.”

Source: Ray KK, Seshasai SR, Wijesuriya S et al.: Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 373(6977), 1737–1772 (2009).



Researchers urge people to follow a healthier lifestyle

Investigators from the Department of Family Medicine, Medical University of South Carolina, Charleston (SC, USA) analyzed two large-scale studies of the US population during 1998–1994 and 2001–2006, and compared them. The benefits of a healthy lifestyle including physical activity, eating fruits and vegetables, maintaining a healthy weight, moderate alcohol intake and not smoking, are well-known. Dana E King, lead author of the article found that only a small percentage of adults pursue such a lifestyle. In fact, the numbers are declining even though these lifestyle choices are associated with the risk of cardiovascular disease and diabetes.

In the 18 years between the two studies, the percentage of adults aged 40–74 years, with a body mass index greater than 30, went from 28 to 36%; partaking in physical activity 12 times a month or more

has decreased from 53 to 43%, eating five or more fruits and vegetables a day has decreased from 42 to 26%; moderate alcohol use has increased from 40 to 51%; and smoking rates have not changed significantly. The number of people adhering to all five healthy habits has decreased from 15 to 8%.

Individuals diagnosed with cardiovascular disease, diabetes, hypertension and high cholesterol were included in the sample, and the researchers wished to find out whether these people were adhering to the healthy habits to a greater or lesser degree than people without those conditions, and whether this adherence had changed over time. It was concluded that despite being subject to a greater risk of severe disease, these individuals were no more likely to have a healthy lifestyle than people without such risk factors.

Dana King explains the benefits of a healthier lifestyle, “The potential public health benefits from promoting a healthier lifestyle at all ages, and especially ages 40–74 years, are substantial. Regular physical activity and a prudent diet can reduce the risk of premature death and disability from a variety of conditions, including coronary heart disease, and are strongly related to the incidence of obesity. In the USA, medical costs due to physical inactivity and its consequences are estimated at US\$76 billion in 2000 dollars. Research indicates that individuals are capable of adopting healthy habits in middle age, and making an impact on cardiovascular risk.”

Source: King DE, Mainous AG 3rd, Carnemolla M, Everett CJ: Adherence to healthy lifestyle habits in US adults, 1988–2006. *Am. J. Med.* 122(6), 528–534 (2009).

Unfamiliar type of heart failure associated with diabetes will require novel therapeutic strategies

A presentation at the Heart Failure Congress 2009 has emphasized the risk of heart failure that accompanies obesity and diabetes. It is predicted that with the increasing prevalence of obesity and Type 2 diabetes, we will also see a dramatic increase in sufferers of heart failure, which is already the most prevalent chronic cardiovascular disease worldwide.

Obesity and heart disease are associated with an increased risk of coronary artery disease, leading to heart attack, and myocardial infarction, which leads to the well-known type of heart failure with ventricular dilatation and impaired systolic function. It is also thought that the epidemics of obesity and diabetes can lead to a different type of heart failure, characterized by preserved systolic function, but impaired diastolic function, without macrovascular coronary artery disease. John McMurray, President of the Heart Failure Association claimed that “Obesity is at least as great a risk factor for heart failure

as it is for heart attack or stroke ... obesity more than doubles the risk.”

McMurray reported that approximately two-thirds of heart failure patients have evidence of diabetes, and stresses that patients with both conditions are very difficult to treat, posing a challenge for physicians to provide effective treatment. The causes of this type of ‘metabolic heart failure’ are thought to be mitochondrial dysfunction, oxidative stress, collagen deposition, formation of advanced glycation end products, cardiac autonomic neuropathy and microvascular alterations. This unfamiliar type of heart failure will require novel therapeutic strategies to be developed for its management.

The mechanisms linking obesity and heart failure are unclear, but it is thought they could involve adipose cells acting as endocrine tissue and secreting adipokines to the detrimental effect of cardiac tissue and blood vessels. An indirect effect via hypertension has been demonstrated, and obesity

has a direct effect on heart muscle itself. “We know that the underlying changes in the structure and function of the heart may be different in obese and nonobese patients with heart failure,” McMurray explained. The link between diabetes and a doubled risk of heart failure is also unclear. Diabetics who experience heart failure are reported to have a higher risk of hospitalization and death, as well as worse symptoms, than nondiabetics, suggesting a unique underlying pathophysiology in heart failure in diabetic patients. McMurray suggests that there is an intersection between the two conditions, where diabetics have an increased risk of heart failure, and those with heart failure have an increased risk of developing diabetes. He concludes, “...whichever is the causative factor, it’s very bad news for those with both conditions.”

Source: Heart Failure Congress 2009 Webcast ‘Implications of the obesity and diabetes epidemic for heart failure: The European view’. www.escardio.org/congresses/HF2009/webcast



Less than one in five heart problems are diagnosed prior to the appearance of symptoms

In a study of 13,877 people, researchers from Oregon, Maryland and Delaware, USA, have discovered that just over 11% of the respondents had been diagnosed with heart disease, but only 19% of those individuals (who had been involved in the study for 2 years) said that they were diagnosed during routine screening.

It appears that clinicians are missing golden opportunities to spot heart disease prior to the arrival of symptoms, since more than half of the diabetic patients with heart disease (54%) reported that their heart disease was diagnosed after they experienced symptoms, and 15% were identified during treatment for other conditions.

“Our study showed that not enough patients with heart disease are being picked up during routine screening or treatment for conditions like diabetes, which are commonly associated with heart problems” explained lead author Dr Sandra J Lewis from the Northwest Cardiovascular Institute in Portland, OR, USA. “The majority of those who took part in the study were not diagnosed until they started displaying symptoms.”

Accounting for more than 450,000 deaths a year, coronary heart disease (CHD) is the leading cause of death in the USA.

“Many individuals do not show symptoms and go undiagnosed until the disease is in an advanced state, often when they have actually had a heart attack”, Dr Lewis clarified. “That is why it is so important to diagnose CHD before patients experience their first crisis, by looking at major risk factors such as smoking, having high blood cholesterol, having high blood pressure, being overweight, being physically inactive or just getting older.”

“Guidelines recommend that all adults over the age of 20 should receive risk factor screening from their family doctor every 2–5 years. There are more specific guidelines for patients with Type 2 diabetes as their risk of a heart attack is twice as high as the general population.”

Analysis from the Study to Help Improve Early evaluation and management of risk factor Leading to Diabetes (SHIELD study) was carried out to assess whether recommendations for improved screening in the USA were leading to more patients being diagnosed with heart disease before the

appearance of symptoms. Out of 13,877 participants who had diabetes or another cardiometabolic risk factor, 1573 had been diagnosed with heart disease. A total of 36% of patients with CHD and diabetes were diagnosed after 2001, at which time a number of guidelines on screening and prevention had been published.

It seems that despite awareness of risk factors, many individuals are not diagnosed with heart disease until they are symptomatic. Dr Kathleen Fox from Strategic Healthcare Solutions (MD, USA) highlights the importance of the study, “The fact that only a small percentage of the SHIELD respondents were diagnosed through screening indicates that there is a missed opportunity to diagnose heart disease during earlier, less severe stages of the disease ... Our study demonstrates the need for improved targeted education aimed at both patients and doctors to reduce heart disease before symptoms occur.”

Source: Lewis SJ, Fox KM, Grandy S; SHIELD Study Group: Self-reported diagnosis of heart disease: results from the SHIELD study. *Int. J. Clin. Pract.* 63(5), 726–734 (2009).

Hope for new treatments as scientists discover novel mechanisms for glucose-induced vessel damage

Researchers from the Medical college of Georgia (MCG), GA, USA, believe that new evidence for how the elevated glucose levels in diabetics damage blood vessels could direct us to novel treatments that prevent this process from occurring.

Scientists at the American Society of Hypertension 24th Annual Scientific Program in San Francisco, CA, USA, reported that an outcome of high levels of blood glucose is the resultant low blood concentrations of nitric oxide, a powerful vasodilator. This increases the risk of blood pressure and causes eventual blood vessel narrowing. “We know diabetes is a major risk factor for cardiovascular disease and we think this is one of the reasons,” remarks Dr Rita C Tostes, from the MCG School of Medicine.

Usually, glucose goes straight into cells where it is used to create ATP. However, approximately 5% of glucose is converted to O-GlcNAc, another sugar moiety that can modify proteins. After conducting experiments in healthy mice, Dr Tostes and her team realized that the increased activity of O-GlcNAc competes with another protein modification mechanism, phosphorylation. Phosphorylation modifies nitric oxide synthase, which in turn produces nitric oxide. Adding more O-GlcNAc therefore caused a reduction in phosphorylation and, consequently, a decrease in the production of nitric oxide. Furthermore, the longer that O-GlcNAc levels were high, the worse the problem became.

This discovery was confirmed using an animal model for hypertension. “Now we

are trying to see why this is happening and what comes first. Is increased blood pressure leading to changed O-GlcNAc, or are augmented levels of O-GlcNAc contributing to the change we see in the vasculature of hypertensives?” explained Dr Tostes. “If we know how this changes vascular function, we can understand some of the dysfunction that we see in diabetes.”

There is hope that drugs could be designed to inhibit OGT, the enzyme that adds O-GlcNAc to the protein, and that these drugs could help reduce the cardiovascular risk associated with diabetes.

Source: Medical College of Georgia: <https://my.mcg.edu/portal/page/portal/News/archive/2009/New%20evidence%20of%20how%20high%20glucose%20damages%20blood%20vessels%20could>