Impact of Inflammasome Activation in Chronic Pain Patients by Medical Marijuana (MM)

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Background

•Chronic pain is a common, yet debilitating condition in older adults, often associated with inflammation and immune dysregulation. There is growing interest in alternative therapies such as medical marijuana (MM) for pain management.

•MM contains cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), which may have analgesic and anti-inflammatory effects. However, the biological mechanisms are not well understood.

•Emerging evidence suggests that the inflammasome, a key component of the innate immune system, plays a role in the link between chronic pain and inflammation (1). The NLRP3 inflammasome responds to tissue damage and activates cytokines like interleukin-18 (IL-18). Other key markers include ASC, Caspase-1, and TREM2.

•CBD and THC reduce LPS-induced cytokine storms in human macrophages and airway epithelial cells, potentially via NLRP3 and STAT3 signaling (2).

•Although cannabinoids show anti-inflammatory properties, limited studies have examined their effects on inflammasome activity in humans, particularly in older adults with chronic pain.

Objective

This pilot study examined the effects of MM on inflammasome biomarker expression and pain levels among older adults with chronic pain. Specifically, we evaluated (1) the association between pain severity and inflammasome levels in plasma, and (2) the differences in pain and inflammasome levels by plasma cannabidiol (CBD) or delta-9-tetrahydrocannabinol (THC) and their metabolites.

Methods

Study Design: We capitalized on existing plasma samples and patient/clinic data collected from the NIH-funded prospective cohort study, the Study on Medical Marijuana and its Long-Term Effects (SMILE). This pilot analysis focused on evaluating changes in inflammasome biomarker levels and pain severity over time in relation to cannabinoid usage.

Study Population and Outcome Variables: The study was conducted in accordance with the University of Florida's Institutional Review Board, and informed consent was obtained from each participant. Plasma samples were collected at baseline and a 3-month study follow-up and stored at –80°C. Pain severity was assessed using the Brief Pain Inventory (BPI), which evaluates worst, least, and average pain levels. Inflammasome biomarkers measured from plasma samples included ASC, Caspase-1, IL-18, and TREM2. MM exposure was classified based on the detection of THC or CBD metabolites in plasma at the study follow-up.

Methods: Biomarker assays were performed using ELISA methods. Participants were grouped into MM users or non-users based on plasma cannabinoid detection at follow-up. Pain scores and biomarker levels were compared across time points and between MM exposure groups.

Statistical Analysis: Paired t-tests, Wilcoxon signed-rank tests, Fisher's Exact or Chi-Square tests for categorical variables, and Satterthwaite t-tests for demographic comparisons were used. Analyses were conducted in SAS 9.4.

Results

Table 1 Participant Demographics by Medical Marijuana Use

Characteristic	Non-MM Group (n=24)	MM Group (n=14)	P-Value
Age, mean (SD)	65.95 (9.53)	64.93 (9.12)	0.7438
BMI, mean (SD)	33.53 (10.66)	32.29 (8.22)	0.3330
Sex at Birth			**0.0052**
Male	6 (25.0%)	10 (71.4%)	
Female	18 (75.0%)	4 (28.6%)	
Race			0.5427
White	21 (87.5%)	12 (85.7%)	
Black	3 (12.5%)	1 (7.1%)	
Other	0 (0.0%)	1 (7.1%)	
Ethnicity			0.3684
Hispanic/Latino	0 (0.0%)	1 (7.1%)	
Non-Hispanic/Latino	24 (100.0%)	13 (92.9%)	
Insurance Status			0.4389
Insured	23 (95.8%)	14 (100.0%)	
Uninsured	1 (4.2%)	0 (0.0%)	

Note: Values are n (%) or mean (SD). P-values from Fisher's Exact or Chi-Square tests; Satterthwaite t-test used for unequal variances. Groups defined by detectable plasma THC/CBD at 3-month study follow-up.

Table 2 Pain Scores at 3 Months Post-Study Entry by THC and CBD Use

THC/ CBD Use		N (%)	Worst Pain		Least Pain		Average Pain		Current Pain	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
THC	Yes	14 (37%)	3.21	4.02	1.21	2.15	2.00	2.63	3.31	3.01
	No	24 (63%)	4.83	3.40	2.13	1.85	3.08	2.30	3.21	1.84
			p-value	0.26	**p-value**	**0.07**	p-value	0.16	p-value	0.65
CBD	Yes	9 (24%)	3.67	4.39	1.78	2.54	2.44	3.00	3.50	2.51
	No	29 (76%)	4.41	3.49	1.79	1.84	2.76	2.31	3.17	2.33
			p-value	0.72	p-value	0.68	p-value	0.68	p-value	0.72

Note: Group comparisons used the Wilcoxon exact test. THC and CBD groups were based on detectable plasma metabolites at 3-month study follow-up.

Table 3 Inflammasome/inflammation Biomarker Levels at 3 Months Post-Study Entry by THC and CBD Use

THC/ CBD Use		N (%)	ASC		Caspase 1		IL-18		Trem 2	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
THC	Yes	14 (37%)	283.07	125.12	2.08	0.99	250.07	121.28	18888.00	11672.68
	No	24 (63%)	256.58	79.67	1.79	0.80	253.36	130.75	22412.17	9737.53
			p-value	0.52	p-value	0.68	p-value	0.83	p-value	0.18
CBD	Yes	9 (24%)	229.11	60.97	1.71	0.58	237.33	110.50	17003.44	11243.23
	No	29 (76%)	277.90	105.15	1.96	0.95	256.74	131.51	22389.41	10091.39
			p-value	0.27	p-value	0.38	p-value	0.62	**p-value**	**0.09**

Note: Group comparisons used the Wilcoxon exact test. THC and CBD groups were based on detectable plasma metabolites at 3-month study follow-up.

Table 4. Inflammasome Levels and The Worst Pain Outcome by MM Use

Biomarker Change	Worst Pain	Non-MMJ Group			MMJ-Group			Total		
		N (%)	Mean	SD	N (%)	Mean	SD	N	Mean	SD
ASC	Decreased	8 (33%)	-9.75	59.09	6 (43%)	-1.33	46.35	14	-6.14	52.20
	Increased	7 (29%)	40.57	58.81	6 (43%)	39.33	47.50	13	40.00	51.67
		p-value	**0.09**		p-value	0.11		**p-value**	**0.03**	
Caspase 1	Decreased	8 (33%)	0.05	0.52	6 (43%)	0.08	0.51	14	0.06	0.50
	Increased	7 (29%)	0.41	0.66	6 (43%)	0.19	0.50	13	0.31	0.58
		p-value	0.18		p-value	0.94		p-value	0.40	
IL-18	Decreased	8 (33%)	23.70	52.79	6 (43%)	2.00	53.93	14	14.40	52.37
	Increased	7 (29%)	-18.29	41.50	6 (43%)	29.00	44.78	13	3.54	47.94
		p-value	0.12		p-value	0.23		p-value	0.77	
Trem 2	Decreased	8 (33%)	1193.80	5211.20	6 (43%)	1386.20	5465.90	14	1276.20	5111.10
	Increased	7 (29%)	1143.70	2180.10	6 (43%)	872.30	3094.90	13	1018.50	2527.30
		p-value	0.95		p-value	0.81		p-value	0.75	

Note: Group comparisons used the Wilcoxon exact test. THC and CBD groups were based on detectable plasma metabolites at 3-month study follow-up.

Discussions & Conclusions

This pilot study provides emerging evidence that medical marijuana (MM) use may impact chronic pain through modulation of inflammatory/ inflammasome pathways in older adults with chronic pain. Reductions in ASC levels were associated with decreases in worst pain scores (p = 0.026), suggesting that inflammasome activity may play a role in pain perception. Patients with detectable THC at follow-up experienced lower pain, particularly for least pain (p = 0.07), supporting potential analgesic properties of THC. Further, individuals with CBD exposure at study follow-up had lower levels of TREM2, a macrophage-related inflammatory marker (p=0.086), suggesting potential immunomodulatory effects. These findings point to a possible dual role of MM in reducing both pain symptoms and inflammation. If validated in larger longitudinal studies, inflammasome biomarkers such as ASC and TREM2 could serve as predictive biomarkers of MM response, informing more targeted and personalized approaches to pain management. These findings also support further research into the biological effects of MM on inflammatory pathways and clinical outcomes in other populations, including cancer.

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