MDH Minnesota Department *of* Health
OFFICE OF MEDICAL CANNABIS

Diabetes: Blood Sugar Control

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Diabetes mellitus is a group of conditions that affect the body's ability to produce or use insulin, a pancreatic hormone circulated through the bloodstream that acts to regulate blood glucose levels. This includes chronic diabetes (type I and type II diabetes) and reversible diabetes (prediabetes and gestational diabetes).

Type I Diabetes

The exact cause of type I diabetes is unknown, but believed to be a combination of genetic and environmental factors. This condition occurs when the immune system attacking and destroying insulin-producing β-cells in the pancreas. As a result, there is very little to no insulin available to regulate blood glucose levels (Mayo Clinic).

Type II Diabetes and Prediabetes

The cause of poor blood glucose control in prediabetes and type II diabetes is insulin resistance that develops over time: cells need increased amounts of insulin to respond and the pancreas cannot produce enough to meet the increased demand. As with type I diabetes, prediabetes and type II diabetes develop due to a combination of genetics and environmental factors; overweight and obesity are contributing, though not necessary, factors. Prediabetes is characterized by a state of impaired glucose control which has not yet advanced to full diabetes, but will likely do so in the absence of intervention. Type II diabetes is a progressive condition which may require ongoing modifications to the treatment plan. (Mayo Clinic)

Gestational Diabetes

Gestational diabetes is caused by insulin resistances in cells caused by the release of hormones during pregnancy which increase insulin resistance.

Diagnosis

Diagnosis of type I and II diabetes and prediabetes involves a blood test for glycated hemoglobin (HbA1c) levels, which reflects the percentage of blood sugar attached to hemoglobin and indicates average blood sugar level over the past two to three months (Mayo Clinic). Normal HbA1c levels are below 5.7%; prediabetes is indicated by HbA1c levels between 5.7% and 6.4%; levels of 6.5% or more indicate diabetes. In addition to measuring HbA1c levels, random or fasting blood sugar tests or an oral glucose tolerance test can be used to diagnose diabetes. Gestational diabetes is diagnosed through an initial glucose challenge test and follow-up glucose tolerance testing.

Complications and Consequences

Serious complications are associated with diabetes, and the risk of such complications rises with poor glycemic control. Acute consequences of poor blood glucose control include hyperglycemia, or high blood sugar, and hypoglycemia, or low blood sugar. Acute hyperglycemia can progress to ketoacidosis, or a diabetic coma. Acute hypoglycemia can progress to seizures, loss of consciousness and a coma. Complications include macrovascular complications such as heart disease, heart attacks or stroke, as well as microvascular complications including neuropathy which can result in severe pain and loss of feeling in affected limbs, nephropathy which can ultimately lead to kidney failure, and retinopathy which can lead to blindness. Another common diabetes complication is foot damage, resulting from neuropathy or poor circulation; this can lead to infections and ultimately amputation (Mayo

Clinic). Finally, diabetes is associated with premature death from all-cause mortality, mortality related to vascular causes, cancer and other causes, with worse outcomes associated with increased blood glucose levels (The Emerging Risk Factors Collaboration 2011).

Prevalence

The Centers for Disease Control and Prevention (CDC) estimated in a 2014 report that 29.1 million Americans, or 9.3% of the population had diabetes mellitus, of which as estimated 8.1 million were undiagnosed. Type I diabetes cases were estimated at 1.25 million, or 4% of the diabetes burden. Estimates for prevalence of prediabetes are much higher: 86 million Americans over 20 years of age had prediabetes (CDC National Diabetes Statistics Report, 2014).

Current Therapies

The American Diabetes Association describes a comprehensive evaluation following diagnosis that involves a thorough review of medical history, a physical examination, laboratory evaluation and referrals to specialized medical care. The goals of such an evaluation are to classify the patient, detect any diabetes-related complications that have arisen and develop an individualized care plan for future management of the disease. Treatment for diabetes often involves a holistic approach which includes targeting health behaviors, including a healthy diet and regular physical activity. Glycemic control (management of blood sugar) is a primary measure of diabetes care, as it has been shown to decrease incidence of microvascular complications including retinopathy, nephropathy and neuropathy (Diabetes Control and Complications Trial Group [DCCT/EDIC] 2000). Two major clinical trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that maintenance of HbA1c levels at approximately 7% is associated with fewer long-term complications, though treatment regimens that achieved these levels were associated with weight gain and increased risk of hypoglycemia (Lawson 1999). The American Diabetes Association position statement on standards of medical care recommend target ranges of HbA1c and plasma glucose but stress that treatment goals should be individualized and include consideration of balancing the risk of hypoglycemia with benefits from glycemic control.

Prediabetes patients can often successfully manage their blood glucose through lifestyle modification; a randomized clinical trial from the Finnish Diabetes Prevention Group found that lifestyle intervention (counseling on nutrition and weight loss) reduced the risk of developing diabetes in prediabetic subjects by 58% over the 3.2 year average study follow-up (Tuomilehto 2001).

Type I diabetes patients require insulin therapy; type II diabetes patients do not necessarily require pharmacotherapy. Some type II diabetes patients can manage blood glucose levels with diet modifications and exercise alone, however use of oral antidiabetic medications is very common. There are a few classes of oral antidiabetic medications; the most commonly

used is metformin, which decreases the amount of glucose released from the liver. Other oral antidiabetic groups include sulfonylureas, meglitinides and DPP-4 inhibitors, which stimulate insulin release; thiazolidinediones, which increase insulin sensitivity; and alpha-glucosidase inhibitors, which slow the absorption of carbohydrates into the blood stream. Combinations of oral antidiabetic agents are also commonly used to achieve greater glycemic control. It is not uncommon for patients with type ll diabetes to progress to the point where insulin is required.

Insulin regimens for diabetes are often characterized as either intensive therapy or conventional therapy. Conventional therapy was defined in the DCCT as typically consisting of multiple daily injections including mixed short-acting and intermediate-acting insulin, along with self-monitoring of urine and blood glucose and adjustments made occasionally based on overall health. Intensive therapy was defined in the trial as involving more frequent injections of both short-acting and long-acting insulin, where the dosage is calculated based on periodic blood glucose tests throughout the day, food intake and anticipated exercise. Intensive therapy has more stringent target ranges for blood glucose levels. There is evidence that intensive therapy regimens reduce the risk of microalbuminuria (Coca 2012), one of the complications associated with poor glycemic control which is associated with poor renal and cardiovascular outcomes (Basi 2008).

The CDC report estimated the prevalence of different diabetic therapies in the U.S. using 2010-2012 data from the National Health Interview Survey: an estimated 2.9 million American adults use insulin only; 3.1 million adults use both insulin and oral antidiabetic agents; 11.9 million use oral antidiabetic medications only and 3 million use neither therapy for the treatment of diabetes (CDC National Diabetes Statistics Report, 2014).

Individual management of blood glucose requires diligent adherence to a prescribed medication regimen often combined with lifestyle modification; as a result, many diabetic patients do not maintain their blood glucose within the recommended ranges. Cross-sectional health data from the U.S. collected from 2005-2010 reports that approximately 41.2% of diagnosed diabetes cases may not maintain HbA1c levels below 7%, based on laboratory testing at the time of survey administration (Selvin 2014).

Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors to which cannabinoids bind, is still a relatively new field of scientific inquiry. Translational research has shown that endocannabinoids play an important role in lipid and glucose metabolism in peripheral organs (Silvestri 2013) and therefore may be a target in diabetes therapy whose goal is to manage glucose levels. There is a limited number of animal studies examining the effects of cannabinoids on metabolic processes and dysfunction; one aspect of these processes of interest in diabetes treatment is the regulation of glucose tolerance and insulin sensitivity. The following is a sample of animal studies which address the relationship between cannabinoids and regulation of blood glucose levels. The two studies described below represent the level of

evidence currently available in pre-clinical studies to describe the effect of cannabis on measures of diabetes disease burden.

Levendal R-A, Schumann D, Donath M, Frost CL. Cannabis exposure associated with weight reduction and β-cell protection in an obese rat model. Phytomedicine 19(2012) 575-582.

This study used rat models to examine the effect of cannabis on β-cell secretory function in obese rats. Four groups were observed over a four-week period: an untreated lean control group, a cannabis-treated lean experimental group, an untreated obese control group, and a cannabis-treated obese experimental group. Rats in both experimental groups were injected with 5 mg THC/kg cannabis extract; control groups were injected with an equivalent amount of the vehicle solution. Insulin sensitivity was measured through blood glucose levels after a glucose bolus injection. Post-experiment plasma insulin levels were also examined using a rat insulin radioimmunoassay. Plasma levels of interleukin-1α and interleukin-1β, interferon-γ and tumor necrosis factor-α were also measured. The study found that cannabis exposure significantly increased food consumption in lean experimental rats compared to lean control rats but decreased food intake in obese experimental rats compared to the obese control group, though intake was still higher in this group compared to lean rats. The experimental data was used to generate a predictive polynomial model for body weight; the model showed that body weight increased for all groups, but cannabis exposure was associated with lower weights in both the obese and lean experimental groups compared to the obese and lean control groups, respectively. Analysis of plasma insulin and glucose levels found that while differences were noted between obese rats and lean rats (significantly lower blood glucose levels), no differences were found when comparing experimental rats to control rats in either obese or lean groupings.

No significant differences were found in glucose tolerance when comparing cannabis-exposed rats to unexposed rats in either the lean or obese groupings. In lean rats exposed to cannabis, increases in interleukin-1α and interleukin-6 compared to lean control rats were observed. In obese control rats compared to lean control rats, lower levels of interleukin-1α, interleukin-6 and interferon-γ were observed. Obese experimental rats had higher levels of interleukin-6 and interferon-γ compared to obese control rats.

These findings support the idea that the endocannabinoid system mediates feeding behavior and energy balance and that THC interacts with appetite regulation in a biphasic mechanism- stimulating appetite at low doses and suppressing appetite at high doses. Previous research has found THC retention in fat tissue to be much higher than other tissue; thus high THC levels accumulated in fat tissue could work to suppress appetite. The authors suggest this may account for differences observed between lean and obese rats. However, lean rats were observed to have higher blood glucose levels than obese rats. No differences in plasma insulin levels were observed across groups.

The authors conclude that exposure to cannabis may reduce the negative impact of diet-induced obesity by "reducing weight gain,… maintaining insulin levels, altering cytokine and gene expression levels that induce increased energy expenditure, while protecting

pancreatic tissue from apoptosis," within a rat model. Protection of β-cell function could be a mechanism of preventing or reducing the severity of diabetes, although this was not directly demonstrated from the scope of this study.

Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity, March 2006; 39(2):143-151.

This study aimed to examine whether cannabidiol (CBD), a component of the cannabis plant known to have anti-inflammatory properties, could prevent or delay diabetes occurrence in non-obese mice with a high propensity for developing type I diabetes. Cannabidiol was extracted from cannabis resin and injected into female mice with existing insulitis but without overt disease, who were "chosen to approximate the immunological status of a pre-type 1 diabetic human patient." Onset of overt diabetes, which was ascertained through urine glucose assays, analysis for insulitis, and pancreatic histopathology studies of beta cell integrity, occurred approximately at 14 weeks after birth within the study colony; therefore CBD injections were administered to mice up to 12 weeks old. All mice had normal blood glucose levels at the study inception; at ages 6-12 weeks mice in the treatment group were given 10-20 injections of 5mg/kg CBD.

In the control group, 86% of the mice developed overt diabetes at a mean age of 14 weeks; in the treatment group, a reduction in diabetes incidence was observed: 30% of treatment group mice developed overt diabetes ($p<0.001$). The treatment group mice who developed diabetes had a later onset (median age of 20 weeks, $p=0.0001$).

While this study may suggest that CBD may play a role in either preventing or delaying the onset of diabetes in patients with prediabetes or who are predisposed to type I diabetes without full onset, it is unclear from the results what role CBD might play in directly modulating insulin resistance or managing blood glucose levels.

Clinical Trials

Currently there are no clinical trials, either complete or underway, examining the effect of whole plant cannabis, THC, or CBD on blood glucose control. There are, however, the two trials noted below- one completed but unpublished and the other underway- that use tetrahydrocannabivarin (THCV), a cannabinoid typically present in small amounts in cannabis. THCV is a homologue of THC. It has a propyl side chain instead of THC's pentyl group, which makes it produce different effects than THC.

GW Pharma completed a Phase IIa randomized clinical trial of 62 diabetic patients, where two treatment arms were given oral THCV for the treatment of type II diabetes for a 13-week period. The study results are not published, but the GW Pharma website states the findings were that the oral cannabinoid reduced fasting plasma glucose levels, increased fasting insulin levels, improved pancreatic β-cell functioning; additionally it had other antidiabetic effects including increasing serum adiponectin, reducing systolic blood pressure and serum interleukin-6 levels. Non-significant findings include increased insulin sensitivity,

reduced HbA1c levels, improvement in glucose and insulin response to glucose load, increased glucagon-like peptide-1 levels and reduced C-reactive protein levels. More information about this trial can be found GW Pharma's Research and Development: http://www.gwpharm.com/Diabetes.aspx.

A follow-up trial of the same oral THCV product as an adjunct therapy with metformin in the treatment of type II diabetes is currently enrolling in Romania and the United Kingdom. The trial will last approximately 12 weeks and primary outcome measure will be changes from baseline to trial completion in mean HbA1c level. The principal investigator is Melanie Davies from the Leicester Diabetes Center in Leicester, UK. The projected completion was July 2016; more information can be found at A Study of GWP42004 as Add on to Metformin in the Treatment of Participants With Type 2 Diabetes: https://clinicaltrials.gov/ct2/show/study/NCT02053272.

Observational Studies

There are a number of relatively recent epidemiologic studies examining cross-sectional survey data which report mixed findings on the relationship between marijuana use and either the incidence of diabetes or markers of glycemic control (such as insulin and insulin sensitivity, and HbA1c levels). The following summaries are not a complete collection of studies on this topic, but they represent the wide range of results and the complexities of interpreting cross-sectional data. While there are serious limitations in interpreting any reported associations, the strength of these studies is the large and representative population sample they include.

Penner EA, Buettner H, Mittleman MA. The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults. The American Journal of Medicine. 2013 July; 126(7):583-589.

This paper analyzes data from the National Health and Nutrition Examination Survey (NHANES) from 2005-2010 to characterize the relationship between marijuana use and metabolic processes through the clinical metrics of fasting insulin, glucose and insulin resistance. The study cohort, from a nationally-drawn probability sample, included 4,567 adults and captured both self-reported survey responses and fasting blood samples tested for fasting insulin, blood glucose and homeostasis model assessment of insulin resistance (HOMA-IR) which provides an estimate of insulin resistance. To ascertain marijuana use, subjects were asked if they have ever smoked marijuana or hashish, how long since they last used marijuana/hashish and how many days in the past 30 days they used marijuana/hashish. Responses were categorized as past users (no marijuana use in the past 30 days), current users (use within the past 30 days) and never users, the largest group (n=2103).

Since the study data spanned several years of survey administration, there was variation in the data collected. Some survey cycles included HDL cholesterol testing; others included HbA1c measurements. Other clinical measurements included blood pressure, body mass index (BMI) and waist circumference.

In the study population there were 579 current marijuana users and 1975 past users. After weighting to adjust for the NHANES sampling design and adjustment for potential confounders (age, sex, race/ethnicity, education level, income, marital status, tobacco use, physical activity level, and alcohol use), both past and current marijuana use was associated with 16% lower fasting insulin levels and 17% lower HOMA-IR when compared to the never users; past and current users also had significantly lower BMI. Additionally, current marijuana use appeared to be significantly protective against low HDL cholesterol and high waist circumference. Other metabolic indicators examined were triglyceride levels and systolic and diastolic blood pressure but no significant associations were found between marijuana use and these outcomes. The authors state that the results of their analyses were not different when they eliminated subjects who were known to have diabetes.

Limitations of this study include the cross-sectional study design which makes any interpretation of associations more difficult than randomized clinical trials or studies with retrospective or prospective follow-up. The authors point out that improved metabolic indicators may be the result of a diabetes diagnosis, in which a subject may modify their lifestyle with the intent to improve their health as a response to receiving a new diagnosis. There is also a possibility that other confounders which were not measured as part of this study are in fact mediating the relationship between insulin resistance and marijuana use.

Rajavashisth TB, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, Friedman Tc. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open. 2012 Feb 24.

This study examined the relationship between diabetes occurrence and marijuana usage in data from the National Health and Nutrition Examination Survey III, a cross-sectional study which used a sample generated from highly stratified probability sampling across the US with oversampling for minority groups and older subjects. Marijuana use was classified as non-users which included both never users and subjects who had not used marijuana within the past month. Current users were categorized as either light users (≤4 days per month) or heavy users (≥5 days per month). Marijuana products included hash, pot, grass, or other references to the cannabis plant; both smoking and ingestion were included.

Diabetes was identified by asking subjects whether they were told they have diabetes or high blood sugar, or with fasting blood glucose levels over 125mg/dl. Of the 8,127 subjects aged 20-59 with complete laboratory data, 719 were identified to have diabetes.

Among all subjects aged 20-59 years regardless of missing laboratory data (n=10,896), 6,667 (62%) were non-users, 3,346 (31%) were past users, 557 (5%) were light current users and 326 (3%) were heavy current users. After adjustment for possible confounders (age, gender, race/ethnicity, BMI, education level, tobacco and alcohol use, physical activity, cholesterol – serum total, HDL and LDL- triglycerides, vitamin D, C-reactive protein, ferritin, fibrinogen, white blood cell count, and uric acid) both past and current marijuana users had lower prevalence of diabetes, although there were no differences in prevalence of hypertension, stroke, myocardial infarction, or heart failure compared to non-users. Of all

usage groups, current light marijuana users had the lowest prevalence of diabetes; current heavy users and past users also had lower prevalence of diabetes compared to never users. The authors postulate that this effect may be due to anti-inflammatory properties of cannabis.

The authors point out that the major limitation of this study is that it examines purely cross-sectional, self-reported data. Though potential confounders were examined carefully, no causal relationships can be determined due to the lack of retrospective or prospective study. Furthermore, the survey only captured information on recreational use without any examination of quantity, formulation or mode of usage (smoked versus ingested). It is therefore difficult to generalize any associations found in this study to cannabis usage through medical cannabis programs.

Thompson Ca, Hay JW. Estimating the association between metabolic risk factors and marijuana use in U.S. adults using data from the continuous National Health and Nutrition Examination Survey. Annals of Epidemiology 25(2015) 486-491.

The authors of this paper examine the conclusions from a number of other studies based on National Health and Nutrition Examination Survey (NHANES) and similar large-scale datasets. The study reviews NHANES survey data from 2005-2012 to estimate the effect of marijuana use on markers of metabolic disease, including insulin resistance and fasting insulin. Citing that reports have produced mixed conclusions on whether marijuana use is associated with lower risk of metabolic syndrome, the authors used outcome variables of fasting insulin, fasting glucose, insulin resistance, HDL cholesterol, triglycerides, blood pressure, BMI and waist circumference and adjusted for known risk factors of metabolic syndrome: age, sex, race, BMI, tobacco use, physical activity, income, alcohol consumption, carbohydrate intake and postmenopausal status, along with educational level, including imputed values for missing data and including a squared term for age to account for a non-linear relationship between age and any outcomes. As a final check for robustness, alcohol use was substituted for marijuana use in each multivariate model.

The study found that in models adjusted for known risk factors and demographics, fasting insulin, insulin resistance, BMI and waist circumference were all lower in current marijuana users than in never users. The analyses were then stratified by age and sex to account for any effect modification between the predictors; this had a diminishing effect on the associations. All significant effects of marijuana disappeared for subjects 40 years or older, and in subjects under 40, marijuana use remained a predictor of only insulin, insulin resistance and waist circumference. Stratification by sex showed no association between marijuana use and outcomes in women; in men, marijuana use was associated only with reduced HDL cholesterol, BMI and waist circumference. Associations with insulin and insulin resistance dropped out. Finally, replacing marijuana use with alcohol use showed a similar pattern of association: alcohol consumption was associated with higher HDL cholesterol, lower fasting insulin, lower insulin resistance, BMI and waist circumference. The authors conclude that their analyses suggest that previous examinations into the relationship between marijuana use and metabolic risk factors have not been rigorous and therefore the conclusion that marijuana use may lower risk of metabolic diseases, including diabetes, is suspect.

Alshaarawy O, Anthony JC. Cannabis Smoking and Diabetes Mellitus: Results from Meta-Analysis with Eight Independent Replication Samples. Epidemiology. 2015 July; 26(4):597-600.

This meta-analysis examines the role of cannabis smoking with type 2 diabetes using epidemiologic estimates from eight independent replications from the NHANES data and the National Surveys on Drug Use and Health (NSDUH) from 2005-2012. The authors note that some preclinical studies have found that activation of cannabinoid receptors is linked with increased appetite and insulin resistance, but a number of epidemiologic studies find an inverse relationship between cannabis use and prevalence of diabetes- specifically, prevalence of obesity and biomarkers associated with impaired glucose metabolism.

Both NHANES and NSDUH use probability sampling to generate a sample representative of U.S. residents. Both studies deploy surveys using audio computer-assistant self-interview assessment protocols; NHANES supplements self-reported data with clinical and lab assessments. Diabetes is measured by NSDUH through self-reported questions; NHANES includes self-report but also collects insulin or antidiabetic medication use and lab values to generate a composite diabetes indicator. Cannabis smoking is captured as the following: recently active cannabis smokers, past cannabis smokers, and never smokers. Multiple logistic regressions were performed to produce adjusted odds ratios of diabetes across cannabis use categories; as a follow-up to this analysis, time to onset of diabetes as a function of cannabis use was modeled, as well as time to onset of cannabis use as a function of diabetes incidence to examine the direction of potential causality. The meta-analytic odds ratio, adjusted for age, sex, ethnicity, education, income-poverty ratio, alcohol and tobacco use, for diabetes among recently-active cannabis users (using never users as the reference group) was 0.7 (95% confidence interval: 0.6, 0.9). Additional onset-age analyses as described above were limited by sample size but suggested that cannabis use preceded diabetes onset and reinforced the inverse relationship between cannabis use and diabetes, though not robustly.

Limitations of this study include the cross-sectional nature of the source data and self-reported diagnosis data. Furthermore, the direction of causality remains to be proven as there may yet be confounders which were not measured or adjusted for in this analysis. Nevertheless, the authors conclude that these data show a possible protective effect of cannabis use on the incidence of diabetes.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of blood glucose were found.

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