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Original article

Cannabis is associated with blood pressure reduction in older adults – A 24-hours ambulatory blood pressure monitoring study

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ABSTRACT

Background: Medical cannabis use is increasing rapidly in the past several years, with older adults being the fastest growing group. Nevertheless, the evidence for cardiovascular safety of cannabis use is scarce. The aim of this study was to assess the effect of cannabis on blood pressure, heart rate, and metabolic parameters in older adults with hypertension.

Methods: We conducted a prospective study of patients aged 60 years or more with hypertension and a new prescription of cannabis. We have performed the following assessments: 24-hours ambulatory blood pressure monitoring, ECG, blood tests, and anthropometric measurements prior to the initiation of cannabis therapy and 3 months afterward. The primary outcome was change in mean 24-h blood pressure at 3 months.

Results: Twenty-six patients with a mean age of 70.42 ± 5.37 years, 53.8% females completed the study. At 3 months follow-up, the mean 24-hours systolic and diastolic blood pressures were reduced by 5.0 mmHg and 4.5 mmHg, respectively ($p<0.001$ for both). The nadir for the blood pressure and heart rate was achieved at 3 hours post-administration. The proportion of normal dippers changed from 27.3% before treatment to 45.5% afterward. No significant changes were seen in the different metabolic parameters assessed by blood tests, anthropometric measurements, or ECG exam.

Conclusion: amongst older adults with hypertension, cannabis treatment for 3 months was associated with a reduction in 24-hours systolic and diastolic blood pressure values with a nadir at 3 hours after cannabis administration.

Introduction

The use of medical cannabis in recent years is growing rapidly [1–3], frequently based on limited knowledge regarding safety and efficacy in varied indications such as: chronic pain, chemotherapy-induced nausea and vomiting, multiple sclerosis, Parkinson's disease, epilepsy and more [4–6]. Older adults have become the fastest growing group of medical cannabis users [7–9], ranging from approximately 7% to more than one third, depending on the country [10–12].

Despite the significant rise in use, the current evidence on the cardiovascular safety of medical cannabis in older adults is scarce [13, 14]. Recently, the American Heart Association (AHA) issued a position statement urging caution in use of medical cannabis in older adults due to the possible detrimental cardiovascular effects [15]. A series of studies that evaluated an oral drug containing pure delta 9-tetrahydrocannabinol (THC) in older adults found mixed results, with some showing a small increase in systolic blood pressure while causing a decrease or no change in heart rate and diastolic blood pressure [16,17], and others reported non-significant changes [18]. Furthermore, a number of retrospective studies done primarily in young individuals

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showed an association between cannabis use and cardiac arrhythmias [19–23].

The aim of this prospective study was to assess the medium-term effects of herbal cannabis on blood pressure, heart rate, electrocardiogram (ECG), and metabolic parameters in older adults with arterial hypertension. Our hypothesis was that cannabis use will not have a significant effect on blood pressure after 3 months of cannabis use.

Methods

Study design and population

The study was designed according to the 2007 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23] as a multi-center prospective, single-arm study with specific inclusion and exclusion criteria. The recruitment was performed at three sites: Soroka University Medical Center (SUMC), Assuta Ashdod Academic Medical Center (AAAMC) and NiaMedic Healthcare and Research Services clinic, all in Israel. Participants were recruited from pain, neurology, hematology-oncology, and geriatric outpatient clinics from November 2018 to February 2020 and were followed until May 2020. Inclusion criteria were age over 60, diagnosis of hypertension and a physician recommendation to use medical cannabis for one of the approved indications [24]. Exclusion criteria were New-York Heart Association (NYHA) functional classification class III-IV [25], life expectancy of less than 1 year and previous use of cannabis in the year preceding the enrollment date.

Procedures

After signing informed consent, participants had a baseline evaluation that included 24-hours ambulatory blood pressure monitoring (ABPM), ECG, blood tests, anthropometric measurements, demographics, and medical history. Cannabis type, mode of administration and dosing were determined by the treating physician. After 3 months of cannabis treatment, participants had a follow-up evaluation that included the same measurements as the first visit and a questionnaire about cannabis use, dosing, adverse events, emergency department visits, hospitalizations, and changes in medication regimens.

Assessments and outcomes

Blood tests included lipid profile, hemoglobin A1C (HbA1C), fasting plasma glucose, fasting insulin, C-reactive protein, kidney function tests and electrolytes. For ABPM assessment, participants received diaries in which they were asked to specify their exact sleeping hours, exact time of medications and cannabis use. ABPMs were performed with an Oscar 2 device (SunTech Medical, Inc, Morrisville, North Carolina) that has been validated in different studies [26,27]. Measurements were taken every 20 minutes during the day and every 30 or 45 minutes during the night. Measurements qualified to be included in the analysis had a minimum of 20 valid daytime (awake) and seven nighttime (asleep) measurements [28]. Daytime and nighttime were defined by participant diaries or by reports of usual sleeping hours, and in case of missing data daytime was defined as 8:00AM-22:00PM and nighttime as 22:00PM-8:00AM. Dipping patterns were classified according to European Society of Hypertension position paper on ambulatory blood pressure monitoring [29].

Cannabis dosage was determined according to the reports of the participants. Every cigarette puff was calculated as containing 55.5 mg of active substances and each drop of oil as 0.05 ml [30]. These values were multiplied by the exact concentration of every specific cannabis product. For the analysis of the immediate effects of cannabis, time of cannabis use, as reported by the patients, was defined as time 0. Heart rate and blood pressure were calculated as mean values per hour, before and after time 0. Some patients used cannabis more than once a day. In these cases, each time of cannabis use was defined as another time 0 and the follow-up time after each cannabis use was 2 hours for cannabis smoking and 4 hours for cannabis oil [31,32]. Participants who did not report exact times of cannabis use during their ABPM were not included in this analysis but were included in the analysis of 24-h data.

The primary outcome was the change in the mean 24-h blood pressure after 3 months of cannabis treatment. Secondary outcomes included incidence of new arrhythmias, changes in heart rate, rate pressure product (RPP, heart rate $\times$ systolic blood pressure, marker of myocardial oxygen consumption), anthropometric measurements, blood tests evaluated, and adverse events.

Sample size

Based on a standard deviation of 15.6 mmHg in systolic ABPMs in older adults [33], power or 80%, alpha of 15% and a mean paired difference of 7 mmHg after treatment with cannabis [34], the required sample size for the primary outcome was 27 participants.

Statistical analysis

The results are presented by means $\pm$ SDs for continuous variables, medians and interquartile ranges for ordinal variables, and percentages for categorical data. All the analyses are of paired data, McNemar's test was used for categorical variables, paired t-test for normally distributed continuous variables and Wilcoxon test for non-normally distributed continuous variables. SPSS IBM software, version 25.0, was used for statistical analysis.

Ethics

The study was approved by the Ethics Committee (EC) of each participating site (confirmation number in SUMC is 228-18 and in AAAMC is 103-18). All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All participants signed informed consent forms prior to their enrollment to the study.

Data availability

The data used in the analysis of this study are not publicly available due to the national regulations but are available from the corresponding author upon request.

Results

Cohort characteristics

A total of 38 participants were recruited to the study and 26 of them continued cannabis treatment and completed follow-up of 3 months since treatment initiation (Fig. 1). The five patients who stopped cannabis treatment due to adverse effect reported the following reasons for stopping: nausea, decreased appetite, somnolence, dizziness, anxiety, headaches, and delusions.

The mean age of the participants was 70.42 $\pm$ 5.37 years and 53.8% were females (Table 1). The most common anti-hypertensive drug used (57.7%) was either angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), followed by beta-blockers (42.3%).

Most participants used cannabis oil (76.9%) and only 4 participants (15.4%) used smoking. The median daily doses of cannabidiol (CBD) and THC were 21.3 mg and 21.1 mg, respectively. The indications for cannabis treatment were various types of chronic pain, with neuropathic pain being the most common (34.6%). Of participants who continued treatment, 80.8% reported at least one adverse event, with dizziness being the most common (34.6%, Table 2).

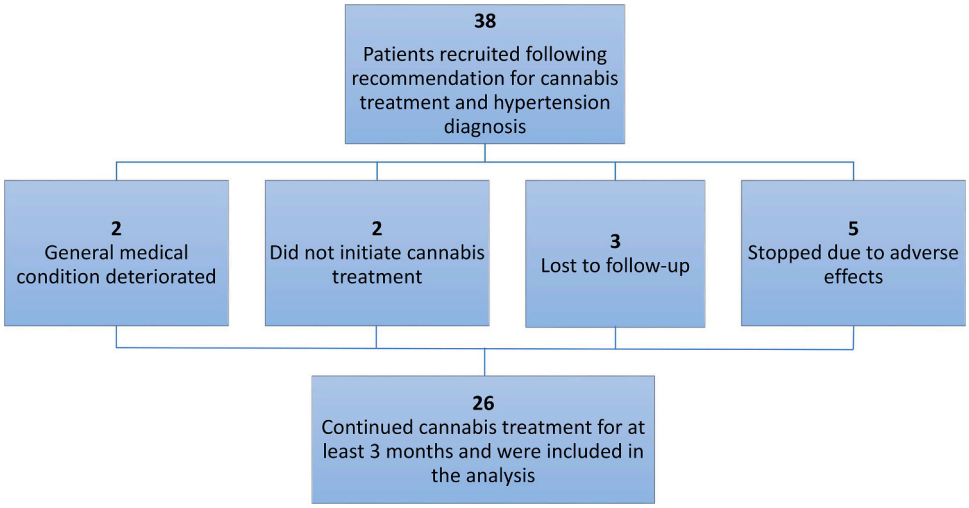

Fig. 1. Flowchart of the study and the analysis.

Table 1
Baseline characteristics of the patients.

Variable	All patients (N=26)
Age (years, mean ± SD)	70.42 ± 5.37
Female (n, %)	14 (53.8%)
Comorbidities (n, %)	
Dyslipidemia	17 (65.4%)
Diabetes Mellitus	12 (46.2%)
Parkinson's Disease	8 (30.8%)
Osteoporosis	7 (26.9%)
Obesity	5 (19.2%)
Benign Prostatic Hyperplasia	4 (15.4%)
Fibromyalgia	4 (15.4%)
Asthma	3 (11.5%)
Peripheral vascular disease	3 (11.5%)
Chronic Kidney disease	2 (7.7%)
Chronic obstructive pulmonary disease	2 (7.7%)
Chronic Medications (number of patients, %)	
Anti-platelets	15 (57.7%)
Beta blockers	11 (42.3%)
Thiazides	7 (26.9%)
ACEI / ARB	15 (57.7%)
Calcium channel blockers	8 (30.8%)
Glucose lowering drugs	10 (38.5%)
Statins	16 (61.5%)
Ezetimibe	5 (19.2%)
Fibrates	1 (3.8%)
Marital Status (n, %)	
Married	20 (76.9%)
Widowed	3 (11.5%)
Divorced	3 (11.5%)
Education (n, %)	
Academic	12 (46.2%)
High school	11 (42.3%)
Less than high school	3 (11.5%)

ACEI – angiotensin converting enzyme inhibitor, ARB - angiotensin II receptor blocker.

Table 2
Characteristics of cannabis use.

Variable	All patients (N=26)
Cannabis way of administration	
Oil	20 (76.9%)
Smoking	4 (15.4%)
Oil & smoking	2 (7.7%)
CBD and THC composition of cannabis products at treatment initiation (n, %)	
THC 5% / CBD 10%	9 (29%)
THC 10% / CBD 2%	8 (25.8%)
THC 10% / CBD 10%	7 (22.6%)
THC 1% / CBD 20%	3 (9.7%)
THC 3% / CBD 15%	2 (6.5%)
THC 15% / CBD 3%	1 (3.2%)
THC 20% / CBD 1%	1 (3.2%)
Cannabis dosing	
Cannabis administration once a day (n, %)	9 (34.6%)
Cannabis administration twice a day (n, %)	9 (34.6%)
Cannabis administration ≥3 day (n, %)	8 (30.8%)
Total THC dose per day (mg, median, IQR)	21.1 (12.75 – 41.45)
Total CBD dose per day (mg, median, IQR)	21.3 (7.75 – 43.83)
Indication for cannabis (n, %)	
Neuropathic pain	9 (34.6%)
Parkinson's Disease associated pain	8 (30.8%)
Hematologic malignancy associated pain	4 (15.4%)
Other indication	5 (19.2%)
Cannabis adverse events (number of patients, %)	
Any adverse event	21 (80.8%)
Dizziness	9 (34.6%)
Dry mouth	3 (11.5%)
Fatigue	2 (7.7%)
Palpitations	2 (7.7%)
Constipation	2 (7.7%)
Psycho-active sensation	2 (7.7%)
Severe adverse event	0 (0%)

THC – tetrahydrocannabinol, CBD – cannabidiol, IQR - interquartile range.

When asked to globally assess the effects of cannabis treatment on their condition, 18 patients (69.2%) reported some degree of improvement, and 6 of them (23.1%) defined it as significant improvement; six patients (23.1%) reported no change and one patient (3.8%) reported deterioration following the treatment.

Blood pressure and heart rate

Cannabis treatment for 3 months was associated with a reduction in systolic and diastolic blood pressure, as well as heart rate and RPP.

Fig. 2 shows that both systolic and diastolic blood pressures were lower after cannabis treatment for 3 months throughout most hours of the day and night. The mean differences in 24-hours systolic and diastolic blood pressures were 5.0 mmHg and 4.5 mmHg, respectively.

The effect on systolic blood pressure was slightly more prominent on daytime, whereas on diastolic blood pressure it was on nighttime (Table 3).

The nadir for the blood pressure and heart rate was achieved at 3 hours post-administration (Fig. 3A). To account for the dipping effect,

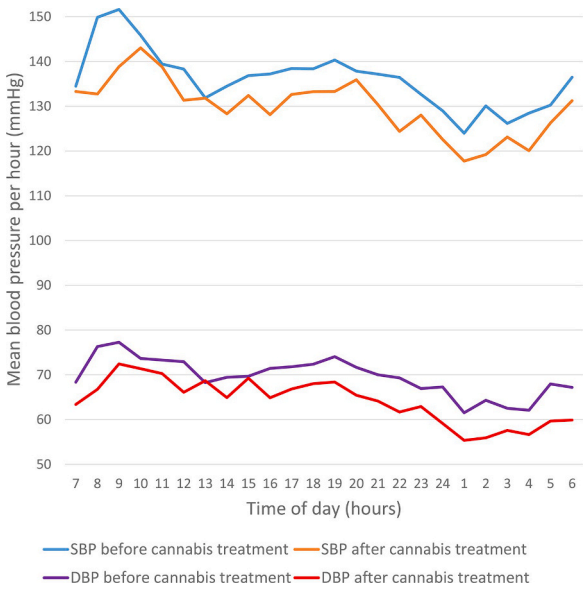

Fig. 2. Mean hourly systolic and diastolic blood pressure of all patients (N=26) as determined by 24-h ambulatory blood pressure monitor comparing values before and after 3 months of cannabis treatment. SBP – Systolic blood pressure; DBP – Diastolic blood pressure.

Table 3
Blood pressure, heart rate and dipping patterns before and after cannabis treatment.

Variable	Before treatment	After treatment	P-value
24-h mean			
Systolic blood pressure (mmHg, mean ± SD)	135.73 ± 24.33	130.76 ± 21.48	<0.001
Diastolic blood pressure (mmHg, mean ± SD)	69.48 ± 13.34	65.03 ± 12.73	<0.001
Heart rate (beats per minute, mean ± SD)	72.06 ± 11.67	70.82 ± 11.55	0.02
Mean arterial pressure (mmHg, mean ± SD)	91.57 ± 15.65	86.95 ± 14.16	<0.001
Pulse pressure (mmHg, mean ± SD)	66.25 ± 17.9	65.73 ± 16.63	0.49
Rate pressure product (HR X SBP, mean ± SD)	9827 ± 2474	9295 ± 2214	<0.001
Daytime mean			
Systolic blood pressure (mmHg, mean ± SD)	138.57 ± 22.54	133.21 ± 20.25	<0.001
Diastolic blood pressure (mmHg, mean ± SD)	71.6 ± 11.62	67.78 ± 12.37	<0.001
Heart rate (beats per minute, mean ± SD)	73.93 ± 11.03	72.95 ± 11.04	0.15
Nighttime mean			
Systolic blood pressure (mmHg, mean ± SD)	129.86 ± 26.81	125.7 ± 23.09	0.03
Diastolic blood pressure (mmHg, mean ± SD)	65.1 ± 15.49	59.33 ± 11.55	<0.001
Heart rate (beats per minute, mean ± SD)	68.18 ± 12.05	66.42 ± 11.38	0.01
Dipping pattern (n, %)			
Normal dippers (night/day BP ratio <0.9 and >0.8)	6 (27.3%)	10 (45.5%)	0.79
Non-dippers (night/day BP ratio <1 and >0.9)	10 (45.5%)	6 (27.3%)	0.48
Risers (night/day BP ratio ≥1)	5 (22.7%)	5 (22.7%)	0.82
Extreme dippers (night/day BP ratio <0.8)	1 (4.5%)	1 (4.5%)	0.87

HR – Heart rate; SBP – Systolic blood pressure; BP – Blood pressure.

separate analysis of cannabis use before bedtime and during the day showed a nadir after 2 hours during the day, as opposed to after 3 hours at night (Figs. 3B-3C).

Analysis of the dipping patterns revealed that the proportion of normal dippers changed from 27.3% before treatment to 45.5% after the 3 months of cannabis use (Table 3). This change was unrelated to the timing of cannabis administration.

Blood tests and metabolic parameters

No significant changes were seen in the different metabolic parameters assessed by blood tests or anthropometric measurements. Analysis of fasting plasma glucose by sex showed difference between males and females – in males there was a mean decrease of 15.58 ± 24.36 mg/dL after treatment, while in females there was an increase of 5.36 ± 13.91 mg/dL after treatment. The difference between the sexes was not evident in any of the other parameters assessed (Table 4).

ECG and arrhythmias

No significant changes were seen in the different parameters of the ECG exam and no new sustained arrhythmias developed (Table 5). One participant developed inversion of T waves and visited the emergency department complaining of chest pain but was discharged without treatment or further follow-up.

Discussion

In this prospective cohort study of older adults with hypertension, we have shown that cannabis treatment for 3 months was associated with a reduction in both systolic and diastolic blood pressure values, as measured by consequent 24-hours ABPM tests. No significant changes were found in blood lipids profile, HbA1C, fasting insulin, C-reactive protein, kidney function tests, electrolytes, anthropometric measurements, and ECG parameters. Fasting plasma glucose was significantly decreased only among men.

A number of placebo controlled studies have shown an increase in systolic blood pressure after cannabis use [35–37], while others, also placebo controlled, did not show any effect or showed a decrease in diastolic blood pressure [38]. These studies were conducted on younger individuals and analyzed the immediate or short-term effects of cannabis on blood pressure, as opposed to the longer-term effects evaluated in our study. A previous study determined that the threshold for blood pressure reduction resulting in decreased composite cardiovascular endpoints was 4.6 mmHg for systolic blood pressure and 2.2 for diastolic blood pressure [39]. Thus, the effect observed in our study was statistically and clinically significant both during daytime and in nighttime but was more pronounced during the latter. It was proposed that cannabinoids have a biphasic effect on blood pressure with lower doses causing sympathetic stimulation while higher doses resulting in parasympathetic stimulation [40]. Our results did not imply that there is a dose-response relationship between either CBD or THC to blood pressure. Chronic pain is associated with hypertension [41], and the analgesic effect of cannabis is another possible explanation for the observed reduction in blood pressure as most of the participants in the study were satisfied with the therapeutic effect of cannabis. However, analgesia is expected to decrease both heart rate and blood pressure, and we did not see an accompanying decrease in heart rate. It should be noted that most of the patients were treated for hypertension and therefore had normal or near normal blood pressure values, especially the diastolic blood pressure. It is unknown whether this effect of cannabis on blood pressure will be the same with substantially elevated values of blood pressure.

It seems there is also a temporal relationship between cannabis administration and blood pressure – the most meaningful reduction in blood pressure values was 3 hours after cannabis administration.

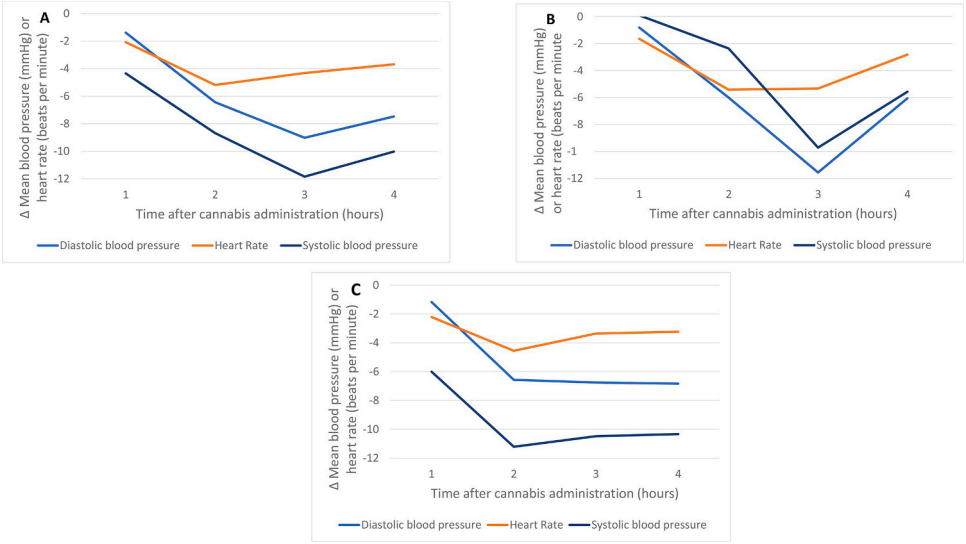

Fig. 3. Changes in blood pressure and heart rate following cannabis administration. A – all patients (n=23); B – only patients who administrated cannabis 2 hours prior to bedtime (n=12); C – only patients who administrated cannabis during daytime (n=16).

Cannabis oil was used by 76.9% of the participants in our study; the pharmacokinetic studies of oral cannabis administration reported slow and erratic absorption, with usual maximal plasma concentrations that were observed 1-2 hours after administration [32]. These effects have to be taken in the context of older adults with reduced metabolism which may behave differently than the young healthy adults on which the pharmacokinetic data are based [42]. Additionally, cannabinoids have an effect on CYP metabolism enzymes which might cause a change in the levels of a variety of drugs, including anti-hypertensives [43]. The clinical meaning of this effects remains to be elucidated. The effects of cannabis administration between daytime and nighttime were similar. The deeper nadir in Fig. 3C is explained by the dipping effect as all measurements that are 3 hours or more after cannabis administration were actually at nighttime.

Cannabis, and specifically THC, has a well proven tachycardic effect [44], but it has been shown that tolerance to this effect develops within days to weeks [35,45]. In accordance with the development of tolerance, the results in our study did not show an increase in heart rate after 3 months of cannabis use.

The rate of adverse effects in our study is substantial and is significantly higher than in most studies, including in a large cohort of older adults published by our group [46]. Dizziness, the most common adverse event in our study, might be attributed to one of the characteristics of our cohort – hypertension. Patients with persistent elevated blood pressure might perceive the reduction in blood pressure as more meaningful, which can cause a sensation of dizziness. This explanation is supported by a study that showed a marked decrease in blood pressure and cerebral blood velocity following cannabis administration, leading to severe dizziness [47]. A different possible explanation for the high rate of adverse effects is the multiple comorbidities of most of the participants in our study, which might cause them to be more susceptible to adverse effects of cannabis.

Several studies reported increased rates of arrhythmias among cannabis users [19,20]. Generally, our study showed that the prevalence of arrhythmias did not change significantly after 3 months of cannabis use. Nevertheless, the rhythm assessment (two ECG recordings) used in the study has a low sensitivity in detecting arrhythmias [48]. Continuous methods for monitoring, such as 24-hours ECG monitoring or longer, and a larger sample size are needed to better determine changes in rates of cardiac arrhythmias.

Several studies reported that cannabis use is associated with lower levels of low-density lipoprotein (LDL) cholesterol, fasting insulin, fasting plasma glucose, homeostasis model assessment of insulin resistance (HOMA-IR), HbA1C, body mass index (BMI) and waist circumference [49–51]. It is known that the endocannabinoid system modulates lipogenesis via cannabinoid receptors type 1 on adipocytes and in various other mechanisms [52]. We found no significant difference in any of the metabolic parameters assessed, except for fasting plasma glucose in men. This might be explained by inadequate sample size and further research is needed to clarify the relationship of cannabis, blood lipids and sugar metabolism.

Strengths and limitations

The strengths of this study include the focus on older adults, a population with increasing rates of cannabis treatment, but with little research focusing on the cardiovascular implications. Blood pressure and heart rate were assessed by 24-hour ambulatory blood pressure monitoring, which is superior to single office measurements. This was a "real-world" study that included participants with multiple comorbidities and very few exclusion criteria.

However, this study also had several limitations. First, this study had no control group, and the reported changes could be spontaneous. Second, we did not use blood samples to measure THC, CBD or other cannabinoids and levels of active substances. Nevertheless, the concentrations of THC and CBD use were reported for all patients and we calculated exact dosages for each patient. Third, we aimed to assess the medium-term effect of cannabis and therefore there was no evaluation of the immediate effects of initiating cannabis treatment in older adults; this time frame might be after development of tolerance to some cardiovascular effects. Fourth, sample size was calculated for changes in blood pressure and might have been inadequate to assess cardiac arrhythmias and changes in metabolic parameters. Fifth, not all participants used the same kind, same dose, and same composition of cannabis. However, adjustment for THC and CBD dosing did not seem to alter the results. Sixth, some of the effects might be attributed to the subjective effect of using cannabis due to the unblinded nature of the study.

Conclusions

Amongst older adults with hypertension, cannabis treatment for 3 months was associated with a clinically meaningful reduction in 24-hours systolic and diastolic blood pressure values with a nadir at 3 hours after cannabis administration. This drop is possibly associated

Table 4
Blood tests and metabolic parameters before and after cannabis treatment.

Variable	Reference Range	Before treatment	After treatment	P-value
Urea (mg/dL, mean ± SD)	17-43	45.48 ± 21.74	48.91 ± 24.88	0.10
Uric acid (mg/dL, mean ± SD)	3.5-7.2 (male) 2.6-6 (female)	5.54 ± 1.33	5.77 ± 1.67	0.22
Creatinine (mg/dL, mean ± SD)	0.67-1.17 (male) 0.51-0.95 (female)	1.11 ± 1.01	1.14 ± 1.15	0.67
Sodium (mEq/L, mean ± SD)	135-145	139.77 ± 2.16	139.38 ± 2.68	0.66
Potassium (mEq/L, mean ± SD)	3.5-5.1	4.54 ± 0.49	4.8 ± 0.96	0.23
Chloride (mEq/L, mean ± SD)	98-106	102.76 ± 3.49	102.85 ± 3.26	0.80
Calcium (mg/dL, mean ± SD)	8.5-10.5	9.39 ± 0.78	9.25 ± 0.63	0.12
Total cholesterol (mg/dL, mean ± SD)		158.81 ± 48.93	160.81 ± 41.11	0.74
Non-HDL Cholesterol (mg/dL, mean ± SD)		106.92 ± 44.8	108.77 ± 34.61	0.60
LDL cholesterol (mg/dL, mean ± SD)		77.28 ± 32.68	85 ± 32.79	0.13
HDL cholesterol (mg/dL, mean ± SD)		52.5 ± 16.91	52.12 ± 14.02	0.84
LDL/HDL Ratio		1.56 ± 0.69	1.67 ± 0.61	0.43
Triglycerides (mg/dL, mean ± SD)		124.65 ± 62.25	118.77 ± 39.78	0.93
Fasting plasma glucose (mg/dL, mean ± SD)				
All patients	70-100	116.23 ± 27.38	111.92 ± 30.55	0.32
Males		115.33 ± 29.22	99.75 ± 24.18	0.05
Females		117.0 ± 26.78	122.36 ± 32.34	0.17
Hemoglobin A1C (%, mean ± SD)	4-5.7	6.11 ± 1.01	6.07 ± 1.07	0.78
Fasting insulin (mU/ml, mean ± SD)	5-25	13.17 ± 8.86	12.04 ± 8.96	0.18
HOMA-IR		3.99 ± 3.12	3.46 ± 2.79	0.15
C-reactive protein (mg/dL, mean ± SD)	0.02-0.5	0.77 ± 0.86	1.06 ± 1.48	0.87
Body mass index		29.25 ± 5.98	28.76 ± 5.79	0.06
Waist-to-hip ratio – males		0.98 ± 0.07	0.97 ± 0.06	0.15
Waist-to-hip ratio – females		0.91 ± 0.06	0.96 ± 0.09	0.21

HOMA-IR – Homeostasis Model Assessment of Insulin Resistance; LDL – Low-Density Lipoprotein; HDL – High-Density Lipoprotein.

with a higher rate of dizziness. Cannabis treatment was not associated with a change in metabolic, anthropometric measurements, and ECG parameters. Further larger randomized trials are needed to evaluate the safety of cannabis use in older adults and its possible efficacy for hypertension management.

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Table 5
ECG parameters before and after cannabis treatment.

Variable	Before treatment	After treatment	P-value
Heart rate, bpm (mean ± SD)	70.85 ± 12.49	68.23 ± 8.94	0.17
Normal heart rate (n, %)	21 (80.8%)	23 (88.5%)	0.63
Rhythm – irregular (n, %)	2 (7.7%)	1 (3.8%)	1.0
Atrial fibrillation/flutter (n, %)	1 (3.8%)	1 (3.8%)	1.0
PR Segment, ms (mean ± SD)	168.67 ± 25.43	167.5 ± 26.64	0.72
Prolonged PR Segment (n, %)	4 (16.0%)	3 (12.0%)	1.0
2^{nd} or 3^{rd} degree AV block (n, %)	1 (3.8%)	0 (0%)	–
QRS complex, ms (mean ± SD)	105.50 ± 22.16	104.73 ± 22.98	0.95
Abnormal QRS complex (n, %)	7 (26.9%)	6 (23.1%)	1.0
Left ventricular hypertrophy (n, %)	1 (3.8%)	0 (0%)	–
Left bundle branch block (n, %)	0 (0%)	0 (0%)	–
Right bundle branch block (n, %)	6 (23.1%)	5 (19.2%)	1.0
VPBs/APBs (n, %)	2 (7.7%)	0 (0%)	1.0
Abnormal T wave (n, %)	9 (34.6%)	8 (30.8%)	1.0
Abnormal ST segment (n, %)	3 (11.5%)	3 (11.5%)	1.0
QTc interval, ms (mean ± SD)	432.42 ± 24.9	429.42 ± 21.67	0.42
Prolonged QTc interval (n, %)	6 (23.1%)	4 (16.0%)	0.63

Ms – milliseconds; bpm – beats per minute; VPB – ventricular premature beat; APB – atrial premature beat; AV – atrioventricular.

Declaration of Competing Interest

None.

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None.

References

[1] Park JY, Wu LT. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. Drug Alcohol Depend 2017;177:1–13. https://doi.org/10.1016/j.drugalcdep.2017.03.009.
[2] Fairman BJ. Trends in registered medical marijuana participation across 13 US states and District of Columbia. Drug Alcohol Depend 2016;159:72–9. https://doi.org/10.1016/j.drugalcdep.2015.11.015.
[3] Hamilton HA, Brands B, Ialomiteanu AR, Mann RE. Therapeutic use of cannabis: Prevalence and characteristics among adults in Ontario. Canada. Can J Public Heal 2017;108:e282–7. https://doi.org/10.17269/cjph.108.6130.
[4] Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use. JAMA 2015;313:2456–73. https://doi.org/10.1001/jama.2015.6358.
[5] Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clin Psychopharmacol Neurosci 2017;15:301–12. https://doi.org/10.9758/cpn.2017.15.4.301.
[6] Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. N Engl J Med 2015;373:1048–58. https://doi.org/10.1056/NEJMra1407304.
[7] Han BH, Palamar JJ. Trends in Cannabis Use among Older Adults in the United States, 2015-2018. JAMA Intern Med 2020;180:609–11. https://doi.org/10.1001/jamainternmed.2019.7517.
[8] Baumbusch J, Sloan Yip I. Exploring New Use of Cannabis among Older Adults. Clin Gerontol 2020. https://doi.org/10.1080/07317115.2020.1746720.
[9] Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R. National estimates of marijuana use and related indicators - National Survey on Drug Use and Health, United States, 2002-2014. MMWR Surveill Summ 2016;65:1–25. https://doi.org/10.15585/mmwr.ss6511a1.
[10] Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. Eur J Clin Pharmacol 2013;69:1575–80. https://doi.org/10.1007/s00228-013-1503-y.
[11] Kaskie B, Ayyagari P, Milavetz G, Shane D, Arora K. The Increasing Use of Cannabis among Older Americans: A Public Health Crisis or Viable Policy Alternative? Gerontologist 2017;57:1166–72. https://doi.org/10.1093/geront/gnw166.
[12] Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The Medicinal Use of Cannabis and Cannabinoids-An International Cross-Sectional Survey on Administration Forms. J Psychoactive Drugs 2013;45:199–210. https://doi.org/10.1080/02791072.2013.805976.
[13] Abuhasira R, Ron A, Sikorin I, Novack V. Medical Cannabis for Older Patients—Treatment Protocol and Initial Results. J Clin Med 2019;8:1819. https://doi.org/10.3390/jcm8111819.

[14] Bar-Lev Schleider L, Abuhasira R, Novack V. Medical cannabis: aligning use to evidence-based medicine approach. Br J Clin Pharmacol 2018;84:2458–62. https://doi.org/10.1111/bcp.13657.
[15] Page RL, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, et al. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation; 2020. https://doi.org/10.1161/CIR.0000000000000883.
[16] Van Den Elsen GAH, Ahmed AIA, Verkes RJ, Feuth T, Van Der Marck MA, Olde Rikkert MGM. Tetrahydrocannabinol in Behavioral Disturbances in Dementia: A Crossover Randomized Controlled Trial. Am J Geriatr Psychiatry 2015;23:1214–24. https://doi.org/10.1016/j.jagp.2015.07.011.
[17] van den Elsen GAH, Ahmed AIA, Verkes R-J, Kramers C, Feuth T, Rosenberg PB, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. Neurology 2015;84:2338–46. https://doi.org/10.1212/WNL.0000000000001675.
[18] Ahmed AIA, van den Elsen GAH, Colbers A, van der Marck MA, Burger DM, Feuth TB, et al. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: A randomized controlled trial. Eur Neuropsychopharmacol 2014;24:1475–82. https://doi.org/10.1016/j.euroneuro.2014.06.007.
[19] Kariyanna PT, Wengrofsky P, Jayarangaiah A, Haseeb S, Salciccioli L, Hegde S, et al. Marijuana and Cardiac Arrhythmias: A Scoping Study. Int J Clin Res Trials 2019:4. https://doi.org/10.15344/2456-8007/2019/132.
[20] Richards JR, Blohm E, Toles KA, Jarman AF, Ely DF, Elder JW. The association of cannabis use and cardiac dysrhythmias: a systematic review. Clin Toxicol 2020:1–9. https://doi.org/10.1080/15563650.2020.1743847.
[21] Korantzopoulos P, Liu T, Papaioannides D, Li G, Goudevenos JA. Atrial fibrillation and marijuana smoking. Int J Clin Pract 2008;62:308–13. https://doi.org/10.1111/j.1742-1241.2007.01505.x.
[22] Abuhasira R, Novack V. Increased risk of cardiac arrhythmias with cannabis use – more studies are needed. Eur J Intern Med 2020. https://doi.org/10.1016/j.ejim.2020.08.008.
[23] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8. https://doi.org/10.1136/bmj.39335.541782.ad.
[24] Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products – regulations in Europe and North America. Eur J Intern Med 2018;49:2–6. https://doi.org/10.1016/j.ejim.2018.01.001.
[25] The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Mass: Little, Brown & Co: Boston; 1994.
[26] Goodwin J, Bilous M, Winship S, Finn P, Jones SC. Validation of the Oscar 2 oscillometric 24-h ambulatory blood pressure monitor according to the British Hypertension Society protocol. Blood Press Monit 2007;12:113–7. https://doi.org/10.1097/MBP.0b013e3280acab1b.
[27] Jones SC, Bilous M, Winship S, Finn P, Goodwin J. Validation of the OSCAR 2 oscillometric 24-hour ambulatory blood pressure monitor according to the International Protocol for the validation of blood pressure measuring devices. Blood Press Monit 2004;9:219–23. https://doi.org/10.1097/00126097-200408000-00007.
[28] Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32:1359–66. https://doi.org/10.1097/HJH.0000000000000221.
[29] O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European society of hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013;31:1731–68. https://doi.org/10.1097/HJH.0b013e328363e964.
[30] Israeli Medical Cannabis Agency. Information booklet and medical guide IMC-GCP sub-circular to the Israeli Ministry of Health Director Hebrew only 2019. https://www.health.gov.il/hozer/mmk154_2016.pdf. accessed April 15, 2020.
[31] Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers 2007;4:1770–804. https://doi.org/10.1002/cbdv.200790152.
[32] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42:327–60. https://doi.org/10.2165/00003088-200342040-00003.
[33] Staessen Jan A, Thijs Lutgarde, Fagard Robert, O'Brien Eoin T, Clement Denis, Leeuw Peter Wde, Mancia Giuseppe, Nachev Choudomir, Palatini Paolo, Parati Gianfranco, Tuomilehto Jaakko. John webster M for the SH in ETI. predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. JAMA 1999:282:539. https://doi.org/10.1001/jama.282.6.539.
[34] Ahmed AIA, van den Elsen GAH, Colbers A, Kramers C, Burger DM, van der Marck MA, et al. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. Psychopharmacology (Berl) 2015;232:2587–95. https://doi.org/10.1007/s00213-015-3889-y.
[35] Ponto LLB, O'Leary DS, Koeppel J, Block RI, Watkins GL, Richmond JCW, et al. Effect of acute marijuana on cardiovascular function and central nervous system pharmacokinetics of [15o]water: effect in occasional and chronic users. J Clin Pharmacol 2004;44:751–66. https://doi.org/10.1177/0091270004265699.
[36] Jouanjus E, Raymond V, Lapeyre-Mestre M, Wolff V. What is the current knowledge about the cardiovascular risk for users of cannabis-based products? a systematic review. Curr Atheroscler Rep 2017:19:26. https://doi.org/10.1007/s11883-017-0663-0.
[37] Kayser RR, Haney M, Raskin M, Arout C, Simpson HB. Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. Depress Anxiety 2020. https://doi.org/10.1002/da.23032. da.23032.
[38] Karschner EL, Darwin WD, McMahon RP, Liu F, Wright S, Goodwin RS, et al. Subjective and physiological effects after controlled Sativex and oral THC administration. Clin Pharmacol Ther 2011;89:400–7. https://doi.org/10.1038/clpt.2010.318.
[39] Verdecchia P, Gentile G, Angeli F, Mazzotta G, Mancia G, Reboldi G. Influence of blood pressure reduction on composite cardiovascular endpoints in clinical trials. J Hypertens 2010;28:1356–65. https://doi.org/10.1097/HJH.0b013e328338e2bb.
[40] Latif Z, Garg N. The impact of marijuana on the cardiovascular system: a review of the most common cardiovascular events associated with marijuana use. J Clin Med 2020;9:1925. https://doi.org/10.3390/jcm9061925.
[41] Bruehl S, Olsen RB, Tronstad C, Sevre K, Burns JW, Schirmer H, et al. Chronic pain-related changes in cardiovascular regulation and impact on comorbid hypertension in a general population: The Tromsø study. Pain 2018;159:119–27. https://doi.org/10.1097/j.pain.0000000000001070.
[42] Mangoni AA JS. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2003;57:6–14. https://doi.org/10.1046/j.1365-2125.2003.02007.x.
[43] DeFilippis EM, Bajaj NS, Singh A, Malloy R, Givertz MM, Blankstein R, et al. Marijuana Use in Patients With Cardiovascular Disease. J Am Coll Cardiol 2020;75:320–32. https://doi.org/10.1016/j.jacc.2019.11.025.
[44] Singh A, Saluja S, Kumar A, Agrawal S, Thind M, Nanda S, et al. Cardiovascular Complications of Marijuana and Related Substances: A Review. Cardiol Ther; 2017. https://doi.org/10.1007/s40119-017-0102-x.
[45] Sidney S. Cardiovascular consequences of marijuana use. J Clin Pharmacol 2002;42. https://doi.org/10.1002/j.1552-4604.2002.tb06005.x. 64S–70S.
[46] Abuhasira R, Schleider LBL, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med 2018;49:44–50. https://doi.org/10.1016/j.ejim.2018.01.019.
[47] Mathew RJ, Wilson WH, Humphreys D, Lowe JV, Wiethe KE. Middle cerebral artery velocity during upright posture after marijuana smoking. Acta Psychiatr Scand 1992;86:173–8. https://doi.org/10.1111/j.1600-0447.1992.tb03247.x.
[48] Diederichsen SZ, Haugan KJ, Kronborg C, Graff C, Højberg S, Køber L, et al. Comprehensive evaluation of rhythm monitoring strategies in screening for atrial fibrillation: insights from patients at risk monitored long term with an implantable loop recorder. Circulation 2020;141:1510–22. 10.1161/CIRCULATIONAHA.119.044407.
[49] Meier MH, Pardini D, Beardslee J, Matthews KA. Associations between cannabis use and cardiometabolic risk factors. Psychosom Med 2018:1. 10.1097/PSY.0000000000000665.
[50] Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med 2013;126:583–9. https://doi.org/10.1016/J.AMJMED.2013.03.002.
[51] Rajavashisth TB, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open 2012;2:e000494. https://doi.org/10.1136/bmjopen-2011-000494.
[52] Lazarte J, Hegele RA. Cannabis effects on lipoproteins. Curr Opin Lipidol 2019;30:140–6. 10.1097/MOL.0000000000000575.