Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study

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OBJECTIVE

Cannabidiol (CBD) and Δ^9-tetrahydrocannabivarin (THCV) are nonpsychoactive phytocannabinoids affecting lipid and glucose metabolism in animal models. This study set out to examine the effects of these compounds in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this randomized, double-blind, placebo-controlled study, 62 subjects with non-insulin-treated type 2 diabetes were randomized to five treatment arms: CBD (100 mg twice daily), THCV (5 mg twice daily), 1:1 ratio of CBD and THCV (5 mg/5 mg, twice daily), 20:1 ratio of CBD and THCV (100 mg/5 mg, twice daily), or matched placebo for 13 weeks. The primary end point was a change in HDL-cholesterol concentrations from baseline. Secondary/tertiary end points included changes in glycemic control, lipid profile, insulin sensitivity, body weight, liver triglyceride content, adipose tissue distribution, appetite, markers of inflammation, markers of vascular function, gut hormones, circulating endocannabinoids, and adipokine concentrations. Safety and tolerability end points were also evaluated.

RESULTS

Compared with placebo, THCV significantly decreased fasting plasma glucose (estimated treatment difference [ETD] = −1.2 mmol/L; $P < 0.05$) and improved pancreatic β-cell function (HOMA2 β-cell function [ETD = −44.51 points; $P < 0.01$]), adiponectin (ETD = -5.9×10^6 pg/mL; $P < 0.01$), and apolipoprotein A (ETD = −6.02 μmol/L; $P < 0.05$), although plasma HDL was unaffected. Compared with baseline (but not placebo), CBD decreased resistin (−898 pg/ml; $P < 0.05$) and increased glucose-dependent insulinotropic peptide (21.9 pg/ml; $P < 0.05$). None of the combination treatments had a significant impact on end points. CBD and THCV were well tolerated.

CONCLUSIONS

THCV could represent a new therapeutic agent in glycemic control in subjects with type 2 diabetes.

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The endocannabinoid system (ECS) modulates food intake and energy homeostasis (1,2), and chronic overactivation of the ECS has been identified in obesity and type 2 diabetes (3). The ECS exerts some of its actions by activating cannabinoid receptors 1 (CB_1) and 2 (CB_2). Modulation of CB_1 receptors with rimonabant (a synthetic cannabinoid) led to a significant reduction in body weight, waist circumference, and triglyceride (TG) concentrations, and an increase in HDL cholesterol (HDL-C) and adiponectin concentrations (4), as well as a reduction in HbA_{1c} in subjects with type 2 diabetes (-0.8 to -1.25%; $P < 0.001$). However, marketing authorization for rimonabant was withdrawn in 2008 because of an increased incidence of psychiatric adverse events (AEs) (5). Rimonabant is thought to be a CB_1 receptor antagonist/inverse agonist, but it is unclear whether modulation of other cannabinoid receptor activity could have beneficial metabolic effects without significant psychiatric effects.

Cannabidiol (CBD) is one of the major phytocannabinoids obtained from the *Cannabis sativa L.* plant. In rodent studies, CBD has multiple desirable effects in the context of hyperglycemia, mainly through its anti-inflammatory and antioxidant properties (6–10). In animal models of obesity (*ob/ob* genetically obese mice), 4 weeks of treatment with CBD 3 mg/kg produced a 55% increase in HDL-C concentration and reduced total cholesterol by >25% (C.S., unpublished data). In addition, the same dose reduced liver TGs and increased both liver glycogen and adiponectin concentration. There is also evidence from animal studies showing that CBD modulates cardiovascular response to stress (11).

Unlike the related molecule Δ^9-tetrahydrocannabinol (THC), CBD does not activate CB_1 receptors in the brain and therefore lacks the psychotropic actions of THC. Indeed, CBD may reduce psychosis (12) and mitigate the psychoses associated with cannabis misuse (13). Other receptor sites implicated in the actions of CBD include the orphan G-protein–coupled receptor-55 (GPR55), the putative endothelial cannabinoid receptor, the transient receptor potential vanilloid 1 (TRPV1) receptor, α1-adrenoceptors, μ opioid receptors, and the adenosine transporter and serotonin-1A receptors (14). CBD also activates and has physiological responses mediated by peroxisome proliferator–activated receptor γ (15–17). A CBD/THC combination (Sativex/Nabiximols; GW Pharmaceuticals) is currently licensed in most European Union countries and in Canada, New Zealand, Australia, Malaysia, the United Arab Emirates, and Kuwait, for the symptomatic treatment of spasticity in moderate to severe multiple sclerosis, and CBD alone (Epidiolex; GW Pharmaceuticals) was granted orphan drug designation by the U.S. Food and Drug Administration in February 2014 in Dravet and Lennox-Gastaut syndromes in children, with phase 3 clinical trials ongoing in those conditions.

Δ^9-Tetrahydrocannabivarin (THCV) is a naturally occurring analog of THC, but with different pharmacological effects. It is has been reported to behave as both a CB_1/CB_2 agonist and/or a CB_1/CB_2-neutral antagonist (20–24), probably dose-dependent, with agonism observed at high doses and antagonism at low doses (19). However, there is little evidence of CB_1 agonism in vivo compared with the observed in vivo effects of THC at similar doses. Other target sites of action include GPR55 (23) and transient receptor potential channels (24,25).

Acute intraperitoneal administration of THCV in rodents at 3, 10, and 30 mg/kg body weight caused hypophagia and weight loss, with food intake and body weight returning to normal on day 2 (26). The effect was similar to that of a CB_1 antagonist, AM251, also used in the same study. In another study, involving diet-induced obese mice, oral THCV (2.5–12.5 mg/kg) reduced body fat content, increased energy expenditure, and reduced fasting insulin and 30-min insulin response to oral glucose tolerance test (OGTT) (27). In the same study, in genetically obese (*ob/ob*) mice, a similar increase in 24-h energy expenditure was observed with 3 mg/kg THCV, whereas 12.5 mg/kg THCV caused a significant reduction in liver TGs (27). In genetically obese mice (*ob/ob*), a 1:1 ratio of a combination of THCV and CBD (3:3 mg/kg) reduced change to total cholesterol levels by 19% and increased HDL-C by 50%. The same combination reduced liver TG, increased liver glycogen levels, reduced fasting insulin, and increased energy expenditure (C.S., unpublished data).

The findings from these preclinical studies demonstrate a potential beneficial effect of both CBD and THCV, alone or in combination, in diabetes and lipid metabolism, with very distinct pharmacological profiles, and therefore different side effects, to rimonabant. This prompted the first-ever investigation of the effects of CBD and THCV on dyslipidemia and glycemic control in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects and Study Design

This randomized, double-blind, placebo-controlled, parallel-group, phase IIa proof-of-concept study was conducted at four U.K. centers. The protocol was reviewed and approved by the East Midlands–Leicester Multi Centre Research Ethics Committee (10/H0406/42) and local research and development departments as required and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Subjects aged ≥18 years with type 2 diabetes and HbA_{1c} ≤10% (86 mmol/mol), HDL-C ≤1.3 mmol/L in females and ≤1.2 mmol/L in males, and plasma TGs ≤10 mmol/L were eligible. Subjects needed to either receive no oral hypoglycemic agents or take stable doses of prespecified, noninsulin glucose-lowering therapies (metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, or glucagon-like peptide 1 [GLP-1] therapy) for 3 months prior to screening. Subjects not on statin therapy or on a stable dose of a statin for at least 4 weeks prior to randomization were eligible for inclusion. Subjects were also required not to make any changes to their diet or exercise for 4 weeks prior to randomization and during the course of the study.

Main exclusion criteria (see Supplementary Data for full details) included use of prohibited medications (insulin, fibrates, thiazolidinediones, therapeutic omega-3 fatty acids, and α-glucosidase inhibitors), recent or current use of cannabis, history of significant depression, planned travel outside the U.K. during the course of study, genetic dyslipidemia, or significant cardiac, renal, or hepatic impairment.

There was a 1- to 5-week period between screening (visit 1) and treatment randomization (visit 2). Visit 1 could be split into two separate visits (1A and 1B)

to allow a 21-day washout period of the prohibited medications prior to blood sampling for eligibility. Remaining visits occurred 4, 8, and 13 weeks after initiation of treatment (visits 3, 4, and 5, respectively) or earlier if patients withdrew. A safety follow-up visit occurred 7 days after study completion or withdrawal (visit 6). Visits 4 and 6 were telephone assessments.

Patients were required to take study medication in the fasted state, twice daily, 30 min before breakfast and 30 min before evening meal, typically 12 h apart for 13 weeks.

Study End Points and Assessments

The primary end point was change in mean serum HDL-C from baseline, in CBD and THCV groups, compared with the change in placebo group at week 13. Secondary end points included changes in lipid profile, glycemic control, insulin sensitivity, body weight, visceral adiposity, appetite, and cardiovascular function. Tertiary end points were changes in markers of inflammation, vascular function, adipokines, endocannabinoids, and gut hormone concentrations.

Serum lipid concentrations were analyzed with the Roche modular system using enzymatic calorimetric assays. Nonesterified fatty acid concentrations were quantified on the Roche COBAS 311 system (Roche), using an acyl-CoA synthetase/acyl-CoA oxidase method. Apolipoprotein markers were analyzed on the Roche COBAS 311 system (Roche) using immunoturbidimetric assays based on the principle of immunological agglutination. Plasma VLDL cholesterol (VLDL-C) concentrations were determined by ultracentrifugation.

A standard 75-g OGTT was performed, and plasma glucose and serum insulin were analyzed using the Roche modular system (Roche) and Advia Centaur immunoassay analyzer (Siemens Healthcare), respectively. HOMA-insulin resistance, insulin sensitivity, and β-cell function were calculated using the HOMA2 Calculator v2.2 (Diabetes Trials Unit, University of Oxford).

Plasma endocannabinoids *N*-arachidonoylethanolamine (AEA), 2-arachidonoylglycerol (2-AG), oleoylethanolamine (OEA), and palmitoylethanolamine (PEA) were analyzed using liquid chromatography-tandem mass spectrometry, based on a previously published method (28). Ketones, orexin A, and retinol-binding protein 4 (RBP-4) were analyzed using immunoassay, whereas all other tertiary end points including adiponectin, resistin, leptin, E-selectin, vascular cell adhesion molecule, Von Willebrand factor, C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α, glucose-dependent insulinotropic peptide (GIP), ghrelin, and GLP-1 were analyzed by multiplex analysis, using commercially available kits (Milliplex, HMHMAG-34K, HCVD1-67AK, HADK-1-61K-A, HCVD2-67BK, BPHCVD05-6; Merck Millipore).

Resting blood pressure was measured using a digital blood pressure monitor, whereas cardiovascular parameters including systolic, diastolic, and mean arterial pressure, heart rate, stroke volume, cardiac output, interbeat interval, ejection time, and total peripheral resistance were measured using a Finometer (Finapres Medical Systems), which uses a finger-clamp method to detect beat-to-beat changes in digital arterial diameter with an infrared photoplethysmograph.

Adipose tissue distribution was assessed using whole-body MRI; images were analyzed by a blinded investigator using sliceOmatic (TomoVision, Magog, Canada). Body weight and seven-point skinfold measures were also recorded. Hepatic TG concentration was assessed using MRS and analyzed using JMRUI software.

Patient's Global Impression of Change (PGIC) and Clinician's Global Impression of Change (CGIC) were assessed using an ordinal seven-point Likert scale (1, very much improved, to 7, very much worse). Changes in appetite were established using patients' scores of their appetites that they recorded on daily basis using an appetite 0–10 numerical rating scale (NRS), in which 0 is no appetite (do not feel hungry) and 10 is maximum appetite (completely hungry all the time) (29). The change from mean baseline score (mean of 7 days before start of treatment) was compared with the mean score from the last 7 days on treatment (end of 13 weeks).

Safety assessments included reporting for AEs and serious AEs (SAEs), recording vital signs, pre- and posttreatment laboratory sampling and electrocardiograms, and change from baseline in Beck Depression Inventory-II (BDI-II) scores.

The BDI-II questionnaire, an assessment for anxiety and depression, is a multiple-choice, self-reported inventory and is one of the most widely used and validated instruments for measuring severity of depression (30).

Statistical Methods

An independent statistician produced a schedule for random treatment allocation, which was held centrally and not divulged to any other person involved in the study until the database had been locked. Patients were randomly allocated to treatment groups in a 1:1:1 ratio, stratified by center, according to the randomization schedule. Study site staff identified the pack number to be dispensed to the subject at each of visits 2 and 3 according to the randomization schedule.

Analysis was performed using the intention-to-treat population; all subjects who were randomized received at least one dose of study medication and had on-treatment efficacy data. All statistical tests were two-sided at the 5% significance level. Between-group differences and 95% CIs were also calculated. The primary end point and the majority of secondary end points were analyzed using ANCOVA of the changes from baseline to the end of treatment in the associated parameter, with the exception of the PGIC and CGIC, which were analyzed with ordinal logistic regression using the cumulative proportional odds model. The parameter's baseline values were included as a covariate, and treatment was included as a factor. The tertiary variables were analyzed using ANCOVA with baseline value as covariate and treatment group and sex as factors or using pairwise Fisher exact test, as appropriate. The null hypothesis was one of no difference in the effects of any of the active treatments compared individually with placebo. As this study was a phase 2a proof-of-concept study, no formal sample size calculation was performed.

Changes from baseline in all the plasma markers were analyzed post hoc using a paired *t* test, and the glucose response to OGTT was analyzed using repeated-measures two-way ANOVA.

RESULTS

A total of 125 patients was screened and 62 randomized to the 5 treatment arms. The disposition of subjects enrolled is presented in Fig. 1. Subjects were similar

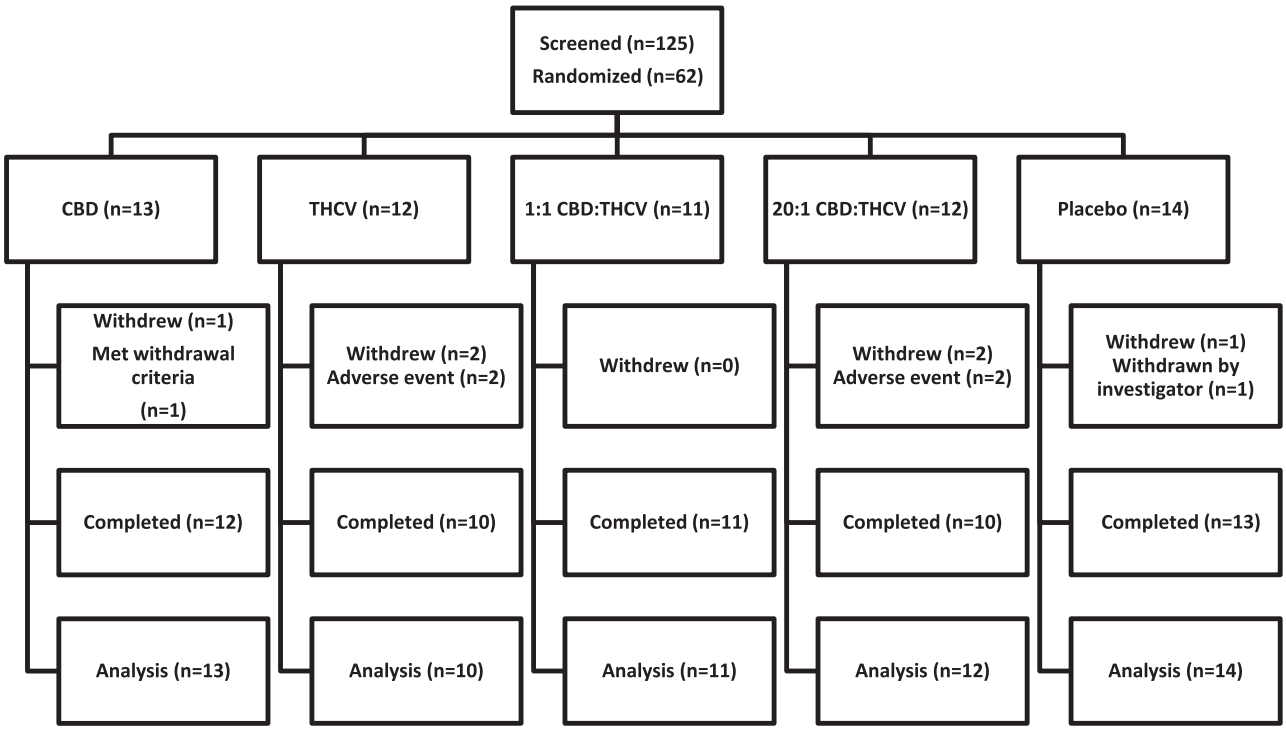

Figure 1—Summary of breakdown of patients enrolled in the study. A total of 125 subjects were screened and 62 randomized to this study.

between treatment groups (Table 1) in terms of baseline characteristics.

Lipids

THCV had no effect on HDL-C concentrations (Table 2), but it increased apolipoprotein A (Apo A) concentrations compared with placebo from baseline to the end of treatment (from 48.5 to 49.1 μmol/L in the THCV vs. 47.3 to 43.9 μmol/L in the placebo group; $P < 0.05$) (Fig. 2*A*). THCV had no effect on LDL cholesterol (LDL-C) concentrations. CBD alone and in combination with THCV did not affect any of the lipid parameters (Table 2).

Glycemic Control

THCV reduced fasting plasma glucose concentration compared with placebo from baseline to the end of treatment (from 7.4 to 6.7 mmol/L in the THCV vs. 7.6 to 8.0 mmol/L in the placebo group; estimated treatment difference [ETD] = -1.24 ± 0.6 [SEM]; $P < 0.05$) (Fig. 3*A*). In line with this, there was a significant increase in HOMA2 β-cell function in the THCV treatment group compared with placebo from baseline to the end of treatment (from 105.1 to 144.4 in the THCV group vs. 96.4 to 94.7 in the placebo group; ETD = 44.6 ± 16.1 [SEM]; $P < 0.01$) (Table 2 and Fig. 3*B*). There was no significant difference in glucose response to OGTT at 2 h. However, when compared with baseline, THCV significantly improved 3-h blood glucose response ($P < 0.05$) (Fig. 3*C*). CBD alone or in combination with THCV had no effect on glycemic parameters (Table 2).

Vascular Function

Compared with placebo, CBD and THCV, alone and in combination, had no effect on cardiovascular parameters (Table 2) or plasma markers of vascular function (Supplementary Table 1).

Adipokines

There was an increase from baseline in adiponectin concentration in the THCV group and a reduction in placebo group; the treatment difference was statistically significant in favor of THCV treatment (ETD -5.9×10^6 pg/mL; $P < 0.01$) (Fig. 3*B*). Plasma concentrations of leptin and resistin remained unchanged with THCV treatment. Compared with baseline rather than placebo, CBD caused a significant reduction in the concentration of resistin (−898 pg/mL; $P < 0.05$) (Fig. 3*C*), but had no effect on leptin or adiponectin. Subjects taking a combination of CBD and THCV had no change in adipokine levels (Supplementary Table 1).

Markers of Inflammation

Both THCV and CBD, or their combination, had no significant effect on plasma markers of inflammation (CRP, tumor necrosis factor-α, and interleukin-6) (Supplementary Table 1).

Gut Hormones

THCV, on its own and in combination with CBD, had no effect on the concentrations of gut signaling hormones including GLP-1, GIP, and ghrelin (Supplementary Table 1). However, in a post hoc analysis, for which posttreatment concentrations were compared with baseline (rather than placebo), CBD caused a significant increase in the concentration of GIP (21.2 pg/mL; $P < 0.05$) (Fig. 3*D*), without any effect on GLP-1 or ghrelin concentrations.

Body Weight

Baseline mean body weight (kg ± SD) in the CBD, THCV, 1:1 CBD/THCV, 20:1 CBD/THCV, and placebo groups were 97.1 ± 13.8, 98.3 ± 17.5, 100.7 ± 14.5, 100.5 ± 17.9, and 94.2 ± 19.1, respectively. There were no statistically significant changes in anthropometric parameters including weight, waist circumference, waist-to-hip ratio, and skinfold thickness in any of the treatment groups (Table 2).

Table 1—Summary of patient demographics and concomitant therapy

	CBD (*n* = 13)	THCV (*n* = 12)	1:1 CBD/THCV (*n* = 11)	20:1 CBD/THCV (*n* = 12)	Placebo (*n* = 14)	Total (*n* = 62)
Male, number of subjects (%)	10 (77)	10 (83)	6 (55)	9 (75)	7 (50)	42 (68)
Female, number of subjects (%)	3 (23)	2 (17)	5 (45)	3 (25)	7 (50)	20 (32)
Age (years), mean (SD)	56.8 (9.9)	62.5 (12.6)	59.3 (8.8)	58.0 (8.1)	58.6 (7.7)	59.0 (9.4)
Weight (kg), mean (SD)	97.2 (13.8)	98.3 (17.5)	100.7 (14.5)	100.5 (17.9)	94.2 (19.1)	98.0 (16.4)
BMI (kg/m^2), mean (SD)	33.2 (5.4)	34.0 (6.5)	36.4 (5.6)	35.4 (4.6)	33.4 (7.0)	34.4 (5.8)
Duration since diagnosis of diabetes (years), mean (SD)	2.8 (3.3)	4.8 (3.6)	4.4 (2.7)	5.1 (3.3)	3.8 (3.5)	4.2 (3.3)
Number (%) of patients on antidiabetic and lipid-lowering therapy						
Metformin	9 (69)	9 (75)	10 (91)	11 (92)	12 (86)	51 (82)
DPP-4 inhibitors	1 (8)	1 (8)	1 (9)	1 (8)	1 (7)	5 (8)
Sulfonylureas	3 (23)	5 (42)	4 (36)	3 (25)	4 (29)	19 (31)
Statins	9 (69)	11 (92)	10 (91)	8 (67)	13 (93)	51 (82)

DPP-4, dipeptidyl peptidase 4.

Visceral Adiposity and Liver TGs

There were no changes in visceral adiposity or liver TG (Table 2) as assessed by MRI/MRS in any of the treatment groups.

Appetite

None of the treatments had any significant impact on appetite as assessed by 0–10 NRS scores (Table 2).

PGIC and CGIC

A full summary of the PGIC and CGIC assessment responses is presented in Supplementary Figs. 1 and 2. Analysis of these responses showed a treatment difference in favor of all the active treatments, to varying degrees, but most notably between the 1:1 CBD/THCV and placebo treatment groups on CGIC. There were reported improvements in 7 out of 11 (63.6%) patients in the CGIC on 1:1 CBD/THCV treatment, compared with only 2 of the 14 (14.3%) patients on placebo, with a recorded improvement on CGIG. This translated to a statistically significant treatment effect of 1:1 CBD/THCV treatment compared with placebo, with an odds ratio of 9.529 ($P < 0.05$) in the CGIC. No other statistically significant effects were calculated for any other active treatment in either assessment.

Endocannabinoids

There was no significant change in the levels of circulating AEA, 2-AG, OEA, and PEA after 13 weeks of any treatment (Table 2).

Post Hoc Analysis in THCV Group Analyzing Glucose Response to OGTT and Changes in HbA_{1c}

An improvement in glucose response to OGTT was noted in the THCV group at 3 h (Fig. 3*C*). When subjects on any form of diabetes treatment other than diet/metformin were excluded from analysis, this effect became more pronounced ($P < 0.05$ at 1 h and $P < 0.01$ at 3 h; $n = 6$) (Fig. 3*D*). In the same group of patients receiving diet/metformin only, compared with placebo, a significant improvement in HbA_{1c} was also observed ($P < 0.05$) (Fig. 3*E*).

Safety

The study medication was well tolerated, with the majority of subjects experiencing AEs that were mild or moderate in severity. Treatment-emergent (all causality) AEs were reported by 11 of 13 (84.6%) subjects in the CBD group, 11 of 12 (91.7%) in the THCV group, 7 of 11 (63.6%) in the 1:1 CBD/THCV group, and 8 of 11 (66.7%) in the 20:1 CBD/THCV group, compared with 13 of 14 subjects (92.9%) receiving placebo.

The more common treatment-related AE reported by subjects in all the groups, except for 20:1 CBD/THCV, was decreased appetite (two subjects [15.4%] receiving CBD, four subjects [33.3%] receiving THCV, one subject [9.1%] receiving 1:1 CBD/THCV, and two subjects [14.3%] receiving placebo). None of the subjects in the 20:1 CBD/THCV group experienced an AE of decreased appetite. Two subjects reported diarrhea with THCV, compared with no subjects in the placebo group. Two subjects (14.3%) on placebo also reported dizziness. All other treatment-related AEs were reported in individual subjects.

No deaths occurred during the study. There were two SAEs in this study. One patient (8.3%) taking 20:1 CBD/THCV treatment experienced an SAE of myocardial infarction that was considered moderate in severity, had recovered by the end of study, and was not considered to be treatment related. One placebo patient experienced an SAE of myocardial ischemia that was not considered to be treatment related, was mild in severity and occurred on day 92 of the study; the SAE was still ongoing at the end of the study.

Mean changes from screening to the end of treatment in BDI-II scores for the CBD, THCV, and 1:1 CBD/THCV treatment groups were 0.85, 0.58, and 0.27 points, respectively, which were not statistically significant from placebo (change from baseline of −0.08 points), and remained within the "minimal depression" range for all treatments. The largest change from baseline to the end of treatment in BDI-II score was in the 20:1 CBD/THCV treatment group (4.91 points). Although this remained in the "minimal depression" bracket, it was statistically significant compared with placebo (ETD = 4.77; $P < 0.01$).

Conclusions

The aim of this pilot study was to investigate the clinical effect and tolerability of two phytocannabinoids, THCV and CBD, alone and in combination, in subjects with type 2 diabetes and dyslipidemia. THCV significantly decreased fasting plasma glucose, and increased β-cell function, adiponectin, and Apo A concentrations, and was well tolerated in patients. These findings suggest that THCV may represent a new therapeutic

Table 2—Clinical data before (baseline) and after (treatment) 13 weeks of randomized treatment

	CBD (n = 13)		THCV (n = 12)		1:1 CBD/THCV (n = 11)		20:1 CBD/THCV (n = 12)		Placebo (n = 14)	
Variable	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
HDL-C (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.1	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.3	1.0 ± 0.2
Total-C (mmol/L)	4.5 ± 0.9	4.3 ± 0.7	3.8 ± 0.9	3.7 ± 1.0	4.2 ± 1.1	3.8 ± 0.7	4.6 ± 0.9	4.2 ± 0.6	4.0 ± 0.7	3.9 ± 0.9
LDL-C (mmol/L)	2.5 ± 0.7	2.4 ± 0.6	2.0 ± 0.6	2.0 ± 0.8	2.2 ± 0.8	2.0 ± 0.5	2.8 ± 0.6	2.5 ± 0.5	2.2 ± 0.6	2.2 ± 0.7
HDL/LDL-C ratio	0.5 ± 0.2	0.4 ± 0.2	0.6 ± 0.3	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.2	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
UC VLDL-C (mmol/L)	0.8 ± 0.4	1.0 ± 0.5	1.0 ± 0.7	0.9 ± 0.7	1.0 ± 0.5	1.0 ± 0.4	1.1 ± 0.4	1.0 ± 0.3	1.0 ± 0.5	0.9 ± 0.4
TG (mmol/L)	2.2 ± 1.4	2.3 ± 1.3	1.7 ± 1.1	1.8 ± 1.5	2.4 ± 1.6	2.2 ± 1.2	1.9 ± 0.7	1.9 ± 0.7	2.1 ± 1.4	2.0 ± 1.1
Apo A (μmol/L)	48.6 ± 9.7	43.6 ± 6.6	48.5 ± 7.0	49.1 ± 6.4[b]	48.7 ± 11.1	46.8 ± 7.4	48.7 ± 10.0	45.7 ± 6.3	47.3 ± 8.8	43.9 ± 7.2
Apo B (μmol/L)	3.1 ± 0.8	3.3 ± 0.7	2.6 ± 0.6	2.7 ± 1.0	3.0 ± 0.9	2.9 ± 0.7	3.4 ± 0.7	3.4 ± 0.6	2.9 ± 0.7	3.0 ± 0.6
Apo B/Apo A ratio	0.6 ± 0.2	0.7 ± 0.2	0.5 ± 0.1	0.5 ± 0.2[a]	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.6 ± 0.2	0.7 ± 0.1
NEFA (mmol/L)	0.6 ± 0.2	0.5 ± 0.3	0.6 ± 0.1	0.6 ± 0.2	0.7 ± 0.3	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Liver TG (%)	26.9 ± 16.9	22.2 ± 17.1	11.9 ± 8.0	11.5 ± 13.5	33.3 ± 18.3	32.2 ± 26.2	23.2 ± 14.3	25.4 ± 17.4	20.5 ± 15.1	18.5 ± 15.4
Fasting glucose (mmol/L)	8.0 ± 2.3	8.4 ± 2.8	7.4 ± 2.3	6.7 ± 1.9[b]	8.5 ± 2.5	8.7 ± 2.0	8.4 ± 2.8	8.8 ± 3.1	7.6 ± 1.4	8.0 ± 1.6
Fructosamine (μmol/L)	259.5 ± 34.4	256.8 ± 44.6	238.2 ± 25.0	239.3 ± 28.7	254.4 ± 35.7	256.0 ± 55.2	253.3 ± 34.8	268.8 ± 58.2	241.4 ± 19.3	253.7 ± 32.0
HbA_{1c} (%)	6.9 ± 0.9	7.0 ± 1.1	6.6 ± 0.6	6.5 ± 0.7	7.2 ± 1.1	7.4 ± 1.5	7.2 ± 0.9	7.3 ± 1.3	7.0 ± 0.7	7.3 ± 1.0
Glucose, 2-h OGTT (mmol/L)	7.4 ± 2.4	6.6 ± 2.7	5.7 ± 3.1	6.2 ± 2.7	8.7 ± 3.8	8.8 ± 2.5	5.6 ± 3.4	6.6 ± 2.3	7.9 ± 2.6	8.4 ± 2.2
Insulin, 2-h OGTT (pmol/L)	604.1 ± 605.2	454.8 ± 387.5	661.0 ± 381.2	724.9 ± 589.6	789.5 ± 677.2	900.2 ± 875.8	659.3 ± 570.4	651.6 ± 730.0	653.6 ± 381.5	619.7 ± 455.3
Fasting insulin (pmol/L)	110.3 ± 42.8	123.8 ± 60.8	152.9 ± 94.2	203.5 ± 197.7	175.3 ± 86.1	185.7 ± 67.6	197.6 ± 107.9	192.2 ± 69.1	171.7 ± 105.0	179.7 ± 75.7
C-peptide (nmol/L)	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.1 ± 0.5	1.2 ± 0.2	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.0 ± 0.4	1.1 ± 0.4
HOMA2-IR	2.3 ± 0.9	2.6 ± 1.5	3.0 ± 1.9	3.8 ± 3.3	3.5 ± 1.6	3.7 ± 1.3	4.2 ± 2.9	4.0 ± 1.5	3.4 ± 2.1	3.6 ± 1.5
HOMA2 insulin sensitivity	51.3 ± 20.1	53.0 ± 36.2	47.3 ± 32.4	53.5 ± 44.3	34.9 ± 17.1	30.4 ± 12.9	30.2 ± 11.4	28.9 ± 11.5	42.4 ± 29.2	37.8 ± 32.2
HOMA2 β-cell function	70.9 ± 27.2	69.6 ± 31.5	105.1 ± 64.7	144.4 ± 110.3[b]	95.7 ± 50.7	93.8 ± 47.5	103.7 ± 60.6	97.9 ± 50.5	96.4 ± 41.4	94.7 ± 39.2
BMI (kg/m^2)	33.2 ± 5.4	33.0 ± 4.9	34.0 ± 6.5	33.8 ± 6.7	36.4 ± 5.6	36.1 ± 5.7	35.4 ± 4.6	35.4 ± 4.4	33.4 ± 7.0	32.9 ± 7.7
Waist circumference (cm)	107.7 ± 10.8	108.0 ± 10.6	115.3 ± 13.1	114.9 ± 13.8	115.4 ± 9.5	116.2 ± 11.8	113.7 ± 13.1	113.5 ± 12.1	109.2 ± 13.0	108.4 ± 13.1
Waist-to-hip ratio	1.0 ± 0.05	1.0 ± 0.1	1.0 ± 0.05	1.0 ± 0.06	1.0 ± 0.1	1.0 ± 0.05	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Neck circumference (cm)	42.4 ± 3.3	42.1 ± 3.7	42.8 ± 3.8	42.8 ± 3.6	42.7 ± 3.3	42.2 ± 3.8	42.8 ± 3.6	42.5 ± 4.0	41.7 ± 4.8	41.1 ± 4.8
Visceral abdominal fat (L)	8.1 ± 1.9	8.5 ± 2.2	9.1 ± 3.5	9.0 ± 3.5	8.5 ± 3.0	8.6 ± 2.7	9.1 ± 2.5	10.2 ± 2.2	7.2 ± 2.4	7.5 ± 3.4
Appetite 0–10 NRS score	5.6 ± 1.0	4.9 ± 1.0	5.4 ± 1.7	5.0 ± 1.5	4.7 ± 1.2	3.6 ± 1.6	5.0 ± 2.2	4.1 ± 1.9	5.1 ± 1.3	4.5 ± 1.3
Systolic BP (mmHg)	133.4 ± 16.4	132.2 ± 13.0	135.9 ± 13.4	132.8 ± 17.1	126.4 ± 11.6	134.3 ± 12.8	132.7 ± 11.0	134.2 ± 14.8	137.2 ± 11.9	140.4 ± 11.2
Diastolic BP (mmHg)	70.1 ± 8.8	70.6 ± 8.8	70.6 ± 12.2	71.0 ± 9.4	73.2 ± 6.8	77.5 ± 7.7	73.5 ± 10.4	72.2 ± 10.5	73.0 ± 9.5	72.3 ± 10.6
Pulse rate (bpm)	71.5 ± 17.7	70.5 ± 15.7	74.5 ± 12.3	74.1 ± 12.4	80.1 ± 12.2	76.6 ± 8.0	77.1 ± 12.1	82.0 ± 15.8	72.1 ± 10.8	75.5 ± 7.3
BDI-II score	3.8 ± 3.5	4.6 ± 3.7	2.8 ± 3.8	3.3 ± 3.3	4.5 ± 5.2	4.7 ± 5.0	2.8 ± 2.7	7.9 ± 7.6	3.5 ± 3.9	3.5 ± 3.2
AEA	0.2 ± 0.1	0.2 ± 0.05	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.04	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
2-AG	5.0 ± 2.9	4.7 ± 2.9	4.3 ± 1.7	13.6 ± 28.6	6.2 ± 3.1	5.0 ± 1.5	3.8 ± 1.5	3.7 ± 1.7	5.0 ± 3.3	5.3 ± 3.4
OEA	2.4 ± 1.1	1.8 ± 0.7	2.4 ± 1.0	2.3 ± 0.6	2.5 ± 0.8	2.2 ± 0.7	2.2 ± 0.5	2.2 ± 0.8	2.4 ± 0.5	2.1 ± 0.5
PEA	2.7 ± 1.9	1.8 ± 0.7	2.7 ± 1.1	2.5 ± 0.7	2.5 ± 0.7	2.4 ± 0.6	2.5 ± 1.2	2.6 ± 1.7	2.9 ± 1.3	2.0 ± 0.4

Data are mean ± SD. Apo B, apolipoprotein B; BP, blood pressure; HOMA2-IR, HOMA2–insulin resistance; NEFA, nonesterified fatty acid; Total-C, total cholesterol; UC, ultracentrifugation. [a]$P < 0.05$; [b]$P < 0.01$ compared with placebo.

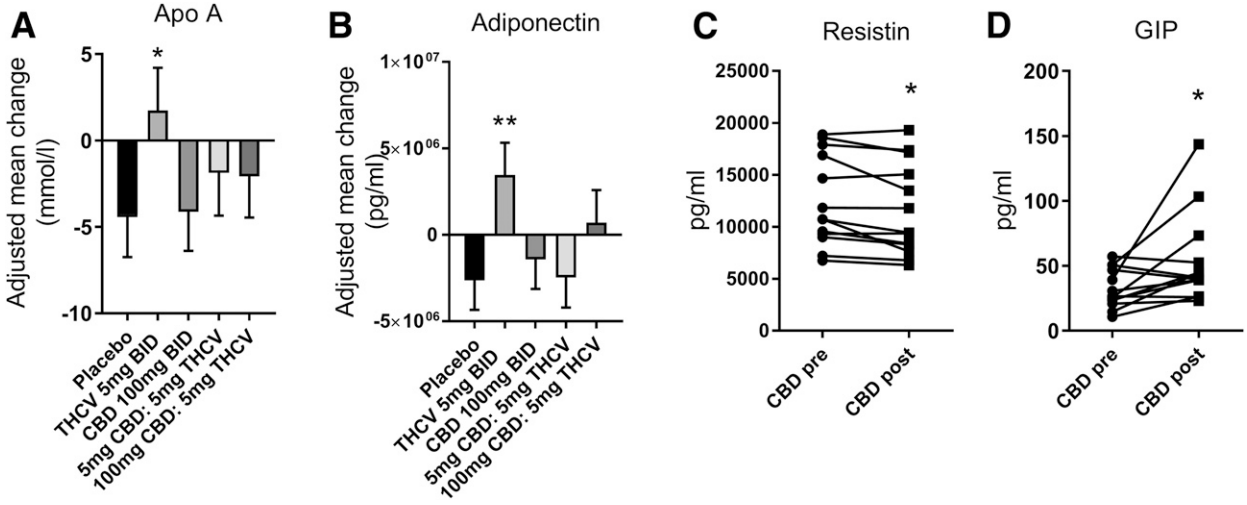

Figure 2—Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A (*A*) and adiponectin (*B*). Data were analyzed by ANCOVA and presented as mean ± SEM. CBD caused a significant reduction in resistin (*C*) and an increase in GIP concentration (*D*), when compared with pretreatment values. Data were analyzed post hoc using paired *t* test and presented as mean ± SEM. BID, twice daily. $*P < 0.05$; $**P < 0.01$.

agent for glycemic control in subjects with type 2 diabetes.

The ECS plays an important role in modulating energy intake and expenditure (for reviews, see Refs. 1,2), and a chronically overactive ECS may have a role in diabetes and its various complications (2). A recent cross-sectional study showed that marijuana use was associated with lower concentrations of fasting insulin, insulin resistance, and waist circumference (31). Some of the favorable metabolic effects seen with smoking cannabis may be due to partial CB_1 agonists like THC, which may act as a functional antagonist in conditions of increased endocannabinoid tonelike obesity, because of its lower CB_1 binding affinity and efficacy in comparison with 2-AG, for which levels are elevated in visceral obesity (32). Rimonabant, a CB_1 receptor antagonist, was the first in its class to be used as antiobesity drug, but led to significant psychiatric AEs (5). Preclinical studies with the plant-derived compound THCV have shown that it produces hypophagia and weight reduction in lean mice (26) and improves glucose tolerance and insulin sensitivity in diet-induced obese mice (27). Similar results have been seen with CBD in *ob/ob* mice (C.S., unpublished data), and CBD has been reported to lower the incidence of diabetes in nonobese diabetic mice (33) and arrest the onset of autoimmune diabetes in nonobese diabetic mice (34). Given the positive metabolic effects of both THCV and CBD in preclinical studies and their potent anti-inflammatory and antioxidant properties (20,35,36), we decided to investigate, for the first time, their efficacy and tolerability in subjects with type 2 diabetes.

THCV Alone

THCV treatment alone had no effect on HDL-C concentration. It did, however, produce a significant rise in serum Apo A, when compared with placebo. Apo A makes up 90% of HDL protein and constitutes an important structural component of the HDL particle. Apo A I, which accounts for 70% of the Apo A (the remaining 20% accounted for by Apo A II), plays an important role in reverse cholesterol transport (37). The significance of this result remains unclear.

THCV significantly reduced fasting blood glucose concentrations, improved HOMA2 β-cell function, and improved the 3-h blood glucose response to OGTT, without any significant difference in insulin response. These findings are in keeping with the recent animal data, in which THCV improved fasting glucose and 30-min glucose response to OGTT and also improved insulin sensitivity by reducing fasting and post–glucose insulin concentrations (27). In the same study, THCV treatment improved insulin-induced phosphorylation of Akt (also known as protein kinase B) in insulin-resistant human hepatocytes and mice myotubes, suggesting improved insulin signaling as one of the possible mechanisms of action.

Although there was an improvement in fasting and 3-h post-OGTT blood glucose, there were no changes in body weight and gut hormone concentrations. In fact, a rise in the concentration of RBP-4 was observed with THCV, an adipokine that has been associated with obesity and insulin resistance (38). Therefore, the mechanism by which THCV improves glycemic control remains unclear.

THCV significantly increased adiponectin concentrations. Adiponectin enhances hepatic insulin sensitivity, increases fatty acid oxidation, and has important antiatherogenic properties. Its concentrations are reduced in obesity and type 2 diabetes (39).

Positive metabolic effects of THCV on glycemic control and adiponectin concentrations were also seen with rimonabant, the first CB_1 antagonist to be licensed as antiobesity medication that was later withdrawn from market due to increased incidence of psychiatric AEs (5). It is, however, important to emphasize that although rimonabant consistently reduced body weight in all the reported randomized clinical trials, no such change was seen with THCV, suggesting clear differences in the mechanisms of action of these compounds. Recent animal data with THCV similarly showed no effect on body weight (27).

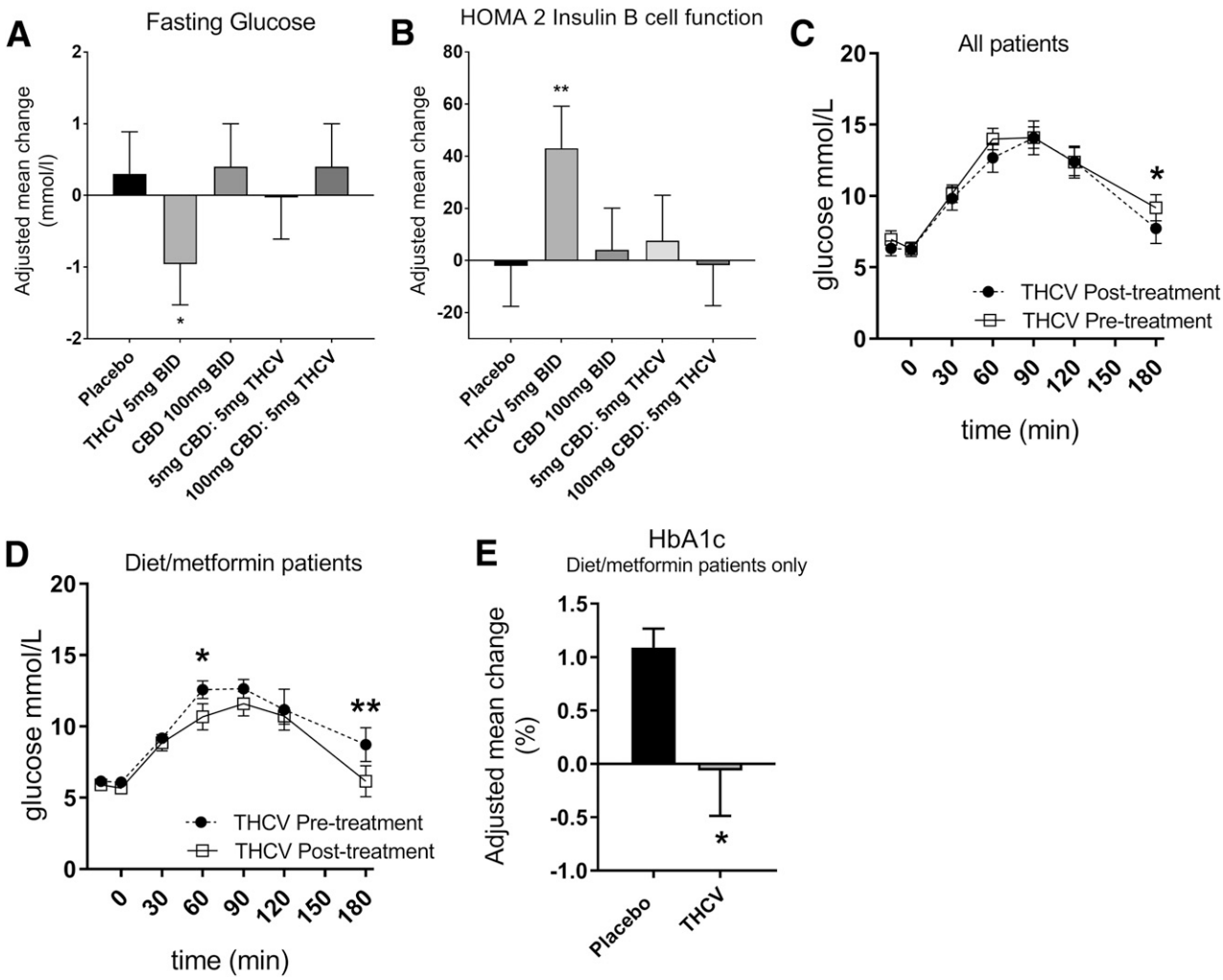

Figure 3—Compared with placebo, THCV alone caused significant improvement in fasting glucose (*A*), and in keeping with this, there was a highly significant improvement in β-cell function measured by HOMA2 (*B*). THCV caused significant improvement in 3-h glucose response during OGTT (*C*), when compared with pretreatment values. Data were analyzed using two-way ANOVA and presented as mean ± SEM. *D*: Compared with pretreatment values, there was a highly significant improvement in 3-h glucose response to OGTT with THCV, when subjects on any oral hypoglycemic therapy other than diet and/or metformin were excluded from analysis ($n = 6$). In the same subgroup (analyzed post hoc), compared with placebo, there was a statistically significant improvement in HbA_{1c} (*E*). Data were analyzed post hoc using repeated-measures two-way ANOVA and paired *t* test, respectively, and presented as mean ± SEM. BID, twice daily. $^*P < 0.05$; $^{**}P < 0.01$.

Moreover, rimonabant improved the lipid profile (increased HDL-C and reduced TG levels), whereas THCV had no effect on lipid parameters in our study (4). There is also a clear difference in chemical structure between THCV and rimonabant. It is therefore reasonable to believe that THCV and rimonabant have different pharmacological and safety profiles. At micromolar concentrations, THCV inhibits the activity of both fatty acid amide hydrolase and monoacyl glycerol lipase, thereby inhibiting the hydrolysis of AEA and 2-AG, respectively (40). THCV, therefore, can act as an indirect agonist at the cannabinoid receptors, by enhancing the activity of the ECS. Because such a change was not seen in our study, it is reasonable to believe that, at the dose tested, THCV was unable to modulate the ECS. Recent animal data from Wargent et al. (27) showed that most of the positive metabolic effects of THCV were seen with 5 and 12.5 mg/kg doses given orally in rodents. In comparison with this, the dose used on our study (10 mg/day, ~0.1 mg/kg in humans) was much lower.

CBD Alone

Although CBD did not produce any effects on the primary and secondary efficacy outcomes compared with placebo, it reduced circulating resistin concentrations from baseline, while increasing the concentration of circulating GIP. Increased concentrations of resistin are associated with obesity and insulin resistance (41). GIP is one of the incretin hormones produced by K cells in the proximal duodenum, which is known to have insulinotropic and pancreatic β-cell–preserving properties (42). Despite having positive effects on resistin and GIP, CBD did not produce any improvement in glycemic control.

CBD is known for its indirect agonism at the CB_1 receptors, by either increasing CB_1 constitutional activity or the endocannabinoid tone. CBD has been reported to inhibit hydrolysis of AEA by fatty acid amide hydrolase (but only at high micromolar levels) and also increases 2-AG levels (39). In a recent clinical study, in subjects with schizophrenia, 800 mg/day

of CBD treatment significantly increased serum AEA levels and was associated with an improvement in clinical profile of these subjects (12). In our study, CBD (albeit at a much lower dose), alone or in combination with THCV, had no effect on the plasma levels of endocannabinoids, suggesting that it had minimal interaction with the ECS at the doses investigated.

Studies in rodents have used intraperitoneal CBD in a dose ranging from 1 mg/kg/day to 20 mg/kg/day, with positive effects on the metabolism seen only with higher dose ranges (7–9). In a 70-kg individual, a 20 mg/kg/day dose equates to 1,400 mg/day. Similarly, human studies have used CBD in higher doses (12,43). The dose used in our study was 200 mg/day, which could possibly explain lack of therapeutic effects seen with CBD.

Combination of CBD and THCV

Except for an improvement in CGIC assessments with 1:1 CBD/THCV treatment, none of the efficacy parameters were affected by 1:1 or 20:1 combination of CBD and THCV. There was a trend toward an improvement in most lipid parameters and the overall incidence of all-causality treatment-related AEs was lowest in the 1:1 CBD/THCV treatment group; these factors could have led to an impression of improvement in subjects' overall condition with this treatment. Although the combination of CBD and THCV did not produce any favorable effects on any of the parameters, the favorable effects of THCV were also lost in the combination treatment. Similarly, the positive effects of CBD on GIP and resistin were not seen in any of the combination treatments. This suggests that CBD and THCV in combination may counteract their individual therapeutic effects at least in the ratios and doses tested in this study. This may be at the level of receptors or due to interference with each other's metabolism or therapeutic half-life and requires further investigation.

Safety

Both CBD and THCV were well tolerated, with the majority of patients experiencing AEs that were mild in severity. The most common AE was reduced appetite with similar incidence across all of the treatment groups. There were no reports of depression and no clinically significant abnormalities on electrocardiogram and laboratory results, including blood count and liver and renal biochemistry, in any treatment groups. There was one SAE of myocardial ischemia in the placebo group and one SAE of myocardial infarction in the 20:1 CBD/THCV group; both were considered unrelated to study medication. With regards to the BDI-II scale, although the change in 20:1 CBD/THCV treatment group was statistically significant, all mean active treatments and placebo scores remained in the "minimal depression" range.

CONCLUSIONS

In this clinical study, the first to study the effects of CBD and THCV in subjects with type 2 diabetes and dyslipidemia, THCV improved glycemic control and therefore warrants further investigation in this therapeutic area. CBD failed to show any detectable metabolic effects despite producing desirable changes in some adipokines and gut hormone concentrations. The incidence of AEs was similar between treatment groups, and both CBD and THCV were well tolerated. No new safety concerns were identified in the study.

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Author Contributions. K.A.J. was involved in study design, researched data, wrote the manuscript, and reviewed and edited the manuscript. S.H.R. recruited patients and reviewed and edited the manuscript. D.A.B. and J.D.B. researched data and reviewed and edited the manuscript. E.L.T. researched data. C.S. was involved in study design and reviewed and edited the manuscript. S.E.O. was involved in study design, wrote the manuscript, and reviewed and edited the manuscript. G.D.T. was involved in study design, served as chief investigator, wrote the manuscript, and reviewed and edited the manuscript. C.S. of GW Pharmaceuticals is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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