Metabolic effects of medical cannabis treatment

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ABSTRACT

Cannabis has a wide range of favorable clinical effects on pain, sleep, mood, gastrointestinal symptom, appetite and physical activity, factors that may affect the metabolic profile of the consumer. In this study, we prospectively evaluated patients recently starting medical cannabis treatment. All patients from the rheumatology clinic, who were just approved for medical cannabis treatment for resistant chronic pain, were recruited. After consent, demographic and clinical parameters were documented, including indication for medical cannabis treatment, way of consumption, type of cannabis and monthly dose of medical cannabis. Fasting morning blood glucose, hemoglobin A1c, insulin, lipid profile, cortisol and uric acid levels, in addition to body weight, were obtained just prior to and 3 months following cannabis consumption. Wilcoxon' sign rank test was used to compare baseline levels to those obtained 3 months later. Twenty-eight patients completed the study. Mean age of the patients was 47.8±9.1 years and ~70% were female patients. 75% of all the patients had fibromyalgia. Mean monthly consumed cannabis amount was 22.21±3.6 g, and 21 (75%) patients used extracts (oil). There was no significant change in any parameter evaluated. The results of our study seem to indicate that medical cannabis, mainly extracts, have no significant effect on any parameter of the metabolic profile of patients with chronic pain syndrome, during 3 months of initial use.

INTRODUCTION

Medical cannabis (MC) is gaining more and more popularity for the treatment of different chronic syndromes and diseases.[1] It is mainly used for the treatment of resistant different chronic pain syndromes, neurological problems, gastrointestinal and other entities.[2–4] Its utility for the treatment of resistant pain (regardless of origin), sleep problems, spasticity, tremor and peripheral numbness had been shown in different studies.[5–7]

The word Cannabis is a taxonomic term referring to a genus (*genus* Cannabis) of flowering plants that are members of the family Cannabaceae. This genus comprises three species: *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*.[8] Hybrids of the first two species are used as MC. Cannabis contains hundred plus of phytocannabinoids, terpenoids and flavonoids. The most active compounds of MC are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD),[9] which belong to the phytocannabinoids. THC is a psychotropic compound while CBD is not. The main difference between the sativa and indica subspecies is the content of THC, which is usually low in the former and higher in the latter. Marihuana plants belong to *Cannabis sativa* and are rich in THC, responsible for the "high" feeling of Marihuana. Cannabis and Marihuana are often used interchangeably by the public.

The general perception is that *Cannabis indica* is an effective pain reliever, with a flat and relaxing high, while *Cannabis sativa* provides a more energizing feeling.[10]

It is believed that following smoking or vaping cannabis, various cannabis compounds work together to create a unique effect and benefit, coined "the entourage effect".[11]

MC is consumed mainly by smoking/vaping of flowers or sublingually/orally of extracts in oil preparations.[12 13] Its most active compounds (THC and CBD) connect to different receptors in the body, mainly CB1 and CB2.[14] CB1 is mainly found in the central nervous system and CB2 mainly in cells and tissues of the immune system. THC is considered a partial agonists of these receptors while CBD is considered an antagonist, explaining the difference of clinical effects of the two substances. Activation of these receptors results in signal transduction leading to production of different compounds including cytokines and others.[15]

Cannabis arouses/improves appetite and treats/prevents nausea and or vomiting, mainly among recent users, with chronic pain syndromes, malignancies, gastrointestinal problems or other entities.[16] However, despite the expanding clinical use of MC, there are few reports on the metabolic effects of MC, with inconsistent findings regarding different parameters including glucose and lipid profiles.[17 18] Other studies relate to marijuana in general but not to MC specifically.

In this study, we prospectively evaluated different metabolic profiles of patients who were treated by MC for different medical reasons.

MATERIALS AND METHODS

All patients who are followed at the rheumatology clinic at the Nazareth hospital, and recently licensed for MC use, by the Israeli medical association agency (IMCA), were asked to participate in our study. After consent, patients were weighed and have blood test following 12-hour night fast for glucose, hemoglobin A1c (HbA1c), insulin level, total

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Table 1 Demographics and clinical parameters of the patients

Parameter	Result (%)
Female:Male	19:9
Age*	47.8±9.1, 28–60
Patients with diabetes	2 (~7)
Patients with hyperlipidemia	4 (~14)
Total amount of cannabis (g)/month*	22.21±3.6, 20–30
% THC	6.75±4, 1–15
% CBD	12.1±4.2, 6–20
Oil:Flowers	21:7
Type of use	
Sublingual	21 (75%)
Smoking	5 (~18%)
Vaping	2 (~7)
Indication	
Fibromyalgia	21 (75)
Osteoarthritis	5 (~18)
CRPS	2 (~7)

CBD, cannabidiol; CRPS, chronic regional pain syndrome; THC, delta-9-tetrahydrocannabinol.

cholesterol, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), morning serum cortisol level and uric acid. Insulin resistance was calculated as blood glucose levels doubled by morning insulin level divided by 25.

Three months later, these tests were repeated as well as the weight. Patients were asked to continue during the study period, the same diet and treatments that were using. A change of <0.5 kg in weight was considered as no change.

Demographics of the patients, indication for MC use, monthly consumed amount of MC, type and way of consumption of MC, were all documented. Extracts of MC in Israel contain only THC and/or CBD.

Exclusion criteria included patients on systemic or topical steroids or who stopped steroid treatment 3 months or less prior to recruitment, patients who initiated or stopped anti-diabetic/lipid/weight treatment (medical or dietary) in the previous 3 months prior to recruitment, and patients who started/stopped meds affecting uric acid levels 1 month or less prior to recruitment.

Wilcoxon's test was used to compare baseline levels to those obtained 3 months later levels.

The IMCA issues a license for MC use to a woman of childbearing age, only following a signed form by her primary physician that the patient is not pregnant, and is not planning pregnancy while using MC.

RESULTS

Thirty-two patients were enrolled and 28 patients completed the study. Two patients were not able to perform a repeated test, and other two patients were started on steroids during the study period. Two patients had diabetes and treated with oral hypoglycemics and four patients diagnosed with hyperlipidemia, two of them treated with statins.

None of the patients were on steroids during the previous 6 months prior to the study.

Table 1 summarizes the demographics of the patients. Mean age of the patient was 47.8±9.1 years, and ~70% of the patients were women. Seventy-five per cent of the patients had fibromyalgia and a similar percentage used extracts only. Monthly mean dosage of consumed cannabis was 22.21±3.6 g, with mean % of THC and % of CBD content of 6.75±4 and 12.1±4.2, respectively.

Table 2 summarizes the different lab tests and weight, prior and 3 months following MC treatment.

DISCUSSION

The main finding in our study is that MC, mainly extracts of THC and CBD, seem to have no significant effect on any of the metabolic parameters evaluated in our study.

It must be remembered that most of our patients were considered healthy ones except for two patients with diabetes and four patients with hyperlipidemia.

Fifty-seven per cent of the patients had a decrease in hemoglobin A1c, mostly 0.1%–0.3%%, but not a significant one. One patient with diabetes had a remarkable decrease in HbA1c levels, decreasing from 11.5 to 6.8. This patient had a slight decrease in its weight by 2 kg during a 3-month period. Our findings regarding serum glucose and HbA1c levels were also supported by the lack of a significant change in insulin resistance.

Some studies had reported that cannabis use was associated with reduced insulin resistance and fasting insulin levels,

Table 2 Metabolic parameters of the patients prior and 3 months following MC consumption

	Result (%)		
Parameter	Prior to MC use	Following MC use	P value
Weight (kg)*	77.4±10.3, 66–112	78.2±10.2, 68–111	0.07
Glucose (mg/dL)*	101.2±18.5, 81–158	104.6±18.7, 80–150	0.272
HabA1c (%)*	6.09±1.35, 5.1–11.5	5.76±0.6, 5–6.8	0.123
Insulin resistance*	57.6±35.7, 19.4–135.7	68.5±58.4, 16.3–252	0.328
Cholesterol (mg/dL)*	179.4±41.8, 99–286	174.6±32.1, 102–242	0.954
Triglycerides (mg/dL)*	150.6±52.1, 60–270	154.2±74.6, 68–425	0.372
LDL (mg/dL)*	102.1±27.4, 42–138	107.3±34.1, 48–189	0.687
HDL (mg/dL)*	44.6±11.1, 26–71	33.8±10.7, 28–69	0.21
Serum cortisol (nmole/L)*	407.4±94.3, 264–577	388.6±97.8, 258–570	0.652
Uric acid (mg/dL)*	5.12±1.99, 2.6–8.6	5.14±1.84, 2.4–7.5	0.612

*Mean±SD, range.
HDL, high-density lipoprotein;LDL, low-density lipoprotein.

in obese but not in non-obese patients.[19] Another study that evaluated metabolic effects of chronic cannabis smoking found visceral adiposity and adipose tissue insulin resistance, with no glucose intolerance of beta cell function.[20]

It would be interesting to see future studies involving patients with diabetes, where higher levels of HbA1c are observed and more room could be there for a potential effect of MC. Normal HbA1c or levels lower than 6%, had appriori little room for a change.

Although cannabis consumption is known to induce appetite, there was no significant change of weight among our patients. Nearly 40% of our patients had an increase in body weight, similar percentage had no change in body weight and the rest had some decrease in their weight. In the literature, the issue of body weight under cannabis consumption seems to be affected by different factors, including primary disease, initial weight and duration of cannabis usage.[21] In a large prospective study, an inverse association was found between cannabis use and weight gain.[22]

Regarding lipid levels, in a study evaluating lupus patients using marijuana, a favorable effect on TG, and LDL was found among users versus non-users.[23] In another study evaluating college students users of marijuana, no significant effect was found on total cholesterol TG, LDL or HDL lipids.[24]

MC in our study had also no significant effect on serum cortisol levels. This despite the fact that serum cortisol is considered as a stress hormone, at the time that MC causes calmness and a state of mental ease in many patients with chronic pain syndromes, where nervousness, one of the characteristics reported by fibromyalgia patients, could be described by some as an uncontrollable. In the literature, there was mixed evidence for how marijuana use, affects basal cortisol levels.[25] It seems that acute marihuana administration raises serum cortisol level, while among chronic users, this effect is blunted.

MC showed no significant effect on uric acid levels, one of parameters in the metabolic syndrome. This finding is not surprising in the face of lack of effects of MC on other metabolic parameters in other studies.

There are some limitations of our study. One is the relatively modest amounts of cannabis used by our patients. Initial allowance of MC licensed by the ministry of health in Israel is usually 20 g per month. Usually 1 g per day is considered a fair dose for fibromyalgia patients.[12] Second is that most of our patients had no metabolic problems to start with. Future studies should involve such patient. Third is that most of patients used extracts that included only THC and CBD in different ratios, without the other constituents of cannabis (other phytocannabinoids, terpenoids and flavonoids), so the impact of cannabis as a whole product was evaluated in the minority of our patients. Last but not least is the lack of standardization of whole products of cannabis flowers where other phytocannabinoids constituents mentioned earlier, besides THC and CBD, are present but not exactly quantified and qualified.

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REFERENCES

1 Pinkas J, Jabłoński P, Kidawa M, *et al*. Use of marijuana for medical purposes. *Ann Agric Environ Med* 2016;23:525–8.
2 Berger AA, Keefe J, Winnick A, *et al*. Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. *Best Pract Res Clin Anaesthesiol* 2020;34:617–31.
3 Lotan I, Treves TA, Roditi Y, *et al*. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. *Clin Neuropharmacol* 2014;37:41–4.
4 Naftali T. An overview of cannabis based treatment in Crohn's disease. *Expert Rev Gastroenterol Hepatol* 2020;14:253–7.
5 Poli P, Crestani F, Salvadori C, *et al*. Medical cannabis in patients with chronic pain: effect on pain relief, pain disability, and psychological aspects. A prospective non randomized single arm clinical trial. *Clin Ter* 2018;169:e102–7.
6 Sznitman SR, Vulfsons S, Meiri D, *et al*. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ Support Palliat Care* 2020;10:415–20.
7 Rice J, Cameron M. Cannabinoids for treatment of MS symptoms: state of the evidence. *Curr Neurol Neurosci Rep* 2018;18:50.
8 McPartland JM, Small E. A classification of endangered high-THC cannabis (cannabis sativa subsp. indica) domesticates and their wild relatives. *PhytoKeys* 2020;144:81–112.
9 Sholler DJ, Moran MB, Dolan SB, *et al*. Use patterns, beliefs, experiences, and behavioral economic demand of indica and sativa cannabis: a cross-sectional survey of cannabis users. *Exp Clin Psychopharmacol* 2021. doi:10.1037/pha0000462. [Epub ahead of print: 15 Apr 2021].
10 Rock EM, Parker LA. Constituents of cannabis sativa. *Adv Exp Med Biol* 2021;1264:1–13.
11 Koltai H, Namdar D. Cannabis Phytomolecule 'Entourage': From Domestication to Medical Use. *Trends Plant Sci* 2020;25:976–84.
12 Habib G, Levinger U. Characteristics of medical cannabis usage among patients with fibromyalgia. *Harefuah* 2020;159:343–8.
13 MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 2018;49:12–19.
14 Mackie K. Cannabinoid receptors: where they are and what they do. *J Neuroendocrinol* 2008;20(Suppl 1):10–14.
15 Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. *Science* 2002;296:678–82.
16 Grimison P, Mersiades A, Kirby A, *et al*. Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial. *Ann Oncol* 2020;31:1553–60.
17 Lazarte J, Hegele RA. Cannabis effects on lipoproteins. *Curr Opin Lipidol* 2019;30:140–6.
18 Scheffler F, Kilian S, Chiliza B, *et al*. Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders. *Schizophr Res* 2018;199:90–5.
19 Ngueta G, Ndjaboue R. Lifetime marijuana use in relation to insulin resistance in lean, overweight, and obese US adults. *J Diabetes* 2020;12:38–47.
20 Muniyappa R, Sable S, Ouwerkerk R, *et al*. Metabolic effects of chronic cannabis smoking. *Diabetes Care* 2013;36:2415–22.
21 Sansone RA, Sansone LA. Marijuana and body weight. *Innov Clin Neurosci* 2014;11:50–4.
22 Alshaarawy O, Anthony JC. Are cannabis users less likely to gain weight? Results from a national 3-year prospective study. *Int J Epidemiol* 2019;48:1695–700.
23 Ekenedilichukwu OJ, Obioma OJ, Chukwuemeka OE. Evaluation of serum lipid profile in male cannabis, smokers of College of health sciences, Nnamdi, Azikiwe University, Nnewi campus, Anambra state, Nigeria. *Int J Health Sci Res* 2018;8:1–6.
24 Orellana CP, Roldan P, Sibbitt W. Medical marijuana use: effect on lipid metabolism and atherosclerosis. *Arteriosclerosis Thrombosis Vascular Biology*;35.
25 Cservenka A, Lahanas S, Dotson-Bossert J. Marijuana use and hypothalamic-pituitary-adrenal axis functioning in humans. *Front Psychiatry* 2018;9:472.