Original Article

Clinical impact of marijuana usage in liver transplant recipients

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Background: Marijuana use for both medical and recreational purposes is increasing in the US. There is a paucity of data on marijuana usage in post-liver transplant patients.

Methods: This is a retrospective descriptive study examining patients >18 years of age who underwent liver transplantation at the University of California Los Angeles Medical Center between 1985 to 2019 who had positive urine drug screen for marijuana post-transplant. Exclusion criteria included lack of blood chemistries at time of positive marijuana screen and a positive marijuana screen obtained only before transplant.

Results: Of 22 patients, 16 (72.7%) were male with an average age at transplant of 39.9 years. Alcoholic cirrhosis (40.9%) and hepatitis C (18.2%) were common indications for transplant. Urine drug screen was done most often for evaluation of transaminitis (6/22, 27.3%) and gastrointestinal symptoms (6/22, 27.3%). Elevated liver enzymes were found in 14 patients, with a cause identified in eight patients. The most common cause of elevated liver enzymes was non-adherence with immunosuppression (6/8, 75%).

Conclusions: Non-adherence with immunosuppression was the most commonly identified cause of elevated liver enzymes. A majority of these patients had biopsy proven rejection. Further studies are needed to evaluate whether there is a link between marijuana usage and immunosuppression non-adherence.

Keywords: Marijuana; clinical decision-making; compliance/adherence

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Introduction

Currently, 33 states in the United States have approved medical marijuana laws while 11 states have approved recreational use of marijuana (1). From a federal standpoint, marijuana is the most commonly used illicit drug (2) and as usage is projected to increase, physicians will be challenged to appropriately counsel their patients on the health effects of marijuana. This is a formidable challenge as the medical literature is still expanding and there is a lack of guidance from professional organizations.

The two most common active compounds in marijuana are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts on CB1 and CB2 receptors (endocannabinoid receptors) and is commonly used to measure the potency of a marijuana formulation and is responsible for its psychoactive effects, a result of CB1 receptor activation in the brain leading to increased release of dopamine. CBD, in contrast lacks the psychoactive high associated with marijuana usage (3). Current FDA approved indications for THC-based medications (dronabinol, nabilone) include nausea in patients undergoing chemotherapy and appetite stimulation in AIDS cachexia, while the CBD-based medication cannabinol (epidiolex, Greenwich Biosciences, Inc., Carlsbad, CA) is approved for Dravet and Lennox-Gastaut syndrome, severe childhood epilepsy syndromes (4). Data also support clinically significant reduction in pain in chronic pain patients and

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improvement in patient-reported spasticity symptoms in multiple sclerosis (5). While the potential of marijuana-based therapies for various conditions is appealing, it must be balanced against data that suggest an association with lower educational attainment, acute impact on cognitive function and increased risk of motor-vehicle accidents and development of schizophrenia (6-9).

What then, should the approach be for patients undergoing or post-liver transplantation? A recent study surveying 49 United Network for Organ Sharing (UNOS) transplant centers in North America found that 14% of programs transplanted patients actively using marijuana while 28% additionally transplanted patients as long as cessation was achieved by time of transplant (10). Furthermore, 7 US states (Arizona, California, Delaware, Illinois, Maine, New Hampshire, Washington) have recently introduced laws that prohibit denial of transplantation based on marijuana use (11). Governing organizations such as the American Association for the Study of Liver Diseases (AASLD) leave the decision to transplant or not up to each transplant center (12). Data that suggest cannabinoids can possibly lead to increased immunosuppression drug (tacrolimus) levels in the blood are also concerning given known systemic toxicities such as nephrotoxicity and neurotoxicity (13). As each organ is a precious resource, concerns regarding marijuana's impact on the allograft, treatment non-adherence, increased risk of infections, and drug-drug interactions are most cited as prohibiting factors for transplant.

More data on marijuana usage in the liver transplant population is needed. In our study, we aim to characterize patients in our center who screened positive for marijuana usage to delineate the demographics, biochemical status and other comorbidities that these patients face with the goal of identifying data that may impact post-transplant success. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-120).

Methods

We performed a retrospective chart review of all patients >18 years of age who underwent liver transplantation at the University of California Los Angeles Medical Center (UCLA) between 1985 to 2019. Inclusion criteria included patients that were actively being followed post-transplant and known usage of marijuana at any point post-transplant defined as a positive screen on urine drug. Exclusion criteria were lack of blood chemistries at time of positive marijuana screen and a positive marijuana screen obtained only before transplant. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the UCLA Institutional Review Board (IRB #19-001546) and individual consent for this retrospective analysis was waived.

Analysis of the UCLA Liver transplant database identified 22 patients who met our inclusion criteria (*Table 1*). Data were obtained by review of the patients' electronic medical record (EMR). Data collected include age, sex, date of transplant, age at transplant, race, indication for transplantation, concurrent drug usage, reason for marijuana usage, type of marijuana used, reason for urine drug screen, liver enzymes at time of positive marijuana screen, immunosuppression regimen and level at time of marijuana usage, abdominal ultrasound and liver biopsy pathology at time of usage. Elevated liver enzymes were defined as an elevation above normal range in either AST, ALT, total bilirubin, or alkaline phosphatase. For patients that were documented to have elevated liver enzymes, electronic medical records were reviewed for an identified cause of elevated enzymes and subsequent management. Of note, the majority of data collected relied on objective measurements which decreased recall bias that could be associated with our study design. Given the descriptive nature of the study, the patients with minimal missing data related to reason for marijuana usage and reason for urine drug screen were not removed from data analysis.

Statistical analysis

All analyses were performed using Excel and Graphpad Prism (GraphPad Prism version 7.00 for Mac, GraphPad Software, La Jolla California USA, www.graphpad.com). Categorical variables were analyzed using Fisher's exact test and numerical variables were analyzed using unpaired two-tailed t-tests. P values <0.05 were considered significant.

Results

Of our 22 patients (*Table 1*), 16 (72.7%) were male and average age at transplant was 39.9 years. Racial breakdown is as follows: Hispanic (8/22, 36.4%), White (6/22, 27.3%), Black (5/22, 22.7%), Asian (1/22, 4.5%) and Other (2/22, 9.1%). Indications for transplant in this population included End stage liver disease (ESLD) secondary to alcoholic cirrhosis (9/22, 40.9%), Hepatitis

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Table 1 Patient demographics

Patient #	Sex	Age	Age at transplant	Date of transplant	Race	Indication for transplant	Concurrent drug usage	Reason for urine drug screen	Elevated Liver enzymes?	Type of Marijuana	Reason for marijuana usage
1	M	37	37	9/25/18	Hispanic	Alcoholic cirrhosis	None	History of usage, Inpatient evaluation of transaminitis	Yes	CBD oil, smoking	Chronic back pain
2	M	35	35	9/7/04	Hispanic	Fulminant Wilson's disease	None	Inpatient evaluation of transaminitis	Yes	Denies usage	Not documented
3	M	49	47	7/3/17	Hispanic	Alcoholic cirrhosis, alpha-1 anti-trypsin disease, HCV	None	Inpatient evaluation for toe cellulitis	Yes	Edibles	Toe pain
4	M	52	51	2/19/19	Hispanic	Alcoholic cirrhosis	Benzodiazepines, ethanol, opiates	ED evaluation of fatigue, nausea, diarrhea	No	CBD gummies	Stress, decreased appetite, energy
5	M	49	44	10/1/14	White	Alcoholic cirrhosis	Amphetamines, alcohol, tobacco	History of usage, psych evaluation during ED visit	Yes	Smoking	Anxiety back pain
6	M	53	50	2/11/16	Hispanic	Alcoholic cirrhosis	Alcohol, opiates	History of usage, Inpatient evaluation of transaminitis	Yes	Smoking	Pain, depression
7	F	41	38	6/24/17	Asian	Alcoholic liver disease, hepatitis B	Tobacco, opiates	ED evaluation for abdominal pain	Yes	Smoking	Chronic pain
8	M	32	29	2/28/17	White	Cryptogenic hepatic fibrosis	E-cigarettes, alcohol	ED evaluation for nausea, abdominal pain	Yes	Vaping, edibles	Pain, nausea
9	F	40	31	11/9/10	Black	Acetaminophen overdose	Methamphetamine, tobacco, opiates	History of usage, admission for Total abdominal hysterectomy-bilateral salpingo-oophorectomy	Yes	Smoking	Chronic shoulder/ back pain
10	F	35	33	5/8/17	Other	Autoimmune hepatitis	None	Inpatient evaluation for transaminitis	Yes	Denies	Denies usage
11	F	60	56	7/19/16	Black	Alcohol liver disease, Hepatitis B	Cocaine, tobacco	Inpatient evaluation of syncope	No	Edibles	Abdominal pain
12	F	64	41	9/22/96	Hispanic	Alcoholic cirrhosis	None	Random drug screen	No	Smoking	Chronic pain

Table 1 (*continued*)

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Table 1 (*continued*)

Patient #	Sex	Age	Age at transplant	Date of transplant	Race	Indication for transplant	Concurrent drug usage	Reason for urine drug screen	Elevated Liver enzymes?	Type of Marijuana	Reason for marijuana usage
13	M	71	65	6/7/13, 2/25/14	Black	Fibrosing cholestatic hepatitis, hepatitis C	None	ED evaluation for acute encephalopathy	No	Smoking	Sleep
14	M	36	5	1/23/88	Black	Biliary atresia	None	Inpatient evaluation for transaminitis	Yes	Smoking	Appetite, stomach pain
15	M	56	50	1/13/14	White	Hepatitis C cirrhosis	None	Drug screen in pain clinic	No	Smoking	Chronic pain
16	M	61	51	1/13/09	Black	Hepatitis C cirrhosis	None	Inpatient evaluation for nausea, vomiting	Yes	Smoking	Not documented
17	M	59	48	4/22/08	Other	Cryptogenic cirrhosis	None	Inpatient evaluation for transaminitis	Yes	Denies	Denies usage
18	M	34	30	2/12/15	White	Alcoholic cirrhosis	Alcohol, opiates	Inpatient evaluation for abdominal pain	Yes	Smoking	Not documented
19	F	55	41	3/15/06	White	Acetaminophen overdose	Vaping	Psychiatric hospitalization for suicidal ideation	No	Smoking, vaping	Insomnia
20	M	25	20	10/10/14	Hispanic	Fulminant Wilson's disease	None	Random drug screen (history of abuse)	No	Smoking	Not documented
21	M	31	22	8/19/10	White	Acetaminophen overdose	None	Inpatient evaluation for nausea, diarrhea	Yes	Smoking, THC chews	Nausea
22	M	67	55	1998, 7/18/07	Hispanic	NASH, hepatitis C cirrhosis	None	Not documented	No	Smoking	Pain

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C (4/22, 18.2%), acetaminophen overdose (3/22, 13.6%), Hepatitis B (2/22, 9.1%), fulminant Wilson's disease (2/22, 9.1%), Cryptogenic cirrhosis (2/22, 9.1%), Non-alcoholic steatohepatitis (NASH) (1/22, 4.5%), biliary atresia (1/22, 4.5%), alpha-1 anti-trypsin disease (1/22, 4.5%), autoimmune hepatitis (1/22, 4.5%) and fibrosing cholestatic hepatitis (1/22, 4.5%). The type of marijuana used included smoking THC (16/22, 72.7%), edible THC (4/22, 18.2%), CBD chews (1/22, 4.5%) and CBD oil (1/22, 4.5%). Interestingly, 3 (13.6%) patients denied marijuana usage. The reasons for marijuana usage were highly varied and most commonly included chronic pain, nausea, insomnia, appetite enhancement and depression. Reasons for why patients underwent a urine drug screen included evaluation of transaminitis (6/22, 27.3%), evaluation of non-specific GI symptoms (6/22, 27.3%), random drug screen (3/22, 13.6%), evaluation of psychiatric symptoms (2/22, 9.1%) and hospital evaluation for non-transplant related reasons (4/22, 18.2%). Concurrent drug usage was found in 9 (40.9%) patients, with most common drugs including alcohol (5/22, 22.7%), opiates (5/22, 22.7%), tobacco (4/22, 18.2%%), vaping (2/22, 9.1%), methamphetamine (1/22, 4.5%), amphetamine (1/22, 4.5%), cocaine (1/22, 4.5%) and benzodiazepines (1/22, 4.5%). Four patients did not have documented reasons for why marijuana was being used, and one patient did not have a documented reason for urine drug screen.

Elevated liver enzymes were present in 14 patients (63.6%), with a cause identified in eight patients (*Tables 2,3*). The most commonly identified cause was noncompliance with immunosuppressive regimen (6/8, 75%), while other causes included biliary obstruction secondary to stone (1/8, 12.5%) and alcoholic hepatitis (1/8, 12.5%). Comparing the patients with elevated liver enzymes to those without (*Table 4*), there was no statistically significant difference in the percentage of patients who smoked THC (11/14, 78.6% *vs.* 7/8, 87.5%, P=1.0), or used CBD products (0/14, 0% *vs.* 1/8, 12.5%, P=0.36). Similarly, when comparing patients by the type of marijuana used (THC *vs.* CBD), there was no significant difference in rates of concurrent drug usage (8/15, 60% *vs.* 3/6, 50%, P=1.0) or presence of elevated liver enzymes (8/15, 60% *vs.* 4/6, 66.7%, P=0.66).

Discussion

This study attempted to better characterize the demographics and hepatocellular function of patients that screened positive for marijuana usage post-liver transplant. Our population was male predominant with transplants indicated most commonly for ESLD secondary to alcohol usage and hepatitis C. The majority of patients were screened for urine toxicology during evaluation of elevated liver enzymes, non-specific GI symptoms or psychiatric issues. Reasons for marijuana usage were varied but most commonly included chronic pain, psychiatric comorbidities such as anxiety and depression, and insomnia. Interestingly, comorbid drug usage was not as common as expected in this population. A possible explanation is that the majority of these patients were using marijuana for medical comorbidities. Although several of our study patients were concurrently using drugs of abuse, it is likely that the majority of patients with significant substance abuse habits did not pass pre-transplant evaluation.

Marijuana's impact on liver function is controversial. One animal study investigating oral CBD usage in mice demonstrated hepatotoxicity of a cholestatic nature secondary to high dose CBD (14). In contrast, CBD may have anti-inflammatory and antioxidant effects (15), with one study by Avraham *et al.* demonstrating improvement in liver function after CBD administration in mice with liver failure (16). The data on THC's effect on liver function are similarly varied, with data implicating worsening fibrogenesis in patients with chronic hepatitis C (17) and hepatomegaly/splenomegaly with elevations in AST, ALT and Alkaline Phosphatase, although this may have been confounded by numerous factors. Clinically significant hepatotoxicity to our knowledge has only been reported in several case reports (18-21). In contrast, THC has also been linked to a decreased prevalence of nonalcoholic fatty liver disease (22) and to have antifibrinogenic properties through apoptosis of pro-inflammatory hepatic stellate cells (23). While our study cannot make conclusions on marijuana's impact on hepatotoxicity, our data suggest that a sizeable portion of our study population presented with liver dysfunction. In our study, there was no significant difference in the presence of elevated liver enzymes between patients using CBD *vs.* THC or a difference in the rates of concurrent drug usage. Significant headway has been made investigating the impact of marijuana on liver function, but further research is necessary given contradictory findings thus far.

Despite the increase of marijuana usage in the US, the data on marijuana usage in relation to liver transplantation is sparse. In the few studies that examine marijuana consumption in liver transplant recipients, survival between users and non-users does not appear to be significant

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Table 2 Patients with elevated liver enzymes and an identified cause of elevation

Patient #	Identified cause of elevated liver enzymes	Type of marijuana used	Reason for marijuana usage	AST	ALT	Total Bilirubin	Alkaline Phosphatase	Immunosuppression	Biopsy results	Management
1	Non-adherence with immunosuppression	Smoking, CBD cream	Chronic back pain	379	686	1.4	530	FK 9.6	Moderate acute T-cell mediated rejection	Steroid pulse, thymoglobulin resume immunosuppression
2	Non-adherence with immunosuppression	Denies usage	Not documented	386	282	6.1	281	Cyclosporine 218	Late onset acute cellular rejection, consider viral, autoimmune/drug induced hepatitis	Steroid pulse thymoglobulin, resume immunosuppression
5	Non-adherence with immunosuppression	Smoking, vaping	Anxiety, back pain	64	31	0.2	77	FK 3.4	Not done	Steroid pulse, resume immunosuppression
7	Biliary obstruction secondary to stone	Smoking	Chronic pain	1,058	504	0.7	172	FK 9.6	No features of acute T cell-mediated rejection, r/o biliary obstruction	ERCP
14	Non-adherence with immunosuppression	Smoking	Appetite, stomach pain	173	317	0.5	155	FK 3.5	Acute t-cell mediated rejection	Steroid pulse, resume tacrolimus, mycophenolate
16	Non-adherence with immunosuppression	Smoking	Not documented	42	70	1.8	99	FK 7.3	Not done	Resume tacrolimus
17	Non-adherence with immunosuppression	Denies usage	Denies usage	490	758	8	278	FK 7.1	Severe acute cellular rejection	Steroid pulse, home tacrolimus, mycophenolate,
18	Alcoholic hepatitis	Smoking	Not documented	126	67	1.2	269	FK 4.5	Not done	Alcohol cessation, tacrolimus, prednisone, ursodiol

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Table 3 Patients with elevated liver enzymes with no identified cause of elevated liver enzymes

Patient #	Identified cause of elevated liver enzymes	Type of marijuana used	Reason for marijuana usage	AST	ALT	Total Bilirubin	Alkaline Phosphatase	Immunosuppression	Biopsy results	Management
3	N/A	Edibles	Toe pain	43	110	0.6	289	FK 8.9	Not done	Resumed home tacrolimus, mycophenolate, prednisone
6	N/A	Smoking	Pain, depression	101	70	3	1,172	Cyclosporine 249	Hepatitis with marked interface and lobular lymphoplasmacytic inflammation	Resume cyclosporine, mycophenolate, ursodiol
8	N/A	Vaping, edibles	Pain, nausea	55	61	0.9	444	FK 10.5	Not done	Resume tacrolimus, prednisone
9	N/A	Smoking	Chronic shoulder/back pain	68	111	0.5	301	FK 7.2	Not done	Resume home tacrolimus, prednisone, mycophenolate, ursodiol
10	N/A	Denies	Denies	442	496	0.9	145	FK 6.2	Moderate acute rejection	Steroid pulse, resume tacrolimus, mycophenolate, prednisone
21	N/A	Smoking, THC chews	Nausea	65	65	0.6	97	FK 6.3	Not done	Continue home tacrolimus

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Table 4 Comparing patients with identified cause of elevated liver enzymes *vs.* no identified cause of elevated liver enzymes

	Identified cause of liver enzymes (n=8)	Confidence interval (95%)	No identified cause of liver enzymes (n=6)	Confidence interval (95%)	P value
Mean AST (SD)	340 (333.9)	60.9–619.1	129 (154.6)	–33.2–291.2	0.18
Mean ALT (SD)	339 (284.9)	100.8–577.2	152 (169.9)	–26.3–330.3	0.18
Mean Total Bilirubin (SD)	2.5 (2.9)	0.08–4.92	1.1 (1.0)	0.05–2.1	0.28
Mean Alkaline Phosphatase (SD)	233 (144.4)	112.3–353.7	408 (394.1)	–5.6–821.6	0.26
Biopsy performed	5/8 (62.5%)	30.4–86.5%	2/6 (33.3%)	9.3–70.4%	0.59
Received steroid pulse treatment	5/8 (62.5%)	30.4–86.5%	1/6 (16.7%)	1.1–58.2%	0.14

different (24), nor do users have increased rates of post-transplant inpatient complications or overall adverse outcomes (25). This suggests that it may be unwarranted to deny marijuana users transplant evaluation strictly based on marijuana usage, indeed Rai *et al.* encourages a holistic evaluation of transplant candidates who use marijuana rather than automatically excluding these patients from evaluation (11).

Interestingly, the most commonly identified cause of liver enzyme elevation in our study was non-adherence with immunosuppression. In a large meta-analysis, Dew *et al.* found that the overall immunosuppressant non-adherence rate among all types of transplants was 22.6 cases per 100 persons per year (PPY). Liver transplant recipients had a lower non-adherence rate to immunosuppressants (6.7 cases per 100 PPY) and illicit drugs (0.2 cases per 100 PPY) (26), which is possibly explained by stricter psychosocial criteria for candidate selection (liver *vs.* kidney) and more severe consequences of graft loss in liver transplant *vs.* kidney transplant. In a multi-site study examining only liver transplant recipients, Rodrigue *et al.* found that risk factors for nonadherence included male sex, time elapsed since transplant and pre-transplant mood disorders and social support instability (27). Unfortunately, substance abuse was not included in that analysis. Lieber found pre-transplant substance abuse to be an independent predictor of post-transplant non-adherence to medical therapy (28). Although our study cannot show causation, our data suggest that liver transplant recipients that use marijuana may be at risk for non-adherence with immunosuppression.

Although this study to our knowledge is the first to characterize marijuana usage post-liver transplant and liver enzymes at time of drug usage, there are several limitations to this study. First, this data is retrospective in nature and cannot be used to determine causation. Secondly, this was a single center study with a small study population meeting our inclusion criteria. Due to our sample size, statistical analysis would likely be underpowered to detect differences between the different sub-populations (elevated liver enzymes *vs.* not, cause identified *vs.* not), and thus we kept our study descriptive. Lastly, although it appears that non-adherence to immunosuppression was common in our study population, an alternate explanation is that males overall are more likely to use marijuana (29), and thus the rate of non-adherence may be more reflective of male sex as a risk factor. Further consideration will be given to expanding the size of this cohort along with non-marijuana users with the goal of comparing these two populations to find statistically significant clinical differences between them. However, the strengths of this study include strict criteria for inclusion (positive UDS), generalizability to other major academic transplant centers and detailed examination of how elevated liver enzymes were managed in these patients.

Understanding how marijuana usage can impact post-liver transplant recipients is of the utmost importance as marijuana usage becomes more common from both a medical and recreational standpoint. We found that liver transplant recipients who use marijuana post-transplant and had elevated liver chemistries were often found to be non-compliant with immunosuppression, leading to transplant rejection in most cases. Although this is concerning, it is not possible to conclude currently whether marijuana usage should be prohibited in pre/post-transplant patients; further studies are needed to determine long term adverse

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effects of marijuana usage and its impact on the graft. Our study suggests that further work should be done to establish if there is a link between marijuana usage and immunosuppression non-compliance, as this has significant implications for post-transplant health and longevity of the graft.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist Available at http://dx.doi.org/10.21037/dmr-20-120

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the UCLA Institutional Review Board (IRB #19-001546) and individual consent for this retrospective analysis was waived.

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