Diabetes Mellitus

Diabetes mellitus is a group of autoimmune diseases characterized by defects in insulin secretion resulting in hyperglycemia (an abnormally high concentration of glucose in the blood). There are two primary types of diabetes. Individuals diagnosed with type 1 diabetes (also known as juvenile diabetes) are incapable of producing pancreatic insulin and must rely on insulin medication for survival. Individuals diagnosed with type 2 diabetes (also known as adult onset diabetes) produce inadequate amounts of insulin. Type 2 diabetes is a less serious condition that typically is controlled by diet. Over time, diabetes can lead to blindness, kidney failure, nerve damage, hardening of the arteries and death. The disease is the third leading cause of death in the United States after heart disease and cancer.

Preclinical and observational studies indicate that cannabinoids are inversely associated with diabetes,[1] may modify disease progression, and that they also may provide symptomatic relief to those suffering from the disease.[2-3] A 2006 study published in the journal *Autoimmunity* reported that injections of 5 mg per day of the non-psychoactive cannabinoid CBD significantly reduced the incidence of diabetes in mice. Investigators reported that 86 percent of untreated control mice in the study developed diabetes. By contrast, only 30 percent of CBD-treated mice developed the disease.[4] In a separate experiment by this same research team, investigators reported that control mice all developed diabetes at a median of 17 weeks (range 15-20 weeks), while a majority (60 percent) of CBD-treated mice remained diabetes-free at 26 weeks.[5] A 2013 study assessing the effect of THCV (tetrahydrocannabivarin) in genetically modified obese mice reported that the cannabinoid's administration produced several metabolically beneficial effects relative to diabetes, including reduced glucose intolerance, improved glucose tolerance, improved liver triglyceride levels, and increased insulin sensitivity. Authors concluded, "Based on these data, it can be suggested that THCV may be useful for the treatment of the metabolic syndrome and/or type 2 diabetes (adult onset diabetes), either alone or in combination with existing treatments."[6]

Other preclinical trials report that cannabinoids may mitigate various symptoms of the disease. Writing in the *American Journal of Pathology*, researchers at the Medical College of Virginia reported that rats treated with CBD for periods of one to four weeks experienced significant protection from diabetic retinopathy[7] -- one the leading cause of blindness in working-age adults. Other preclinical studies show that cannabinoid administration reduces diabetic-related tactile allodynia (pain resulting from non-injurious stimulus to the skin)[8-9] and symptoms of diabetic cardiomyopathy (weakening of the heart muscle). Experts have concluded, "[T]hese results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications."[10]

Randomized placebo-controlled clinical data has replicated some of these preclinical results. For example, a 2015 study published in *The Journal of Pain* reported that vaporized, whole-plant cannabis significantly reduces diabetic neuropathy in subjects resistant to other analgesics. Authors reported: "This small, short-term, placebo-controlled trial of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain. ...

Overall, our finding of an analgesic effect of cannabis is consistent with other trials of cannabis in diverse neuropathic pain syndromes."[11] A 2017 placebo-controlled clinical trial published in the journal *Diabetes Care* reported that the administration of THCV "significantly decreased fasting plasma glucose" levels and improved pancreatic cell function in type 2 diabetics.[12]

Several observational trials have reported that those with a history of cannabis use possess a lower risk of type 2 diabetes than do those with no history of use. For example, researchers at the University of California, Los Angeles assessed the association between diabetes mellitus and marijuana use among adults aged 20 to 59 in a nationally representative sample of the US population of 10,896 adults. They reported that past and present cannabis consumers possessed a lower prevalence of adult onset diabetes, even after authors adjusted for social variables (ethnicity, level of physical activity, etc.), despite all groups possessing a similar family history of diabetes. Researchers did not find an association between cannabis use and other chronic diseases, including hypertension, stroke, myocardial infarction, or heart failure compared to nonusers. Authors concluded, "Our analysis ... showed that participants who used marijuana had a lower prevalence of DM and lower odds of DM relative to non-marijuana users."[13]

Similar observational trial data appeared in the *American Journal of Medicine* in 2013. Researchers at Harvard Medical School and the Beth Israel Deaconess Medical Center in Boston assessed the relationship between marijuana use and fasting insulin, glucose, and insulin resistance in a sample of 4,657 male subjects. They concluded, "[S]ubjects who reported using marijuana in the past month had lower levels of fasting insulin and HOMA-IR [insulin resistance], as well as smaller waist circumference and higher levels of HDL-C [high-density lipoprotein or 'good' cholesterol]. These associations were attenuated among those who reported using marijuana at least once, but not in the past 30 days, suggesting that the impact of marijuana use on insulin and insulin resistance exists during periods of recent use."[14]

Commenting on this study, the journal's Editor-in-Chief wrote in an accompanying commentary: "These are indeed remarkable observations that are supported, as the authors note, by basic science experiments that came to similar conclusions. ... We desperately need a great deal more basic and clinical research into the short- and long-term effects of marijuana in a variety of clinical settings such as cancer, diabetes, and frailty of the elderly. I would like to call on the NIH and the DEA to collaborate in developing policies to implement solid scientific investigations that would lead to information assisting physicians in the proper use and prescription of THC in its synthetic or herbal form."[15]

More recently, investigators from the Conference of Quebec University Health Centers assessed cannabis use patterns and body mass index (BMI) in a cohort of 786 Inuit (Arctic aboriginal) adults ages 18 to 74. Researchers reported that subjects who consumed cannabis in the past year were more likely to possess a lower BMI, lower fasting insulin, and lower HOMA-IR (insulin resistance) as compared to those who did not use the substance.[16] Their findings are consistent with previous research showing an inverse relationship between cannabis use and diabetic markers and are supportive of previous population data showing that those who consume cannabis, typically possess

lower BMI,[17] lower odds of metabolic syndrome[18-19] and non-alcoholic fatty liver disease[20], and are less likely to be obese as compared to those who do not.[21-22]

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